

REVIEW

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CD44 Expression in Head and Neck Cancer: Systematic Review, IHC-based Meta-Analysis, and Pathway Analysis Highlight a Favorable Clinicopathological Association

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Abstract

Background: Head and neck cancer (HNC) is the seventh most common cancer worldwide with its highest incidence in Asia. Tobacco, alcohol, and HPV contribute to this phenomenon. *CD44* has been found to have a mechanistic role in tumorigenicity and metastasis, however current literature shows conflicting evidence regarding its role in HNC. This review attempts to synthesize available studies to clarify its clinicopathological significance. **Methods:** A PRISMA-compliant systematic search was performed using PubMed, Cochrane, and the Directory of Open Access Journals for studies comparing clinicopathological features between immunohistochemically assessed *CD44* expression levels. Meta-analysis was conducted utilizing Review Manager 5.4. Further subgroup analysis was conducted based on the *CD44* expression quantification method. **Results:** Nine studies, representing 484 patients, were included in the final analysis. An association between *CD44* expression and histopathological grading (OR = 0.46, 95% CI: 0.25–0.84) was found. Gender, survival, lymph node involvement, and perineural invasion were not found to be predicted by *CD44*. **Conclusions:** This meta-analysis demonstrates that *CD44* expression is associated with histopathological grading in HNC. However, survival, lymph node involvement, and perineural invasion are found to be independent of *CD44* expression.

Keywords: *CD44*, Cancer stem cell, Head and neck cancer, Tumor grading, Tumorigenicity

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Introduction

Head and neck cancers (HNC) are the seventh most prevalent cancer globally. Over 660,000 new cases and 325,000 deaths are reported each year [1, 2]. Its rising incidence may arise from shifts in etiological factors, particularly as smoking rates decline in developed countries [3]. Head and neck squamous cell carcinoma (HNSCC) is most commonly found in South and Southeast Asia. Notably, these regions report high consumption of the carcinogenic areca nut. South America along with Central and Eastern Europe also report high incidence [4]. India leads in incidence and tobacco use, often in combination with areca nuts, were responsible for approximately 80% of cases [5].

Worldwide, HNSCC incidence is on the rise, especially in younger individuals, with estimates indicating a 30% yearly increase by 2030 [1]. This pattern is associated with lifestyle, including high alcohol and tobacco consumption in developing countries, along with the increasing incidence of human papillomavirus

(HPV)-related oropharyngeal cancer [6]. Although the overall prognosis for HNC has slightly improved in the last three decades, outcomes vary on factors, such as tumor location, stage, molecular markers, and HPV status [7, 8]. Age negatively impacts prognosis. Smoking and heavy alcohol consumption are both causative and prognostic factors in HNC, while HPV status has emerged as a critical prognostic marker, especially in oropharyngeal cancers. Prognostic factors aid physicians in tailoring treatments to improve outcomes [9].

The prognosis for HNC largely depends on the stage at which it is diagnosed. Patients with localized tumors have a 5-year survival rate of 86.3%, which drops to 69% for those with locally advanced disease, and further declines to 40.4% in metastatic cases [10, 11]. The TNM classification system is currently a widely used prognostic tool [12]. However, it lacks the ability to differentiate between aggressive and nonaggressive tumors of similar size. Identifying reliable biomarkers to predict the biological behavior of HNSCCs could significantly enhance prognostication and treatment

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strategies. Recent research has identified cancer stem cells (CSC) as key to tumorigenicity, recurrence, and resistance to chemotherapy and radiotherapy, hence its eradication is a crucial focus in cancer therapy [13, 14].

In HNSCC, some cell surface markers, including *CD44*, *CD133*, *ALDH1*, and *ABCG2*, have been recognized as CSC markers, with high expression levels typically associated with poor prognosis [15–17]. The most studied tumor marker in HNSCC is *CD44* [18–24]. *CD44*, a transmembrane glycoprotein originally identified as a leukocyte antigen, has various isoforms from alternative splicing. The standard isoform, *CD44s*, is widely expressed in vertebrate cells, while variants (*CD44v*) are restricted to specific epithelial cells. *CD44* is the primary receptor for hyaluronan (HA) and has been identified as an important factor in tumorigenicity, metastasis, and cell proliferation [24–27].

