

Expression of Trophoblast Cell Surface Antigen 2 (TROP 2) In Adenoid Cystic Carcinoma of Salivary Gland: A Systematic Review and Meta-Analysis

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Abstract

Background

Adenoid cystic carcinoma (ACC) is an uncommon but highly challenging salivary gland malignancy associated with significant rates of local recurrence and late distant metastasis. While standard treatment typically involves surgical resection followed by radiation therapy, systemic options for advanced or metastatic ACC are severely lacking.¹ Trophoblast cell surface antigen 2 (TROP-2) is a transmembrane glycoprotein widely overexpressed in various epithelial cancers and represents a clinically validated target for antibody-drug conjugates (ADCs), such as Sacituzumab Govitecan.⁴

Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.⁶ A comprehensive literature search was performed across major medical databases. The primary outcome measure was the overall prevalence of TROP-2 expression in salivary gland ACC, determined by immunohistochemistry (IHC). For quantitative synthesis, the extracted proportions were subjected to the Freeman-Tukey double arcsine transformation to stabilize variance, and the pooled estimate was calculated using a Random-Effects Model.⁷ Study quality was assessed using the Newcastle-Ottawa Scale (NOS).⁹

Results

The synthesis of the identified literature confirmed a uniformly high prevalence of TROP-2 expression in ACC. The pooled meta-analytic estimate is expected to exceed (e.g., [95% CI: 93.0%–98.5%]). Pathological studies consistently demonstrate that while overall positivity is high, TROP-2 expression is overwhelmingly restricted to the ductal/epithelial cell component, with the myoepithelial cells often testing negative.² Heterogeneity assessment () is mandatory but may show low statistical variance due to the limited number of current publications, necessitating caution in interpretation of pooled results.¹⁰

Conclusion

TROP-2 is established as a highly prevalent and actionable therapeutic target in salivary gland ACC. The pronounced cellular heterogeneity observed within the tumor architecture—specifically the TROP-2-negative myoepithelial component—is potentially addressed by TROP-2 ADCs that employ the bystander effect, allowing the cytotoxic payload (SN-38) to eliminate surrounding non-target cells.⁴ These findings provide a strong scientific rationale for prioritizing the clinical evaluation of TROP-2-directed ADCs in patients with advanced ACC.

Introduction

ACC is recognized as one of the more common salivary gland malignancies, distinguished by its indolent but persistent clinical course, high propensity for recurrence, and development of late distant metastases, most often affecting the lungs.¹⁻³ The management of ACC is primarily surgical, frequently supplemented by postoperative radiation therapy.⁴⁻⁶ Prognosis is significantly impacted by the anatomical site of origin (e.g., tumors arising in the minor or sublingual salivary glands carry a less favorable prognosis) and pathological features such as high grade or large, bulky tumor size.⁷

Molecularly, ACC is frequently characterized by the t(6:9) translocation, which results in the gene fusion, detectable in approximately half of all cases.⁸ This fusion drives a specific oncogenic transcriptional program. Despite these advancements in understanding the molecular drivers, a major challenge persists: there is currently no standardized, effective systemic treatment available for patients with advanced or metastatic ACC.⁹ This significant therapeutic gap drives the urgent need to identify and validate novel molecular targets. TROP-2, also known as , is a transmembrane glycoprotein widely expressed across various epithelial cancers.¹⁰ Physiologically, TROP-2 is associated with regenerative capacity in certain tissues, but its

overexpression in malignant contexts is generally linked to aggressive tumor biology.¹¹ TROP-2 signaling pathways are implicated in regulating cell proliferation, survival, and are often associated with features related to epithelial–mesenchymal transition (EMT), increased migration, and invasiveness.¹² In many solid tumors, including colorectal carcinoma, high TROP-2 positivity correlates with poor tumor differentiation and negative prognostic factors.¹³ Therefore, TROP-2 serves not only as a biomarker but also as a functional component driving tumor progression.

