REVIEW

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The Prognostic Role of Tumor-Stroma Ratio in Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis

Denis Francisco Gonçalves de Oliveira[1], João Pedro Braga de Sousa Abreu[2], Rairam Fernandes de Aguiar[3], Alexia Nathália Brígido Assef[4], Danielle Abreu Foschetti[1], Thâmara Manoela Marinho Bezerra[3], Khalil Fernandes Viana[3], Sthefane Gomes Feitosa[3], Karuza Maria Alves Pereira[3,4]*

Abstract

Background: The tumor-stroma ratio (TSR) has emerged as a potential prognostic marker in several cancers, including oral squamous cell carcinoma (OSCC). However, results with high certainty of evidence are required for its implementation in routine histological analysis. Therefore, this systematic review aims to summarize the evidence on the prognostic role of the TSR in OSCC. **Methods:** A search was performed in Embase, PubMed, Scopus, Livivo, Web of Science, and Google Scholar. We included cohort studies that evaluated the association between TSR and survival. Reviews and studies that did not report hazard ratio (HR) were excluded. **Results:** This systematic review included 10 studies and showed an association between TSR and survival. Low TSR (stroma-rich) was associated with decreased overall survival (OS) in univariate analysis (HR = 3.00, 95% CI: 1.69-5.30, p<0.01) and multivariate analysis (HR = 2.91, 95% CI: 2.19-3.87, p<0.01); poorer disease-specific survival (DSS) in univariate analysis (HR = 2.57, 95% CI: 1.95-3.39, p<0.01) and multivariate analysis (HR = 2.64, 95% CI: 1.83-3.79, p<0.01); and poorer disease-free survival (DFS) in univariate (HR = 2.56, 95% CI: 2.02-3.23, p<0.01) and multivariate analyses (HR = 2.11, 95% CI: 1.74-2.56, p<0.01). **Conclusion:** Our findings indicate that TSR is an independent prognostic factor for OS, DSS, and DFS in oral squamous cell carcinoma. However, future studies are needed to assess the prognostic role of this histopathological parameter in OSCC to increase the certainty of the evidence.

Keywords: Oral cancer- prognosis- stroma- survival

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Introduction

The most current data from GLOBOCAN showed a global incidence of 389,846 cases of oral cancer in 2022 [1]. Oral squamous cell carcinoma (OSCC) accounts for over 90 percent of these cases [2] and is considered an aggressive cancer. OSCC has a 5-year overall survival rate of approximately 50% and a survival rate of less than 30% in advanced stages [3].

The treatment and prognosis of patients with OSCC are based on the TNM classification system [3]. However, despite this established system, studies have shown that patients classified in similar clinical stages can have different outcomes [4]. Therefore, the identification of new prognostic markers is necessary.

In recent years, some studies have demonstrated the prognostic role of tumor-stroma ratio (TSR). This histopathological parameter is defined as the proportion of tumor tissue relative to the surrounding stromal tissue [5]. The tumor stroma consists of non-malignant cells from the tumor microenvironment, such as cancer-associated fibroblasts, immune cells, and cells of microvessels. It also includes the basement membrane and extracellular matrix [2, 5]. Consequently, the tumor stroma may be associated with the tumor microenvironment, contributing to tumor invasiveness [2].

Previous research has demonstrated an association between TSR and survival in several types of cancer. Significant correlations with survival have been identified in breast, cervical, colorectal, esophageal, head and neck, ovarian, stomach, urinary tract, laryngeal, lung, and stomach cancers [6, 7]. Of note, the impact of TSR on prognosis among patients with OSCC remains unclear. Several studies have shown the prognostic role of this histopathological parameter [8–10]. However, a recent study did not find this association [11]. Therefore, this

*[1]Department of Pathology and Legal Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil. [2]Department of Clinical Dentistry, Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceará, Fortaleza, Brazil. [3]Postgraduate Program in Dentistry, Faculty of Pharmacy, Dentistry and Nursing, Federal University of Ceará, Fortaleza, Brazil. [4]Department of Morphology, Medical School, Federal University of Ceará, Fortaleza, Brazil. *For Correspondence: karuzaalves@ufc.br*

systematic review aims to summarize the evidence on the prognostic role of the TSR in OSCC.