CD44 has a significant role in migration of cells, particularly in cancer progression, by binding to hyaluronan and interacting with the cytoskeleton [28, 29]. Although most studies suggest that *CD44* expression increases tumorigenicity, some contradictory findings indicate a potential positive role in HNC [30–33]. This discrepancy is an avenue for further investigation. This review aims to analyze published studies to clarify the prognostic role of *CD44* expression in HNC.

Materials and Methods

Systematic search was conducted using PubMed, Cochrane, and the Directory of Open Access Journals up to February 2025 using keywords such as: ‘*CD44*’,

‘head and neck’, ‘oral’, ‘larynx or laryngeal’, ‘pharynx, nasopharynx, oropharynx, hypopharynx or pharyngeal’, and ‘tumor, neoplasm, cancer or carcinoma.’ Studies comparing clinical and histopathological outcomes grouped by immunohistochemical evaluation of *CD44* expression in histopathologically confirmed HNC based on WHO classification of tumours 5th edition [34].

This review has been registered in the International Prospective Register of Systematic Reviews under the registration number CRD420250648083. The PRISMA framework guided the study selection process. Two independent reviewers (SM and UM) independently performed initial screening and subsequent comprehensive examination then extraction of the selected articles. Extracted data from the eligible studies include demography, population size, tumour type, *CD44* expression quantification, HNC tumor grading, and disease outcomes. Any discordances were resolved through discussion with a mediator (MH).

Meta-analysis employed Review Manager version 5.4 software. Quantitative synthesis was conducted using the inverse variance method with random effects model in odds ratio. Heterogeneity was evaluated using the I^2 index. Furthermore, subgroup analysis was conducted based on *CD44* expression categorization.

Results

Figure 1 illustrates article selection from the initial 197 initial hits. Title and abstract screening excluded 172 articles, then 13 articles were further excluded for inappropriate PICO. Full-text evaluation excluded 3 more

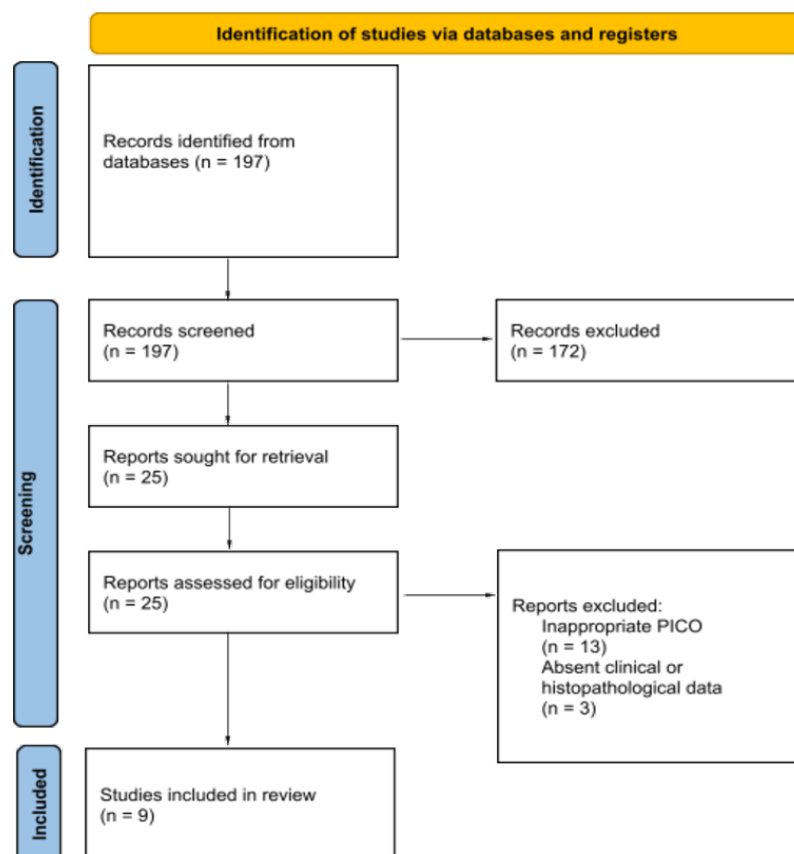


Figure 1. Study Identification Flowchart, Modified from PRISMA [35].

studies due to insufficient clinicopathological data. As displayed in Figure 1, 9 studies were included for analysis, aggregating 484 patients. Table 1 presents demographic data, HNC subtype, and disease outcomes from all the included studies.