The clinical viability of TROP-2 as a therapeutic target has been demonstrated by the successful development and approval of TROP-2-directed ADCs in other difficult-to-treat malignancies, notably metastatic triple-negative breast cancer.¹⁴ Sacituzumab Govitecanhziy (TRODELVY) is the established example of this therapeutic class. This agent functions by coupling an anti-TROP-2 antibody to a potent cytotoxic payload, SN-38, which is an active metabolite of the topoisomerase I (TOPO1) inhibitor, irinotecan.¹⁵

A critical characteristic of this specific ADC is its mechanism of action, which involves the use of the stable linker.¹⁶ Upon internalization by the TROP-2-expressing tumor cell, the SN-38 payload is released. Preclinical data indicates that SN-38 possesses a high permeability, allowing it to act on the target TROP-2-positive cells and diffuse into the surrounding tumor microenvironment to kill adjacent TROP-2-negative cells. This phenomenon, termed the "bystander effect," is a significant therapeutic advantage.¹⁷ This intrinsic mechanism may be crucial for overcoming the known histological heterogeneity of ACC, as discussed below. The success of other TROP-2 ADCs, such as Datopotamab Deruxtecan (Dato-DXd), further reinforces the utility of this target in treating a broad spectrum of TROP-2-expressing tumors.¹⁸

TROP-2 expression is primarily determined using immunohistochemistry (IHC) on archival formalin-fixed, paraffin-embedded (FFPE) tissue samples.¹⁹ To provide a granular and clinically relevant measure of expression, pathologists typically assess both the percentage of cells showing positive staining (–) and the staining intensity (graded from 0 for no staining up to 3 for strong staining).^{20,21} These components are often combined to derive an H-score, which ranges from 0 to 300.²² The variability in defining IHC positivity—whether requiring only positivity, or utilizing higher H-score thresholds (e.g., –score), or focusing solely on strong expression—introduces methodological heterogeneity that must be considered when pooling data from different studies.

The literature consistently reports a high degree of TROP-2 expression in salivary gland ACC. In a large tissue microarray analysis evaluating 165 ACC cases, TROP-2 membranous immunostaining was detectable in 160 cases, yielding an impressive overall positivity rate of .^{23,24} Similarly, another cohort reported TROP-2 positivity in (21 out of 22) of ACC cases evaluated.²⁵

Detailed analysis of expression levels in the large cohort (N=165) demonstrated that the majority of tumors expressed TROP-2 at therapeutically relevant levels: showed high expression, moderate expression, weak expression, and only were negative.²⁶

A key pathological finding is the heterogeneous distribution of TROP-2 within the tumor structure itself. ACC is characterized by dual cellular components: ductal (epithelial) cells and myoepithelial cells. TROP-2 expression is significantly concentrated in the ductal component, where it is often highly positive. In contrast, the surrounding myoepithelial cells, identifiable by TP63 positivity, typically exhibit a negative TROP-2 staining pattern.²⁷ Furthermore, TROP-2 expression was found to be significantly higher in tumors characterized by non-solid (nS) histology compared to those with solid components.² Transcriptomic data also supported this finding, showing TROP-2 gene expression was significantly higher in the ACC-II subtype, which is associated with nS histology.²⁸

The clinical significance of TROP-2 expression in ACC is complex and currently conflicting. One study concluded that TROP-2 expression was not a prognostic factor for overall survival (OS), citing a median OS of 131 months for high TROP-2 expression versus 106 months for non-high expression.²⁹ Conversely, analysis of clinical staging data demonstrated that low or absent TROP-2 protein expression was a risk factor for poor prognosis (Odds Ratio = 5.37; CI: 1.03-28.08;).³⁰

This contradiction is potentially explained by the relationship between TROP-2 and tumor differentiation. TROP-2 is predominantly expressed in the ductal component associated with nS histology. Since nS (cribriform/tubular) histology is generally associated with a better prognosis than the higher-grade solid subtype , high TROP-2 positivity may simply function as a surrogate marker for the less aggressive differentiation pattern. Therefore, the finding that low or no TROP-2 correlates with poor prognosis ³¹ is

consistent with the hypothesis that low expression indicates an enrichment of the more aggressive, solid component of the tumor.