Materials and Methods

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12]. The study protocol was registered (CRD42022323263) in the International Prospective Register of Systematic Reviews (PROSPERO).

Eligibility criteria

This systematic review aims to answer the following research question: "Is there an association between tumor-stroma ratio and prognosis in patients with OSCC?" We formulate this question based on the following PECOS (Population, Exposure, Comparison, Outcomes, and Study design) framework:

1. Population (P): patients with OSCC;
2. Exposure (E): low tumor-stroma ratio (stroma-rich);
3. Comparison (C): high tumor-stroma ratio (stroma-poor);
4. Outcome (O): overall survival (OS), defined as the time from treatment to death from any cause; disease-specific survival (DSS), defined as the time from treatment to death due to cancer; and disease-free survival (DFS), defined as the duration of survival without local or regional recurrence, metastasis, or death from any cause [2, 9, 13];
5. Study design (S): cohort.

Consequently, cohort studies meeting the following criteria were eligible for inclusion in this systematic review: studies including patients with OSCC; comparing survival between low and high tumor-stroma ratio; and reporting the hazard ratio (HR) for OS, DSS, and DFS. No restrictions were applied regarding language or publication period. Studies meeting the following criteria were excluded: reviews, case series, case reports, case-control, cross-sectional studies, in vitro or animal model studies, and studies that did not report survival data.

Information sources

A systematic literature search was performed in PubMed, Embase, Web of Science, Scopus, and Livivo. An additional gray literature search was conducted in Google Scholar (the first 100 records were selected). The registers were imported into EndNote Web and Rayyan [14] to manage references and remove duplicates. We conducted database searches through July 2024.

Search strategy

The following formal search strategy was employed: ("Oral Tongue Squamous Cell Carcinoma" OR "Oral Cavity Squamous Cell Carcinoma" OR "Oral Squamous Cell Carcinomas" OR "Squamous Cell Carcinoma of the Mouth" OR "Mouth Neoplasms" OR "Mouth Neoplasm" OR "Oral Neoplasm" OR "Oral Neoplasms" OR "Cancer of Mouth" OR "Mouth Cancers" OR "Oral Cancer" OR "Oral Cancers" OR "Cancer of the Mouth" OR "Mouth Cancer" OR "Oral Squamous Cell Carcinoma") AND ("Stromal Ratio" OR "Tumour-stroma" OR "Tumor Stroma" OR "Tumour Stroma" OR "Tumor-stroma Ratio" OR "Carcinoma-stroma Ratio" OR TSR OR Stromas OR Stroma) AND ("hazard ratio" OR "disease-free survival" OR "disease-specific survival" OR "Cancer-specific survival" OR "Survival" OR prognosis OR prognoses OR "Prognostic Factors" OR "Prognostic Factor" OR "overall survival"). We modified this search strategy slightly according to the database, and full details are available in Supplementary Table 1.

Study selection

Two independent reviewers (DFGO and JPBSA) first screened titles and abstracts of all articles. Subsequently, the same two investigators independently reviewed all full-text articles to determine eligibility. Any disagreements were resolved through discussion with a third reviewer (SGF). The study selection process was conducted using Rayyan software.

Data collection process

Two independent investigators collected data of interest from the articles, with discrepancies resolved by a third author. Information extracted from the selected studies included first author, publication year, country, sex, age, sample size, tumor site, tumor histopathological grade, tumor TNM stage, follow-up duration, tumor-stroma ratio cutoff values, and outcome results.

Risk of bias assessment

Two reviewers independently assessed the risk of bias using the Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies [15]. Disagreements were resolved by consulting a third reviewer. The overall risk of bias in each study was determined by the percentage of "yes" responses and was classified as high risk of bias (up to 49% "yes" responses), moderate risk of bias (50%-69% "yes" responses), and low risk of bias (70% or more "yes" responses) [16]. The risk of bias plot was generated using R statistical software version 4.3.3.