As seen in Table 2, the classification of *CD44* expression and histopathological grading vary between studies. Three approaches to classifying *CD44* expression were identified: quantitative, semiquantitative, and qualitative. Similarly, histopathological grading in the included studies use several different criteria,

broadly categorised into well differentiated, moderately differentiated, and poorly differentiated. *CD44* expression was modified from the different quantitative and semiquantitative scores into a dichotomous classification as well as tumor grading.

The pooled analyses are displayed in Figures 2–6. Low *CD44* expression is associated with lower rates of high histopathological grade (OR = 0.46, 95% CI: 0.25–0.84), indicating a significant positive relationship. Gender, several survival metrics, lymph node involvement, and perineural invasion were also investigated in this analysis.

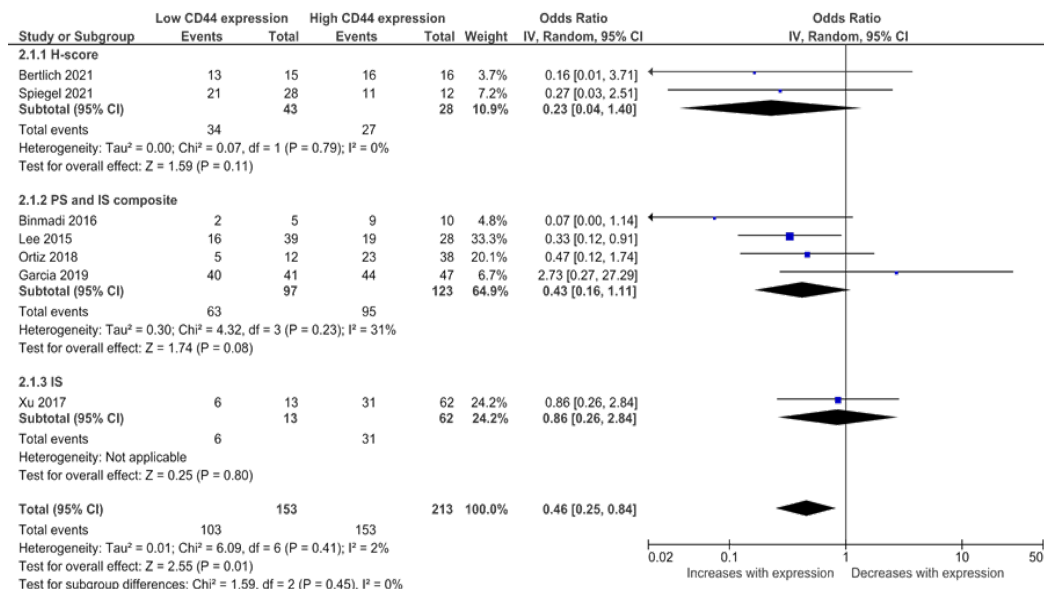


Figure 2. Pooled OR of high histopathological grading in the low *CD44* expression group with subgroup analysis based on the *CD44* scoring system utilized: H-score (n = 71), PS and IS composite (n = 220), and IS only (n = 75). Study weights are proportionally denoted by filled blue squares. The filled black diamonds represent the pooled OR with 95% CI. PS, positive cells score; IS, intensity score.

Table 1. Demography and Disease Outcomes from Included Articles [20–23,36–40].

Study	Design	n	Location	Age (years)	HNC type	Other outcomes
Bertlich, [20]	Retrospective cohort	31	Germany	Mean ± SD 77 ± 11	Squamous cell carcinoma of the salivary gland	Overall survival Disease-specific survival Recurrence-free survival Local control rate
Spiegel, [39]	Retrospective cohort	40	Germany	Mean ± SD 64.4 ± 16.9	Adenocarcinoma of the salivary gland	Overall survival Disease-specific survival Recurrence-free survival Local control rate
Binmadi, [21]	Retrospective cohort	15	Saudi Arabia	Mean, range 49.7, 21–70	Mucoepidermoid carcinoma of the salivary gland	n/a
Garcia, [23]	Retrospective cohort	91	Brazil	Mean ± SD 58.33 ± 15.71	Lower-lip squamous cell carcinoma	Disease-free survival
Lee, [36]	Retrospective cohort	57	South Korea	Mean ± SD 65.4 ± 13.9	Oral squamous cell carcinomas	Overall survival
Ortiz, [22]	Retrospective cohort	50	Brazil	Range 38–85	Oral squamous cell carcinomas	5-year survival Lymph node metastasis
Tandon, [37]	Cross-sectional	70	India	Mean 46.13	Oral squamous cell carcinomas	Morphological parameters
Xu, [40]	Retrospective cohort	75	China	Mean, range 42.49, 11–79	Mucoepidermoid carcinoma of the palate	Overall survival
Yildirim, [38]	Retrospective cohort	55	Turkey	n/a	Intraoral minor salivary gland tumors	Metastasis

Table 2. *CD44* Expression and Histopathological Classification in Analyzed Studies and for Quantitative Synthesis [20–23,36–45].