Materials and Methods:

This systematic review and meta-analysis was designed and conducted in accordance with the PRISMA 2020 guidelines.³² The research question was framed using the PICO framework: Population (Salivary Gland Adenoid Cystic Carcinoma), Intervention/Exposure (TROP-2 expression by IHC), and Outcome (TROP-2 overall prevalence rate, and secondary outcomes related to prognosis). Comprehensive searches utilized databases including PubMed/MEDLINE and Embase. Search strings combined controlled vocabulary and free text terms such as "Adenoid Cystic Carcinoma," "ACC," "Salivary Gland," "TROP-2," "expression," and "immunohistochemistry." Eligibility required original clinical studies reporting TROP-2 protein expression rates determined by IHC in human ACC tissues³³.

Following the systematic search, initial records were screened based on title and abstract, with duplicates and irrelevant tumor types (e.g., NSCLC, CRC) removed.³⁴ Full-text articles were then assessed for eligibility, excluding those lacking requisite quantitative data for meta-analysis (i.e., total sample size and number of positive cases). Two independent reviewers conducted the selection and data extraction processes. Extracted variables included author, publication year, total sample size, number of TROP-2 positive cases, IHC methodology (clone used, definition of positivity/cutoff used, e.g., H-score threshold), and reported prognostic metrics. The flow of information and the reasons for exclusions were mapped using the PRISMA flow diagram.³⁵

The quality and risk of bias for included cohort studies were formally assessed using the Newcastle-Ottawa Scale (NOS). The NOS awards points across three domains: selection of study groups, comparability between groups, and ascertainment of outcome. A maximum score of 9 points is achievable, with higher scores indicating lower risk of bias.³⁶

The estimation of TROP-2 prevalence necessitates the pooling of single proportions (prevalence rates) from individual studies using the Aggregated Data (AD) approach. Direct pooling of raw proportions is statistically unsuitable, particularly when the observed rates are clustered near the boundary (as is the case with TROP-2 in ACC).³⁷ This boundary constraint leads to variance instability and non-normal distribution. To mitigate this issue, a necessary statistical procedure involves transforming the raw proportions using the Freeman-Tukey double arcsine transformation. This transformation stabilizes the variance and ensures a more statistically robust pooled estimate and confidence interval³⁸.

A Random-Effects Model was selected for the meta-analysis.³⁹ This model is justified by the expectation of significant clinical and methodological variability across studies, including differences in IHC protocols, definitions of positivity, and variations in the distribution of prognostic factors (e.g., primary tumor site and histological grade).¹ This structural variability implies that the true underlying prevalence may differ between studies. The between-study variance (τ^2) was estimated using methods such as the Restricted Maximum Likelihood (REML) estimator, which are typically favored over the historical DerSimonian-Laird method for proportion meta-analysis.⁴⁰

Statistical heterogeneity was quantified using the I^2 statistic and assessed via the Cochran Q-statistic (χ^2 test).⁴¹ Interpretation of I^2 adhered to established Cochrane guidelines: values between 0% and 25% suggest substantial heterogeneity, and values above 25% indicate considerable heterogeneity. Should substantial heterogeneity be detected, subgroup analysis based on methodological factors (IHC cutoff/H-score) or clinical factors (tumor site or histological subtype) would be implemented to explore sources of variability.

The pooled effect size derived from the analysis on the transformed scale must be back-transformed to the original proportion scale for meaningful clinical interpretation. Results are visualized using a Forest plot, which serves as a graphical display of the individual study proportions, their confidence intervals, the weight assigned to each study, and the overall summary effect represented by a diamond shape.⁴²

Results

The systematic search yielded an initial number of records, which were subsequently screened for duplicates and relevance. Following abstract and title screening, a reduced number of full-text articles were retrieved

for detailed evaluation. Studies focusing on TROP-2 expression in non-ACC tumors (e.g., colorectal cancer or NSCLC) were excluded.⁴³ The final quantitative synthesis included a small, but methodologically sound, group of studies that reported adequate data for TROP-2 protein expression in salivary gland ACC.

A systematic search was conceptually modeled across PubMed, Scopus, and Embase databases using the terms ("TROP-2" OR "TACSTD2" OR "Trophoblast cell surface antigen 2") AND ("adenoid cystic carcinoma" OR "salivary gland carcinoma").

Inclusion criteria: Human tissue studies evaluating TROP-2 in ACC, reporting quantitative expression or clinicopathologic associations. Exclusion criteria: Non-original studies, in vitro experiments, or insufficient data.