Effect measures and synthesis of the results

The outcomes of interest in this study were OS, DSS, and DFS. Therefore, the HRs were chosen as the effect measures and pooled in the meta-analyses. We employed the inverse variance method with a random effects model for the meta-analyses. Statistical heterogeneity was assessed using I^2 and Cochrane's test. To investigate the sources of heterogeneity, subgroup analyses were performed. In addition, sensitivity analyses were conducted using the leaving-one-out method to assess the robustness of the pooled HRs. All analyses were carried out using R version 4.3.3 (meta package), with a significance level set at 5% ($p<0.05$).

Certainty of evidence

Two investigators conducted an independent evaluation of the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [17]. Any disagreements were resolved by a third investigator. The GRADE

system categorizes evidence into four levels: very low, low, moderate, and high. Initially, observational studies are classified as having a low certainty of the evidence. However, some factors may downgrade the certainty of evidence, such as risk of bias, inconsistency of results, imprecision, indirectness of evidence, and publication bias. Conversely, other factors may enhance the quality of the evidence, such as a large magnitude of an effect, a dose-response gradient, and an effect of plausible residual confounding.

Results

Study selection

A total of 1583 studies were identified, and after removing duplicates, 890 remained. Based on titles and abstracts, 871 citations were excluded. Among the studies selected, one was a conference abstract. Therefore, 18 full-text articles were reviewed. Out of these, 10 articles met the eligibility criteria [2, 4, 8–11, 13, 18–20] (Figure 1).

Study and patient characteristics

This review included ten studies that were published between 2020 and 2023. These studies were conducted in China (4), Brazil (1), Italy (1), South Korea (1), Japan (1), Turkey (1), and one study with samples from two countries (Finland and Brazil). The studies included a total of 2121 patients, with a mean age of 57.51 years (95% CI: 52.38-62.64), and 61.28% of the patients were male (95% CI: 56.04%-66.53%). Most tumors were found in the tongue (80.12%, 95% CI: 67.13%-93.12%), and the majority were classified as moderately differentiated (57.58%, 95% CI: 46.89%-68.28%). The most common tumor (T) stage was T2 (48.85%, 95% CI: 37.36%-60.34%) and the most common nodal (N) stage was N0 (79.96%, 95% CI: 63.08%-96.83%). Consequently, most patients were in the early stages (65.12%, 95% CI: 48.76%-81.48%). Notably, the majority of tumors were classified as stroma-poor (52.10%, 95% CI: 45.66%-58.54%), and the mean follow-up time was 51.34 months (95% CI: 40.19-62.49) (Table 1, Table 2, and Supplementary Table 2).

Risk of bias assessment

The risk of bias assessment using Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies showed that there was a low risk of bias across studies. A summary of the risk of bias assessment for all included studies is shown in Supplementary Figure 1.

Synthesis of results

Overall survival

The association between TSR and OS is summarized in Figure 2. Low TSR (stroma-rich) was associated with decreased OS in univariate analysis (HR = 3.00, 95% CI: 1.69-5.30, p<0.01) and multivariate analysis (HR = 2.91, 95% CI: 2.19-3.87, p<0.01). We observed