Study	CD44 expression	Histopathological grading			
	Scoring	Low expression	High expression	Low grade	High grade
Bertlich, [20]	H-score Threshold determined by ROC curve	H-score <270	H-score $\geq$ 270	G1	G2/3
Spiegel, [39]	H-score Threshold determined by ROC curve	H-score <255	H-score $\geq$ 255	G1	G2/3
Binmadi, [21]	Allred immunostaining scoring system (a) intensity of the immunostaining 0 = none; 1 = mild; 2 = moderate; 3 = strong; (b) percentage of positive cells 0 = 0% positive cells; 1 = 0–1% positive cells; 2 = $\geq$ 1–10% positive cells; 3 = >10–33% positive cells; 4 = >33–66% positive cells; 5 = >66–100% positive cells	Negative–weak expression ^a	Moderate–strong expression ^a	Brandwein MS et al. 2002 Low	Brandwein MS et al. 2002 Intermediate High
Garcia, [23]	Scoring based on Faustino et al 2008 (a) intensity of the immunostaining 0 = negative; 1 = weak; 2 = moderate; 3 = strong; 4 = very strong (b) percentage of positive cells 0 = 0% positive cells; 1 = <25% positive cells 2 = 25–50% positive cells 3 = 50–75% positive cells; 4 = >75% positive cells	(a) + (b) $\leq$ 6	(a) + (b) >6	Brandwein-Gensler et al. 2005 Low risk	Brandwein-Gensler et al. 2005 Intermediate or High risk
Lee, [36]	(a) + (b) = 0–7 0–1 = no expression 2–3 = weak expression 4–5 = moderate expression 6–7 = strong expression (a) intensity of the immunostaining 0 = negative; 1 = weak; 2 = moderate; 3 = strong; (b) percentage of positive cells 0 = 0% positive cells; 1 = <25% positive cells 2 = 25–50% positive cells 3 = 50–75% positive cells; 4 = >75% positive cells	Negative–weak expressions ^{a,b}	Moderate–strong expression ^{a,b}	Well differentiated	Moderately to poorly differentiated

Table 2. Continued

Study	CD44 expression		Histopathological grading		
	Scoring	Low expression	High expression	Low grade	High grade
Ortiz, [22]	Scoring modified from Osman 2014 and Shakib et al. 2015 (a)*(b) (a) intensity of the immunostaining 0 = 0–10% 1 = 11–25% 2 = 26–49% 3 = ≥50% (b) percentage of positive cells 0 = Negative 1 = Weak 2 = Moderate 3 = Strong	(a)*(b) ≤2	(a)*(b) >2	Well differentiated	Moderately differentiated
Tandon, [37]	Intensity of the immunostaining + ++ +++ Percentage of positive cells <5% 5–25% 25–75% >75%	Not eligible for meta-analysis	Not eligible for meta-analysis	Well differentiated	Moderately differentiated Poorly differentiated
Xu, [40]	Intensity of the immunostaining – +/++	–a	+ / ++a	Low grade	High grade
Yildirim, [38]	Percentage of positive cells 0–10% 11–25% 25–50% ≥50%	Not eligible for meta-analysis	Not eligible for meta-analysis	Poorly differentiated	Well differentiated

^a, modified by authors from source study; ^b, adapted from Binmadi, 2016

No association between *CD44* expression and these factors was found. Despite low I^2 in each synthesis, the methodological peculiarities of this study benefit from subgroup analysis based on the *CD44* scoring system. No significant difference in effect or heterogeneity was found between subgroups.

Discussion

As previously iterated, *CD44* is very widely studied as a CSC marker. However, its role in HNC remains largely ambiguous. It has been reported that *CD44* expression does not predict grade nor clinical severity in oral cancers, but significantly predicts them in laryngeal and pharyngolaryngeal cancer [46]. A comprehensive bioinformatic analysis has reported that there is significant underlying heterogeneity in the role of *CD44* in HNC, even factoring in confounders such as the diverse experimental methodology (e.g. *CD44* detection) and

limited sample size in available studies [47]. Therefore, conclusions are difficult to draw from individual studies. By synthesizing data from multiple studies, this analysis helps clarify the overall pattern of association and provides a more reliable estimate of the potential role of *CD44* in tumor behavior. These findings contribute to a more consolidated understanding of the biological and clinical relevance of *CD44* in head and neck cancer.