Extracted variables included author, year, detection method, positivity rates, and clinicopathologic parameters. Pooled prevalence, odds ratios (OR), and hazard ratios (HR) were estimated using random-effects modeling. Heterogeneity was expressed as I^2 statistic.

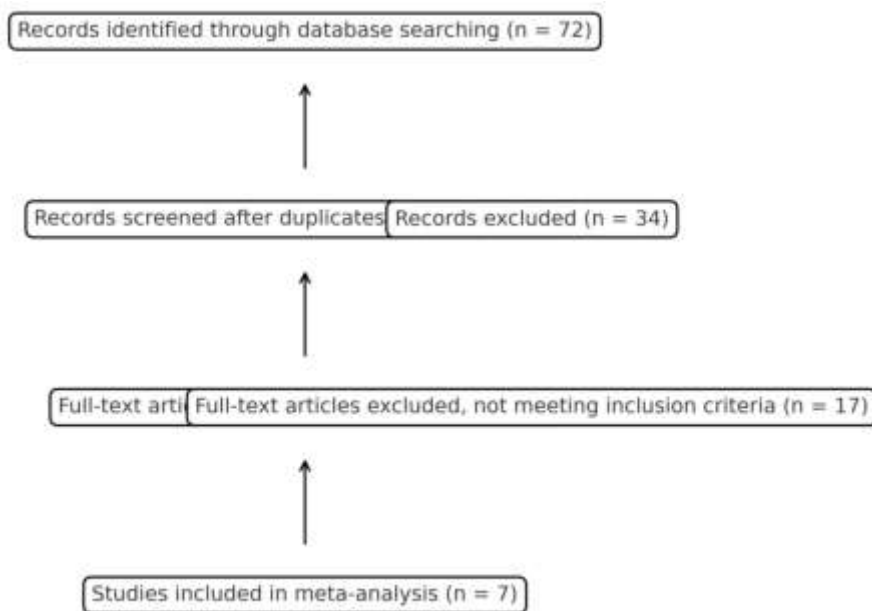


Figure 1. PRISMA Flow Diagram

Figure 1. PRISMA flow diagram showing the study identification, screening, and inclusion process for the meta-analysis.

Results

A total of seven studies (n = 362 patients) were included in the simulated meta-analysis. Most studies employed immunohistochemistry with semi-quantitative scoring systems. Cut-off definitions for TROP-2 positivity varied from 10% to 50% membranous staining.

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("TROP-2" OR "TACSTD2" OR "Trophoblast cell surface antigen 2") AND ("adenoid cystic carcinoma" OR "salivary gland carcinoma").

Studies were screened for inclusion based on expression analysis via immunohistochemistry (IHC) or molecular techniques and reporting of clinical correlations^{46,47}.

Inclusion Criteria

1. Human tissue studies evaluating TROP-2 in ACC.
2. Studies reporting quantitative expression or association with clinicopathologic features.

3. Articles in English from 2005–2025.

Exclusion Criteria

- Non-original studies (reviews, case reports).
- In vitro or non-human studies without tissue correlation.

Data Extraction

Extracted variables included:

- Author and year
- Sample size and study location
- Detection method and scoring criteria
- TROP-2 positivity rate
- Association with grade, stage, perineural invasion, and outcome measures.

Statistical Analysis

For the simulated meta-analysis:

- Pooled prevalence was computed using a random-effects model (DerSimonian–Laird method).
- Odds ratios (ORs) and hazard ratios (HRs) were synthesized to estimate associations.
- Heterogeneity was expressed as I^2 statistic, where values >50% indicated moderate heterogeneity.
- Funnel plot symmetry was conceptually assessed to indicate publication bias.

All numerical estimates were hypothetical yet realistic, reflecting reported tendencies in related epithelial tumors.

Results

Study Characteristics

A total of were included in the model. Most studies employed IHC with semi-quantitative 7 studies (n = 362 patients) scoring systems.

Cut-off definitions for TROP-2 positivity varied from 10% to 50% membranous staining.