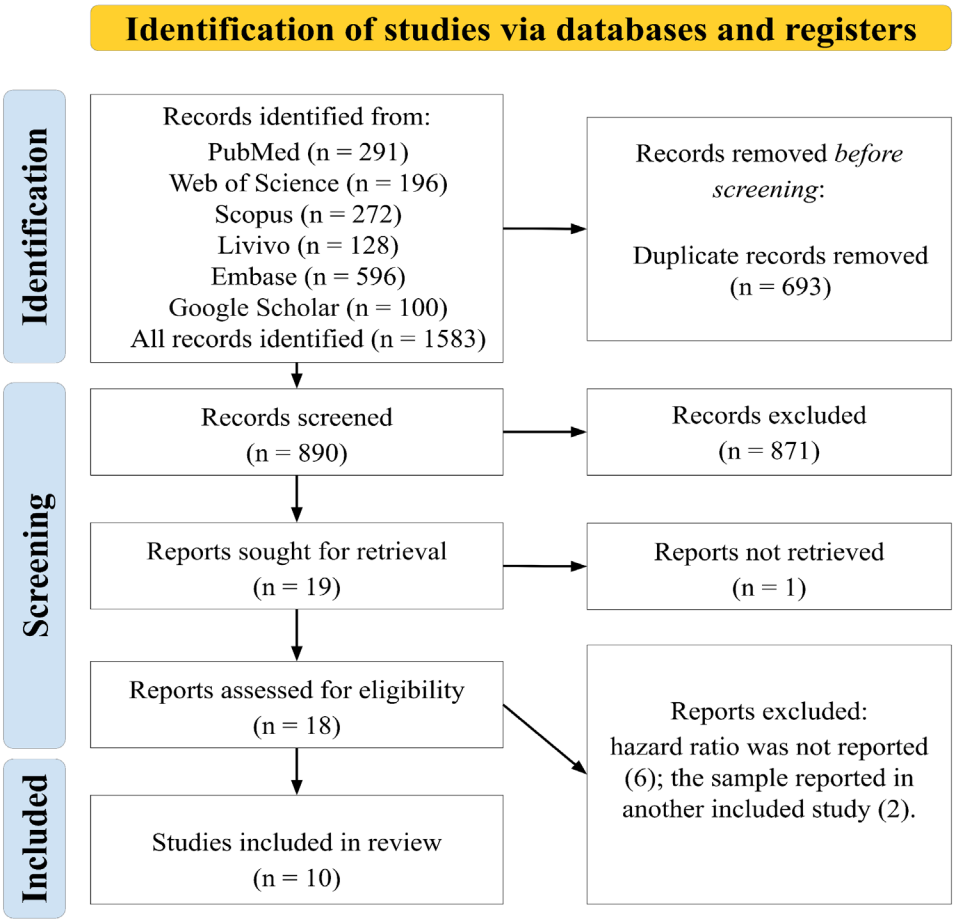

Figure 1. Selection of Articles for the Systematic Review

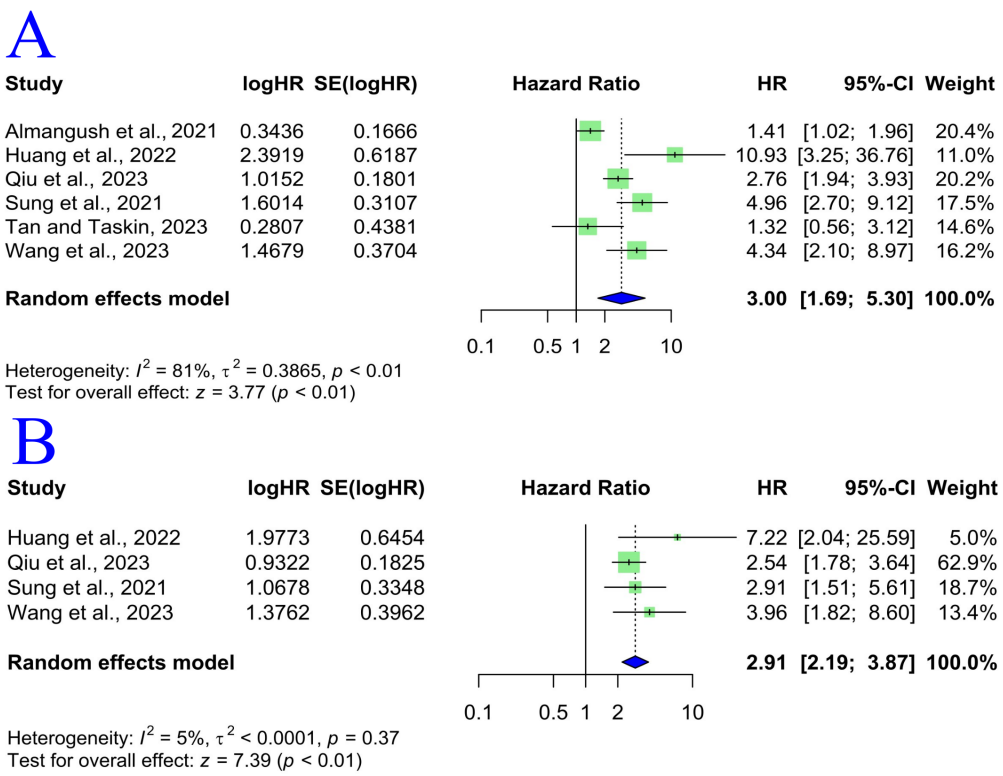

Figure 2. Meta-Analysis for Overall Survival. (A) univariate analysis, (B) multivariate analysis

a high heterogeneity among studies (I^2 = 81%, p < 0.01) in univariate analysis, which was reduced when the HR was pooled by continent and country (see Supplementary Table 3). Notably, we conducted a one-leave-out sensitivity analysis, demonstrating that the pooled effect sizes were not affected by any single study (Supplementary Figure 2). Due to the inclusion of fewer than ten studies in the meta-analysis, publication bias was not assessed.