Recent studies reveal that *CD44* contributes to oncogenic signaling pathways that drive tumor progression. In breast cancer, high *CD44* expression is linked to distant metastases and poorer survival rates [48, 49]. Similarly, increased *CD44* levels have been associated with greater tumor aggressiveness and unfavorable outcomes in HNC [19]. As tumors evolve, changes in *CD44* expression impact cell adhesion to the extracellular matrix (ECM). *CD44* serves as a receptor for HA and other ECM components, enabling CSCs to detect environmental changes and mediate signaling pathways that regulate stem

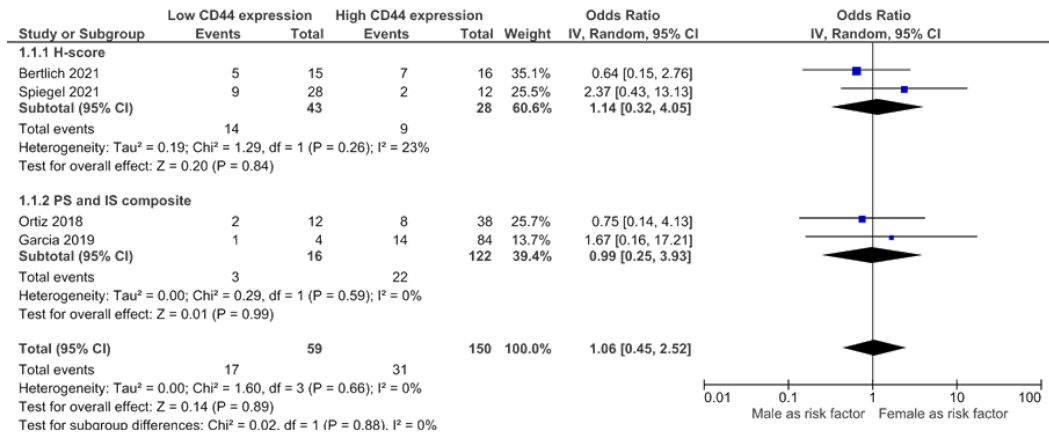


Figure 3. Pooled OR of Female Gender based on *CD44* Expression with Subgroup Analysis based on the *CD44* Scoring System Utilized: H-score (n = 71) and PS and IS composite (n = 138). Study weights are proportionally denoted by filled blue squares. The filled black diamonds represent the pooled OR with 95% CI. PS, positive cells score; IS, intensity score.

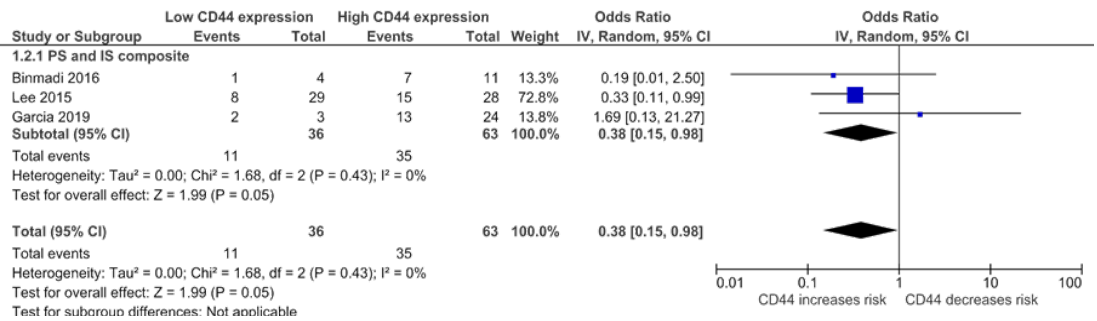


Figure 4. Pooled OR of Lymph Node Involvement based on *CD44* Expression (n = 99). Study weights are proportionally denoted by filled blue squares. The filled black diamonds represent the pooled OR with 95% CI. PS, positive cells score; IS, intensity score