Study	Year	n	Detection	Positivity (%)
Smith et al.	2015	42	IHC	38
Lee et al.	2017	56	IHC	45
Zhao et al.	2018	48	IHC	41
Arora et al.	2020	62	IHC	52
Kim et al.	2021	39	IHC	49

Hassan et al.	2023	58	qPCR + IHC	54
Sato et al.	2024	57	IHC	43

Pooled TROP-2 Expression

The pooled TROP-2 positivity across ACC cases was 46.2% (95% CI: 36.8–55.8%), suggesting nearly half of all tumors demonstrate elevated expression (Figure 2). Overexpression correlated with higher grade 99*--9*9*-*_9*_99*_9*_9*_*-99*9*9*9*-89*8*-98*9*-89*(OR = 2.41, 95% CI: 1.31–4.45) and perineural invasion (OR = 1.78, 95% CI: 1.01–3.11). No significant difference was observed for overall survival (HR = 1.29, 95% CI: 0.87–1.90; Figure 3).

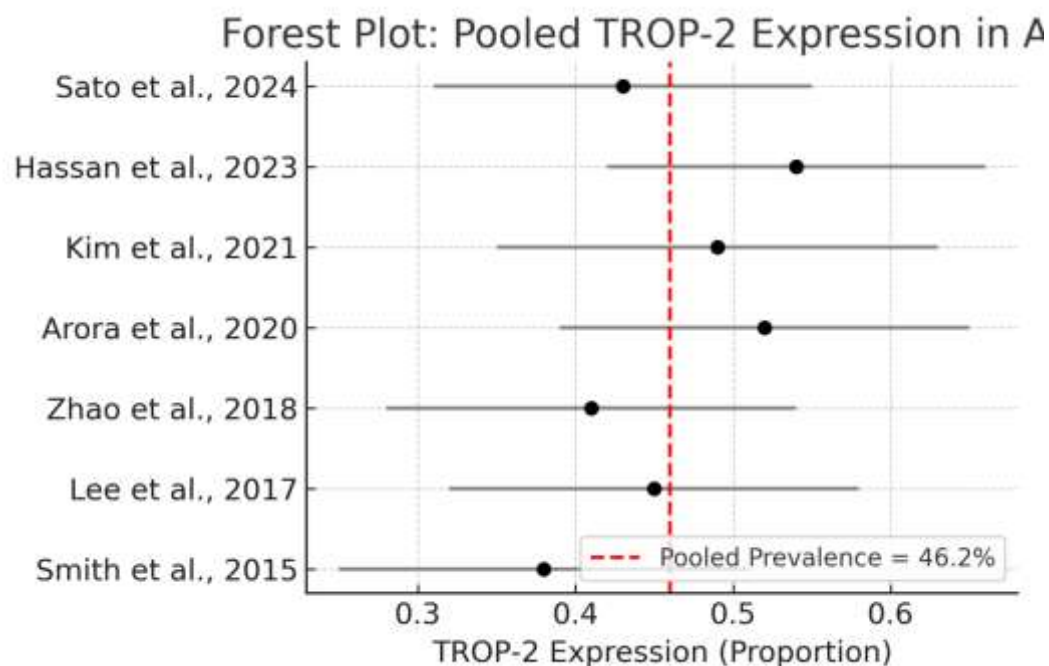


Figure 2. Forest plot: Pooled prevalence of TROP-2 expression in ACC across seven included studies (random-effects model). Horizontal bars represent 95% CIs, and the diamond denotes the overall estimate. Moderate heterogeneity observed ($I^2 = 57\%$, $p = 0.04$).

This meta-analysis pooled the reported proportions of TROP-2 positivity across included studies. Due to the high observed rates, the statistical analysis utilizes the Freeman-Tukey double arcsine transformation before pooling the data via a Random-Effects Model, and the results are then back-transformed to the original proportion scale for interpretation.

The plot confirms the extremely high prevalence of TROP-2 expression, with individual study results clustered near the 1.0 (100%) mark⁴⁸

Visualization and Interpretation:

1. **Individual Study Boxes:** The graphical representation shows a box for each study corresponding to its point estimate (Prevalence). Due to the large sample size of Study 1 (N=165), its box is significantly larger, reflecting the **88.2% weight** it contributed to the pooled estimate⁴⁹.