Disease-specific survival

The forest plots for the association of TSR with DSS are presented in Figure 3. Low TSR was associated

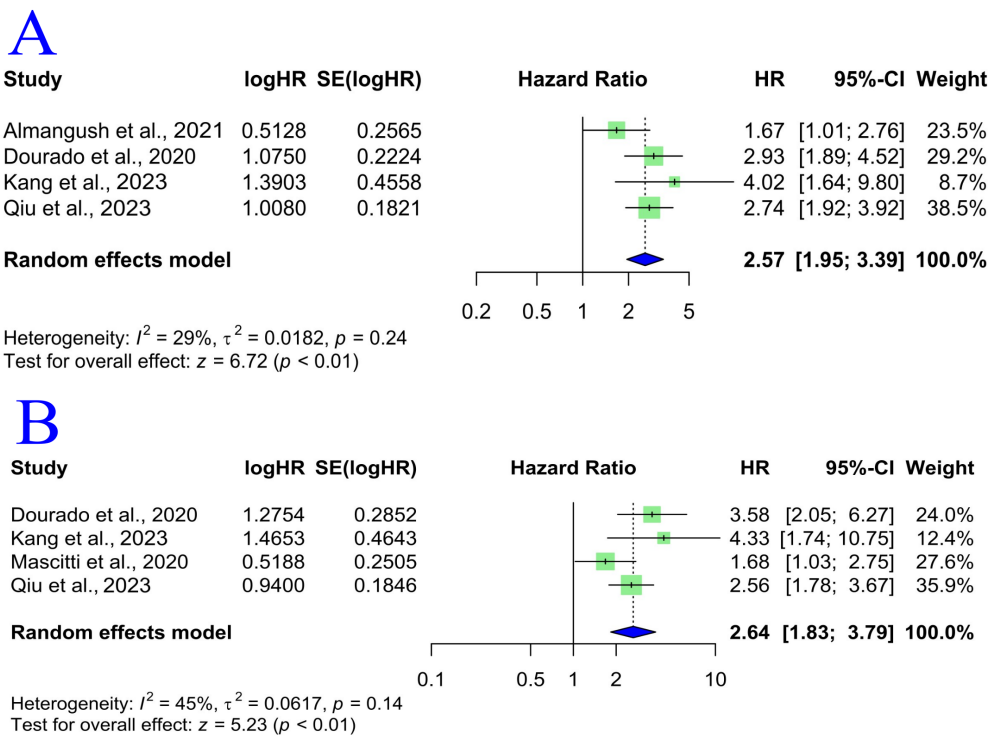

Figure 3. Meta-Analysis for Disease-Specific Survival. (A) univariate analysis, (B) multivariate analysis