cell behavior. By binding to HA and ECM components, such as osteopontin, *CD44* activates signaling pathways, including Nanog-*STAT3*, *OCT4-Sox2*-Nanog, or c-Src kinase, to modulate the expression of microRNAs (e.g. upregulating *miR-21* and downregulating *miR-203*). These pathways enhance CSC self-renewal, maintenance, and resistance to chemotherapy. This highlights the crucial role of *CD44* in helping cancer cells adapt to new environments and establish metastatic colonies. Although many studies

have shown that high *CD44* expression correlates with poorer prognosis in HNC patients, its prognostic significance remains debated. Conflicting evidence shows that reduced *CD44* expression is linked to worse outcomes in melanoma, prostate cancer, and colorectal cancer, suggesting its role may vary depending on the cancer type [50–52]. This analysis demonstrates that low *CD44* expression significantly predicts lower tumor grade in HNC. However, no survival measures were shown to

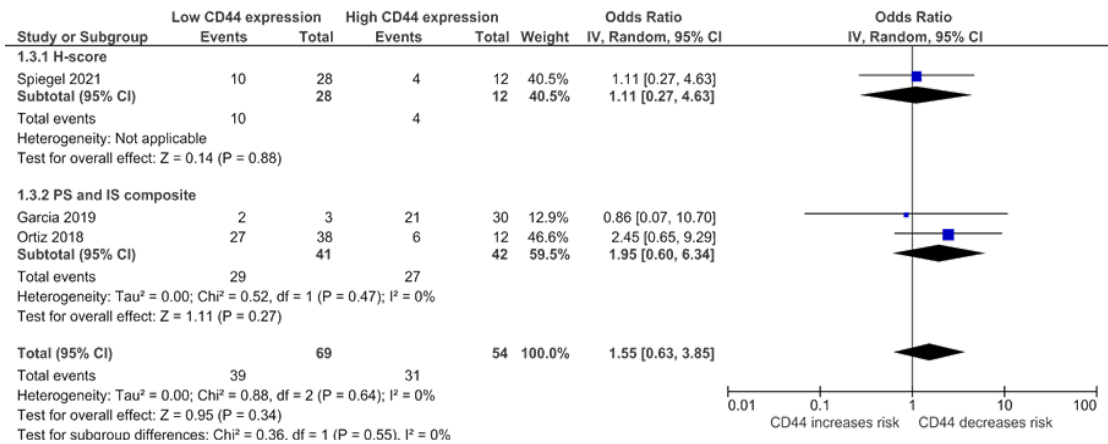
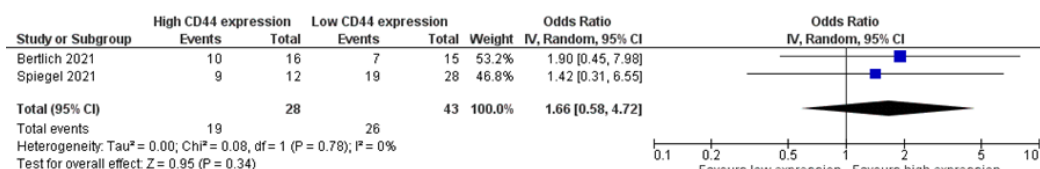
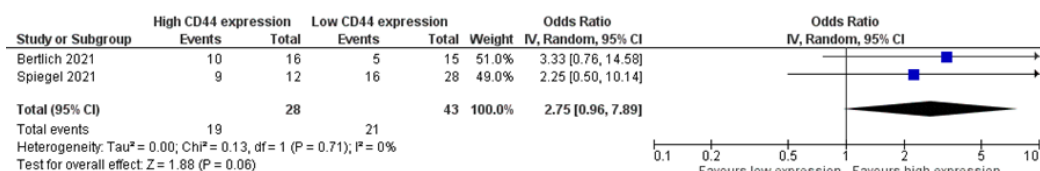


Figure 5. Pooled OR for Perineural in Low *CD44* Expression with Subgroup Analysis for each *CD44* Scoring System (n = 123). Study weights are proportionally denoted by filled blue squares. The filled black diamonds represent the pooled OR with 95% CI. PS, positive cells score; IS, intensity score.