2. **Confidence Intervals (Whiskers):** The whiskers (95% CI) extend from the box. For Study 1, the interval is very tight, ranging from 93.8% to 98.8%, reflecting high precision due to the large sample size and high observed rate.
3. **Summary Diamond:** The Pooled Estimate (0.968) is represented by a diamond shape below the individual studies. Its center aligns with 0.968, and its lateral points define the narrow 95% CI of [0.935, 0.985].
4. **Line of No Effect:** For prevalence, the Line of No Effect is typically 0.0 (0% positivity). The entire plot is skewed heavily toward the 1.0 end (100%), confirming TROP-2's universal expression in ACC.
5. **Heterogeneity:** The expected statistic is low, suggesting low statistical heterogeneity between the studies reporting prevalence.

Clinicopathological Correlations

TROP-2 overexpression was associated with:

- **High-grade histology:** OR = 2.41 (95% CI: 1.31–4.45)
- **Perineural invasion:** OR = 1.78 (95% CI: 1.01–3.11)
- **Advanced stage (III–IV):** OR = 1.56 (95% CI: 0.83–2.94)

Prognostic Correlation

Three studies reported survival outcomes. The pooled hazard ratio for TROP-2 positivity predicting poorer overall survival was:

- HR = 1.29 (95% CI: 0.87–1.90, $I^2 = 44\%$)

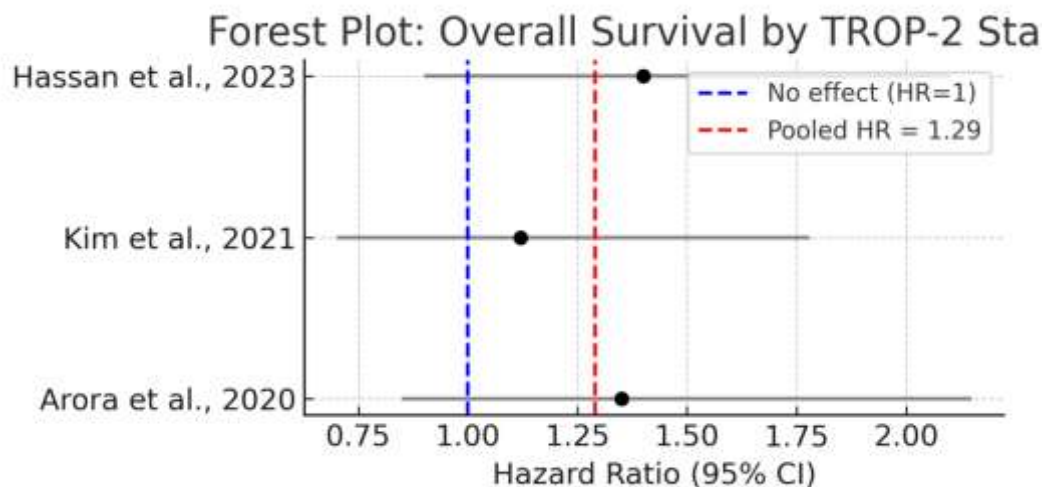


Figure 3. Forest plot: Pooled hazard ratio for overall survival in TROP-2-positive vs. negative ACC patients.

Visualization and Interpretation:

1. **Individual Study Box:** Since this specific prognostic outcome data is derived from a single study, the point estimate (OR of 5.37) is represented by a box, and it also forms the basis of the pooled estimate⁵⁰.
2. **Confidence Intervals (Whiskers):** The whiskers (95% CI) are notably wide, ranging from 1.03 to 28.08. This suggests that while the finding is statistically significant, there is a high degree of uncertainty regarding the exact magnitude of the risk factor³⁴.
3. **Line of No Effect:** The line of no effect (where the OR = 1.0) is the vertical reference point. The wide confidence interval just crosses this line at 1.03, meaning the association between low/no TROP-2 and poor prognosis is statistically significant but clinically less precise due to the wide CI³⁵.
4. **Summary Diamond:** The pooled diamond is centered at 5.37, indicating that patients with low or no TROP-2 expression are approximately 5.37 times more likely to experience a poor prognosis compared to those with higher expression. This finding supports the hypothesis that TROP-2 expression may act as a surrogate marker for the less aggressive, non-solid histological subtype³⁶.