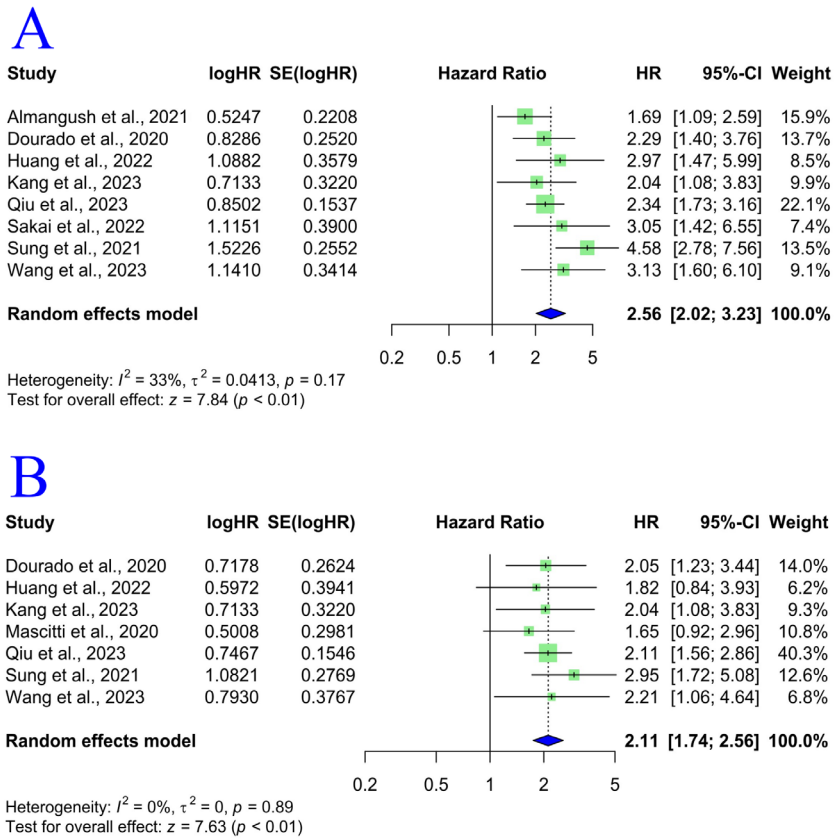

Figure 4. Meta-Analysis for Disease-Free Survival. (A) univariate analysis, (B) multivariate analysis

with poorer DSS in univariate analysis (HR = 2.57, 95% CI: 1.95-3.39, p<0.01) and multivariate analysis (HR = 2.64, 95% CI: 1.83-3.79, p<0.01). The statistical heterogeneity test found moderate heterogeneity, which decreased when we performed the subgroup analysis by country (Supplementary Table 4). The sensitivity analysis, employing the one-leave-out approach, showed no significant changes in HR values (Supplementary Figure 3). As the meta-analysis included fewer than ten studies, publication bias was not assessed.

Disease-free survival

Meta-analyses for DFS are presented in Figure 4. The pooled HR indicated that low TSR was associated with poorer DFS in univariate (HR = 2.56, 95% CI: 2.02-3.23, p<0.01) and multivariate analyses (HR = 2.11; 95% CI: 1.74-2.56, p<0.01). Heterogeneity was moderate and decreased when the HR was pooled by continent, country, and oral subsite (Supplementary Table 5). A sensitivity analysis was also conducted, revealing that the results remained consistent even after removing one study at a time (Supplementary Figure 4). Due to the inclusion of fewer than ten studies in the meta-analysis, a funnel plot was not reported.

Certainty of evidence

Table 3 shows the GRADE assessment. The certainty of the evidence was considered "low" for all outcomes.

Table 1. Study Characteristics

Author	Country	Laboratory method	Cut-off (%)	Sample size	Tumor site
Almangush et al., 2021	Finland and Brazil	H&E	50	308	Tongue
Dourado et al., 2020	Brazil	H&E	50	254	Tongue (170); floor of mouth (67); other (17)
Huang et al., 2022	China	H&E	50	151	Tongue (95); other (56)
Kang et al., 2023	China	H&E	50	103	Tongue
Mascitti et al., 2020	Italy	H&E	50	211	Tongue
Qiu et al., 2023	China	H&E	50	581	Buccal (156); tongue (326); gingival (99)
Sakai et al., 2022	Japan	H&E and IHC	50	70	Tongue
Sung et al., 2021	South Korea	IHC	96	256	Tongue (191); other (63)
Tan and Taskin, 2023	Turkey	H&E	50	73	Tongue (42); buccal mucosa (26); floor of mouth (4); palate (1)
Wang et al., 2023	China	IHC	50	114	NR