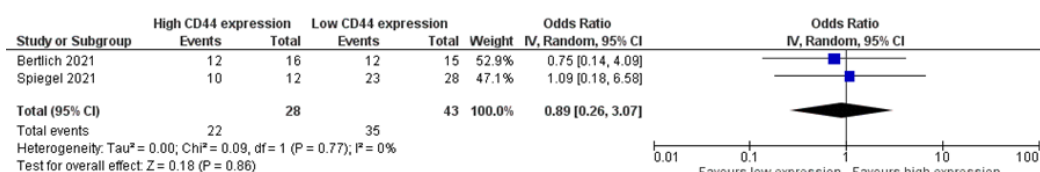
(a) 3-year overall survival



(b) 5-year overall survival



(c) 5-year disease specific survival



(d) 5-year recurrence free survival

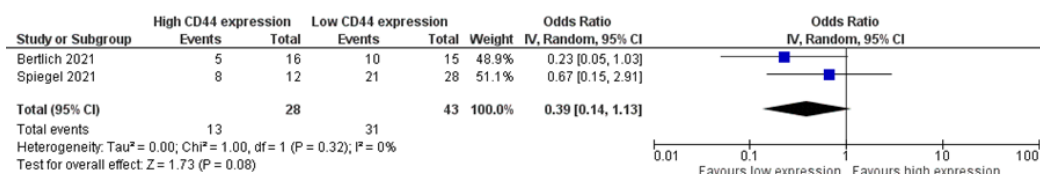


Figure 6. Pooled OR of 3-Year Overall Survival and 5-Year Overall, Disease Specific, and Recurrence-Free Survival and CD44 Expression (n = 71). Study weights are proportionally denoted by filled blue squares. The filled black diamonds represent the pooled OR with 95% CI.

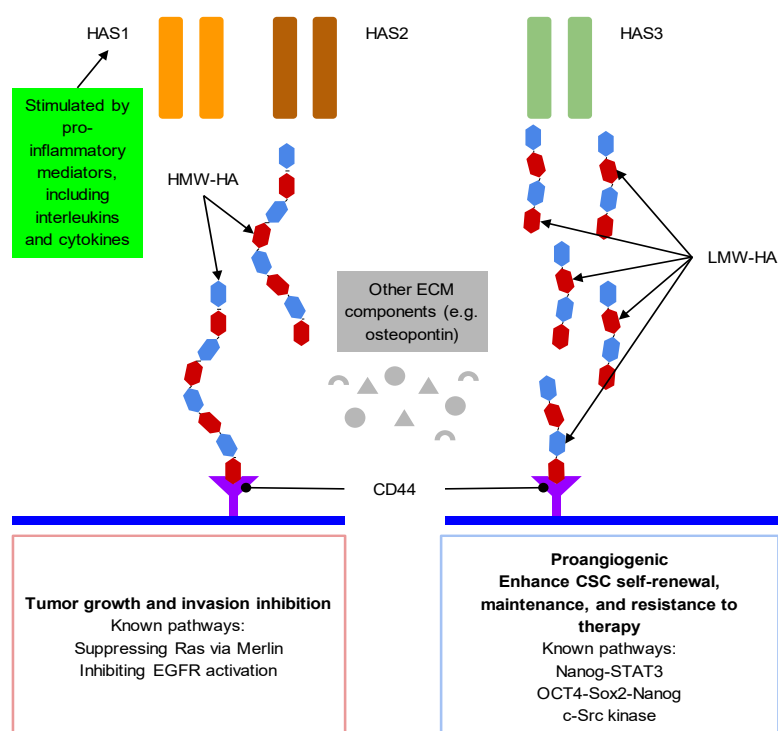


Figure 7. Schematic Representation of CD44–HA–HAS Pathway [50–58].

be predicted by *CD44* expression alone.

Research has shown that *CD44* exhibits distinct responses depending on its interaction with HA [53]. HA is categorized into two forms: high molecular weight (HMW-HA) and low molecular weight (LMW-HA). In normal tissues, HA is primarily in the HMW form, which has anti-angiogenic and anti-inflammatory properties [54]. When *CD44* binds to HMW-HA, it inhibits tumor cell growth and invasion by interacting with Merlin to suppress Ras activation. Additionally, this interaction inhibits the activation of the epidermal growth factor receptor. In contrast, LMW-HA has pro-angiogenic properties, enhancing the proliferation and migration of endothelial cells. When *CD44* binds to LMW-HA, it triggers the activation of signaling pathways that promote cancer cell migration and invasion, producing effects opposite to those observed with HMW-HA [55].