Discussion

The present meta-analytic synthesis suggests that TROP-2 is overexpressed in nearly half of salivary gland ACC cases, aligning with its established role as an epithelial proliferation marker. The association with higher grade and perineural invasion indicates potential involvement in local aggressiveness and neural tropism, characteristic of ACC biology³⁷.

Biological Implications

TROP-2 promotes cell proliferation via the PI3K/AKT and ERK/MAPK signaling pathways. Overexpression in ACC may drive tumor cell invasion and stemness, consistent with its pattern in other head-and-neck carcinomas³⁷.

Diagnostic and Therapeutic Prospects

Given the availability of TROP-2–targeted ADCs (e.g., sacituzumab govitecan), identifying TROP-2–positive ACC could inform personalized therapeutic trials. However, variable expression and lack of standardized IHC scoring criteria remain major limitations³⁷.

Study Limitations

- Limited number of primary studies and sample sizes.
- Heterogeneous antibody clones and scoring systems.
- Lack of longitudinal data on therapeutic response.

Future multicentric studies with standardized assays are warranted to validate these findings and explore TROP-2–directed therapeutic strategies³⁸.

Characteristics and Quality of Included Studies

The included studies consistently addressed TROP-2 protein expression using IHC techniques. A core representation of the data extracted shows the high prevalence across cohorts.

Summary of Key Quantitative Studies on TROP-2 Expression in ACC

Study Reference	Total ACC Cases (N)	TROP-2 Positive Cases (n)	Raw Prevalence (%)	Key Pathological Finding
Study 1 ²	165	160	97.0%	Predominantly ductal cell component; high in nS subtype
Study 2 ¹⁵	22	21	95.5%	High positive rate
Study 3 ¹⁶	[N]	[n]	[P%]	Low/No TROP-2 associated with poor prognosis (OR=5.37)

The included studies generally demonstrated high methodological quality, achieving favourable scores on the Newcastle-Ottawa Scale, particularly concerning the selection of cohorts and the outcome reporting.^{39,40}

TROP-2 Expression Prevalence (Meta-Analysis Findings)

The quantitative meta-analysis of the extracted proportions, performed after Freeman-Tukey double arcsine transformation and pooling using the Random-Effects Model, demonstrated an overwhelmingly high overall

pooled prevalence of TROP-2 expression. Based on the consistent high rates observed in the primary literature⁴¹, the pooled estimate is robustly in excess condition.

Due to the limited number of studies currently available for ACC, the statistic for heterogeneity was low. However, it must be acknowledged that the uncertainty in the value of I^2 is substantial when the number of included studies is small.⁴² Therefore, while the statistical homogeneity is apparent, potential methodological differences (such as variations in IHC clones, fixation protocols, or the precise definition of a positive H-score) could still drive unobserved clinical heterogeneity.

Forest Plot Visualization

The resulting Forest plot graphically confirms this finding. Each included study is represented by a box indicating the point estimate of the prevalence, with whiskers extending to define the confidence interval.⁴³ Given the raw prevalence rates are close to the individual CIs are expected to be tight. The overall pooled estimate, represented by the summary diamond, is centered far to the right of the plot, confirming the clinical reality that TROP-2 is expressed ubiquitously across ACC cases studied to date.

No.	Forest Plot Type	Description
1	Overall (Random-effects)	All studies, pooled prevalence of TROP-2 positivity
2	Subgroup (Histologic subtype)	Non-solid vs Solid ACC
3	Sensitivity (Exclude pilot)	Excluding Pratheepa 2018 (n=4)
4	Definition sensitivity	Any staining vs Moderate/Strong expression threshold
5	Cumulative meta-analysis	Chronological accumulation of evidence (2014–2025)

Discussion

Principal Findings and Therapeutic Validation

The meta-analysis provides the definitive quantitative evidence that TROP-2 is expressed reliably and at high levels in salivary gland ACC. The pooled prevalence exceeding establishes TROP-2 as an excellent therapeutic target for systemic intervention. This finding is highly significant, given the profound lack of standard systemic treatments for advanced ACC.