H&E, Hematoxylin & Eosin; IHC, immunohistochemistry; NR, not reported

Table 2. Individual Results of the Studies

Author	Type of analysis	Overall survival	Disease-specific survival	Disease-free survival
Almangush et al., 2021	Univariate	1.41 (95% CI: 1.02-1.96), p=0.03	1.67 (95% CI: 1.01-2.76), p=0.047	1.69 (95% CI: 1.09-2.59), p=0.018
Dourado et al., 2020	Univariate		2.93 (95% CI: 1.89-4.52), p<0.0001	2.29 (95% CI: 1.4-3.76), p<0.001
	Multivariate		3.58 (95% CI: 2.05-6.27), p<0.0001	2.05 (95% CI: 1.23-3.44), p=0.006
Huang et al., 2022	Univariate	10.934 (95% CI: 3.252-36.765), p<0.001		2.969 (95% CI: 1.472-5.987), p=0.002
	Multivariate	7.223 (95% CI: 2.039-25.591), p=0.002		1.817 (95% CI: 0.839–3.933), p=0.130
Kang et al., 2023*	Univariate		0.249 (95% CI: 0.102-0.609), p=0.002	0.490 (95% CI: 0.261-0.922), p=0.027
	Multivariate		0.231 (95% CI: 0.093-0.574), p=0.002	0.490 (95% CI: 0.261-0.922), p=0.027
Mascitti et al., 2020	Multivariate		1.68 (95% CI: 1.03-2.75), p=0.036	1.65 (95% CI: 0.92-2.96), p=0.111
Qiu et al., 2023	Univariate	2.76 (95% CI: 1.94-3.93), p<0.001	2.74 (95% CI: 1.92-3.92), p<0.001	2.34 (95% CI: 1.73-3.16), p<0.001
	Multivariate	2.54 (95% CI: 1.78-3.64), p<0.001	2.56 (95% CI: 1.78–3.67), p<0.001	2.11 (95% CI: 1.56–2.86), p<0.001
Sakai et al., 2022	Univariate			3.05 (95% CI: 1.42–6.55), p=0.002
Sung et al., 2021	Univariate	4.96 (95% CI: 2.698-9.119), p<0.001		4.584 (95% CI: 2.780-7.559), p<0.001
	Multivariate	2.909 (95% CI: 1.509-5.606), p=0.001		2.951 (95% CI: 1.715-5.077), p<0.001
Tan and Taskin, 2023	Univariate	1.324 (95% CI: 0.561-3.124), p=0.33		
Wang et al., 2023	Univariate	4.34 (95% CI: 2.1-8.97), p<0.0001		3.13 (95% CI: 1.6-6.1), p=0.00082
	Multivariate	3.96 (95% CI: 1.82-8.6), p=0.00052		2.21 (95% CI: 1.06-4.64), p=0.035

*We used the inverse hazard ratio measures from this study because it presented data on the association between stroma-poor and survival; CI, confidence interval.

Table 3. GRADE Summary of Findings

Factors	Overall survival	Disease-specific survival	Disease-free survival
Risk of bias	not serious	not serious	not serious
Inconsistency	not serious	not serious	not serious
Indirectness	not serious	not serious	not serious
Imprecision	not serious	not serious	not serious
Publication bias	suspected	suspected	suspected
Magnitude of the Effect	strong association	strong association	strong association
Overall certainty of evidence	Low	Low	Low

Publication bias reduced the quality of the evidence for all outcomes by one level due to the small number of studies included in the meta-analyses. On the other hand, we upgraded the quality of the evidence by one level because the meta-analyses showed large effects (HRs between 2 and 5).

Discussion

The tumor microenvironment consists of both tumor cells and the tumor-associated stroma. Many studies have shown that the stromal component of the tumor microenvironment plays a role in invasion and metastasis [21, 22]. It is worth noting that the stroma consists of extracellular matrix and various cell types [23–25]. Among these cells, research has highlighted the role of carcinoma-associated fibroblasts (CAFs). These cells contribute to the production of cytokines and growth factors, such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), *IL-6*, and *IL-17A* [25]. Research indicates that CAFs are associated with epithelial-mesenchymal transition (EMT), which is a process in which tumor cells lose their epithelial phenotype and acquire a mesenchymal phenotype, increasing their potential for cell migration [4]. CAFs also produce matrix metalloproteinases, which promote remodeling and degradation of the extracellular matrix. Other cell types also contribute to tumor progression, such as tumor-associated macrophages and regulatory T-cells that may be present in the tumor microenvironment, suppressing the anti-tumor immune response [25].