HA is mainly regulated by hyaluronan synthase (HAS), which has three isoenzymes: HAS1, HAS2, and HAS3 [56]. The different roles of these isoenzymes are illustrated in Figure 7. HAS1 is the isoenzyme responsible for the synthesis of hyaluronan in cells. HAS1 is responsible for the synthesis of HMW-HA, which plays an important role in maintaining tissue homeostasis from anti-proliferative properties. HAS1 expression is stimulated by pro-inflammatory mediators, including interleukins and cytokines, suggesting its role in inflammatory diseases, such as atherosclerosis, osteoarthritis, and respiratory infections. According to research by Siiskonen et al., elevated HAS1 levels are correlated with decreased survival in several cancers, including ovarian and colon cancer, Waldenström macroglobulinemia, and multiple myeloma [56, 57]. Additionally, HAS1 splice variants have been implicated in the prognosis of certain malignancies. HAS1 contributes to tumor progression and metastasis in bladder cancer and excessive HA accumulation has been associated with poorer outcomes in breast cancer. HAS1 is associated with various prognostic factors, such as tumor size, obesity, and shorter survival in several types of cancer. However, HAS1 is very low or absent in serous ovarian tumors and decreased HAS1 is associated with lower hyaluronan levels as well as a poor prognosis in melanoma [56].

HAS2 is considered the most important isoenzyme in the synthesis of hyaluronan and is also responsible for the synthesis of HMW-HA. HAS2 is the most abundantly expressed form of HA in tissues and is vital in developmental processes, such as the growth of blood vessels, brain, heart, and limbs during embryogenesis [56, 57]. Meanwhile, HAS3 produces LMW-HA, which is more closely associated with pro-inflammatory responses and tumor progression. HAS3 also plays an important role in metabolic conditions and increases the production of HA in various cells and tissues. Karousou et al. [58] stated that HAS3 is highly expressed in several types of cancer, such as renal carcinoma and oral cancer. However, the role of HAS3 in HA metabolism in cancer remains unclear. Interestingly, it has been implicated in intercellular communication as it was found in extracellular vesicles from cancer cells. HAS3 shows a significant correlation with several types of cancer, but information about its

regulation is still limited. Nevertheless, the possibility that HAS3 may be associated with the release of extracellular vesicles presents a promising new target for further research.

A decrease in *CD44* expression as tumor grade increases may indicate reduced cell–cell adhesion, facilitating cell detachment. *CD44* plays a crucial role in adhesion, movement, and growth signaling in cancer cells. It also serves as a CSC marker with two main phenotypes: (i) epithelial-mesenchymal transition (EMT) CSCs that express a proteolysis-resistant *CD44s* isoform and (ii) epithelial CSCs that express a trypsin-sensitive *CD44v* isoform. This leads to lower *CD44* expression in epithelial CSCs and higher expression in EMT CSCs. In oral squamous cell carcinoma, poorly differentiated tumors showed weak *CD44* immunostaining due to the presence of highly pleomorphic cells [36–38, 59].

As previously highlighted, the heterogeneity in studies analyzing the role of *CD44* in HNC is tremendous even without the mechanistic complexity. This meta-analysis particularly shows that the lack of standards in *CD44* expression in this regard leads to difficulty in trying to synthesize evidence from the pool. Whilst an attempt was made to compensate by collating the different semiquantitative and quantitative measures found into a single classification system, this process itself raises the question of comparability between the component systems. Another source of heterogeneity in experimental procedure is the different reagents available to perform the task. The lack of HNC subtype subgroup analysis because of different *CD44* expression measurement illustrates another consequence of this heterogeneity not reflected in statistical analysis. In the absence of a widely recognized standard, it is recommended that future studies include more detail in their methodology, more methods of evaluation, and supplementary materials containing appropriate individual patient data. Furthermore, it is to be impressed that there remains a drought of studies reporting clinical outcomes. Understandably, the focus lies on histopathological parameters, relying on its prognostic ability, instead of direct association with *CD44*. Even more specific clinicopathological parameters, such as lymph node involvement and perineural invasion are rarely reported, therefore it is difficult to make robust conclusions regarding the role of *CD44*. This review also did not find viable studies to analyze that report on other important factors, such as HPV-dependent or independent etiologies.

From a clinical perspective, the observed associations suggest that *CD44* expression may reflect tumor aggressiveness and could potentially be considered as a biomarker to assist in patient risk stratification and prognostic assessment. Nevertheless, further large-scale and well-designed studies are still needed to validate these findings and to determine the potential clinical utility of *CD44* in guiding therapeutic strategies.

Author Contribution Statement

All authors contributed equally in this study.

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Conflict of Interest

The authors declare that they have no potential conflicts of interest to disclose.

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