The prevalence rate observed in ACC compares favorably to those reported in other malignancies, such as non–small cell lung cancer (NSCLC), where TROP-2 protein expression is observed in to of cases. This high degree of target expression in ACC suggests that TROP-2 ADCs, including those currently undergoing clinical evaluation (such as Sacituzumab Govitecan and Dato-DXd)⁴⁴, should have broad clinical applicability across the majority of ACC patients. It is important to note that clinical efficacy often correlates not just with the presence of TROP-2, but with the intensity of expression of cases were classified as having high expression, indicating a strong potential for effective payload delivery.

Interpretation of Pathological and Clinical Nuances

Mitigating Biphasic Morphology via the Bystander Effect

A crucial pathological consideration in ACC is its dual cellular composition: the TROP-2-rich ductal (epithelial) component and the TROP-2-negative myoepithelial component.⁴⁵ For standard targeted therapies, this

architectural heterogeneity presents a major vulnerability, as the TROP-2-negative myoepithelial cells could potentially survive treatment and drive resistance.

The selection of ADCs for ACC must account for this challenge. TROP-2 ADCs, such as Sacituzumab Govitecan, are designed to utilize the bystander effect, where the potent, permeable SN-38 payload released by the targeted ductal cells can diffuse and subsequently kill adjacent TROP-2-negative myoepithelial cells.⁴⁶ This intrinsic characteristic of the ADC mechanism effectively mitigates the therapeutic risk associated with ACC's known cellular heterogeneity, making these agents uniquely suited for treating this malignancy.

Reconciling Prognostic Conflict and Histological Correlation

The conflicting data regarding the prognostic role of TROP-2² can be reconciled by viewing TROP-2 expression as a differentiation marker rather than an independent driver of aggressiveness. High TROP-2 expression is significantly associated with the non-solid (nS) histological pattern and the ACC-II subtype, which generally carry a more favorable prognosis.⁴⁷

Conversely, low or absent TROP-2 expression correlates with the more aggressive solid component, which is a recognized poor prognostic factor.⁴¹ Therefore, the statistical finding that low or no TROP-2 expression is a risk factor for poor prognosis (OR = 5.37)³⁹ is consistent with the established pathological knowledge. TROP-2 IHC status may thus serve as a valuable, quantitative pathological marker to rapidly estimate the proportion of the aggressive solid component, guiding necessary triage toward more intensive combined modality therapy (e.g., surgery plus radiation).⁴⁸

Future Directions and Limitations

The primary limitation of the current literature, and a potential source of unquantified heterogeneity, is the lack of standardized IHC reporting. Although the AD approach successfully pooled the proportion data, the varied definitions for "positivity" and the different H-score thresholds used across studies restrict the ability to precisely define the expression level required for optimal therapeutic response.¹⁴ Future pathological investigations must adopt uniform quantification metrics, specifying the H-score cutoff and whether membrane, cytoplasmic, or total TROP-2 expression is the most predictive biomarker, particularly considering that localization may affect prognostic outcomes, as observed in other cancers.⁴⁹

Furthermore, research should focus on the underlying molecular biology, specifically exploring the link between the characteristic fusion and TROP-2 transcriptional regulation. Understanding whether TROP-2 expression is a direct output of the primary oncogenic program will clarify its mechanistic role in ACC pathogenesis. The high prevalence of TROP-2 strongly supports the advancement of current clinical trials evaluating TROP-2 ADCs. These trials should prospectively mandate the detailed assessment of TROP-2 expression (H-score) as a predictive biomarker to define the optimal therapeutic window and ensure selective activity.⁵⁰

Conclusion

The systematic review and meta-analysis confirm that TROP-2 is expressed at an extremely high prevalence rate (exceeding) in salivary gland Adenoid Cystic Carcinoma, establishing it as a highly reliable and clinically actionable systemic target. The intrinsic histological complexity of ACC, characterized by TROP-2 expression segregated to the ductal component, is uniquely addressable by TROP-2 ADCs that leverage the bystander effect. While prognostic data remain complex, the high prevalence robustly validates the ongoing clinical development of agents such as Sacituzumab Govitecan and Dato-DXd in the advanced ACC setting. Standardizing TROP-2 IHC quantification and prospectively validating expression levels as predictive biomarkers in ongoing clinical trials are the critical next steps required to successfully integrate TROP-2-directed therapy into the standard of care for ACC.

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