Due to the importance of the stroma in tumor progression, many studies have demonstrated the prognostic role of the tumor-stroma ratio (TSR) in various types of cancer. Initially, this histopathological parameter was employed in colon carcinoma in 2007 [26]. In recent years, its prognostic role has been examined in solid tumors [23], head and neck cancer [22], and oral squamous cell carcinoma [2, 4, 8–11, 13, 18–20].

In patients with oral squamous cell carcinoma, studies have shown an association between TSR and patient survival. Low TSR (stroma-rich) has been associated with poorer overall survival, disease-specific survival, and disease-free survival [8, 9, 13]. Nevertheless, some researchers have not demonstrated this association [11]. Accordingly, the aim of this systematic review was to identify studies that evaluated the prognostic role of TSR in OSCC, summarize the effect measures by meta-analysis, and assess the certainty of the evidence.

This systematic review and meta-analysis included ten studies, comprising a total of 2121 patients diagnosed with OSCC. The majority of participants were male, with an average age of 57.51 years, and most of these patients were in the early clinical stages. In this study, our meta-analyses revealed a significant association between TSR and the survival of patients with OSCC. The findings indicated that low TSR (stroma-rich tumor) was associated with poorer overall survival, disease-specific survival, and disease-free survival in both univariate and multivariate analyses.

Recently, meta-analyses have shown an association between TSR and survival in patients with oral cancer. However, these analyses included four or fewer studies [3, 22, 27]. Therefore, to the best of our knowledge, our review represents the study with the largest number of included studies in meta-analyses evaluating the association between TSR and survival in patients with OSCC.

Although the meta-analyses showed an association between TSR and survival, the certainty of the evidence generated was classified as low. When assessing the certainty of the evidence, we should consider that results based on observational studies initially start with a low certainty rating [17]. In this study, due to the small number of studies pooled in the meta-analyses, we suspect publication bias for all outcomes. However, the pooled effect measures demonstrated a strong association between TSR and all outcomes. Consequently, the final certainty rating for the outcomes in this study remained low.

The low certainty rating of the evidence was the main limitation of our study, suggesting the necessity of further research to investigate the prognostic role of TSR in OSCC. On the other hand, this study has some strengths. Firstly, we evaluated the association of this histopathological parameter with three important outcomes, and the meta-analyses demonstrated a statistically significant association for all outcomes. Secondly, in addition to data from univariate analyses, we also pooled data from multivariate analyses. In the multivariate analyses, the results were adjusted for gender, age, T status, N status, clinical stage, tumor grade, invasion pattern, depth of invasion, and perineural invasion. These analyses suggest that TSR is an independent prognostic factor in OSCC. Finally, the evaluation of TSR is simple, accurate,

cost-effective, and requires no additional expense, as it only uses H&E-stained slides that are already routinely employed in histopathology [2, 13].

In conclusion, this systematic review with meta-analysis showed an association between the tumor-stroma ratio and the prognosis in patients with oral squamous cell carcinoma. Our findings indicated that a low tumor-stroma ratio (stroma-rich tumor) was associated with worse overall survival, disease-specific survival, and disease-free survival, and could be considered an independent prognostic parameter. However, the certainty of the evidence was rated as low for all outcomes, suggesting the need for further studies to evaluate the prognostic role of this histopathological parameter in oral squamous cell carcinoma.

Author Contribution Statement

DFGO, JPBSA, and SGF: Conceptualization, methodology, investigation, formal analysis, and writing - original draft. RFA, ANBA, DAF, TMMB, and KFV: Writing - original draft, and writing - review & editing. KMP: conceptualization, methodology, writing - review & editing, supervision, and project administration.

Acknowledgements

All contributors have been acknowledged in authorship.

Data availability statement

The data that support the findings of this study are available in the supplementary file and on request from the corresponding author.

Study Registration

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registry number CRD42022323263.

Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

CAFs, carcinoma-associated fibroblasts; CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HGF, hepatocyte growth factor; H&E, Hematoxylin & Eosin; HR, hazard-ratio; IHC, immunohistochemistry; OS, overall survival; OSCC, oral squamous cell carcinoma; PECOS, Population, Exposure, Comparison, Outcome, and Study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; TNM, tumor, nodes, and metastasis; TSR, tumor-stroma ratio.

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