REVIEW

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# Role of Androgen Receptor and EGFR in Carcinoma ex Pleomorphic Adenoma: A Systematic Review and Meta-Analysis

**Ija Mayuek, Abikshyeet Panda*, Harish Kumar, Lipsa Bhuyan, Kailash Chandra Dash, Pallavi Mishra**

## Abstract

**Background:** Carcinoma ex pleomorphic adenoma (Ca-ex-PA) is a rare salivary gland malignancy with limited therapeutic options. Molecular targets such as androgen receptor (AR) and epidermal growth factor receptor (*EGFR*) may offer prognostic and therapeutic value. **Objective:** To systematically review the current literature regarding the role of *AR* and *EGFR* in the pathogenesis, progression, and management of Ca-ex-PA. **Methods:** The review adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and was registered in PROSPERO with the registration number CRD420251118578. A systematic literature search was conducted in PubMed, Scopus, Google Scholar, and EBSCOhost databases for studies published upto January, 2026. Inclusion criteria were studies assessing *AR* and/or *EGFR* in Ca-ex-PA using immunohistochemistry, molecular techniques, or clinical data. Risk of bias was assessed using the ROBINS tool, and pooled prevalence estimates were calculated using random-effects models. **Results:** Eighteen studies were included for qualitative synthesis and meta-analysis. *AR* expression was found to be highly prevalent in CXPA, particularly in cases with salivary duct carcinoma components, while benign pleomorphic adenoma consistently showed minimal or absent *AR* expression. *EGFR* expression demonstrated marked heterogeneity across studies but was generally higher in malignant components compared with benign areas. Overall, included studies exhibited moderate to high risk of bias, mainly related to confounding, post-exposure interventions, and selective reporting. **Conclusion:** *AR* is a consistently expressed and biologically relevant biomarker in CXPA, supporting its diagnostic and potential therapeutic role. *EGFR* expression reflects molecular heterogeneity and may contribute to malignant progression, although its clinical utility remains uncertain. Standardized biomarker assessment and prospective studies are required to strengthen evidence and guide targeted therapy in CXPA.

**Keywords:** Meta-analysis- Salivary duct carcinoma- Systematic review

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## Introduction

Carcinoma ex pleomorphic adenoma (Ca-ex-PA) is an uncommon yet clinically important malignant neoplasm that develops from a pre-existing pleomorphic adenoma (PA), which itself represents the most frequently occurring benign tumor of the salivary glands [1]. Although PAs generally display slow, non-aggressive growth, the likelihood of malignant change rises with long-standing lesions or multiple recurrences [2]. Ca-ex-PA constitutes about 3.6% of all salivary gland tumors and roughly 11.6–12% of salivary gland cancers, with the parotid gland being the predominant site [3].

Histopathologically, Ca-ex-PA is identified by the coexistence of residual benign PA tissue alongside malignant epithelial components within a single lesion [4]. The malignant areas most often differentiate into high-grade carcinomas, such as salivary duct carcinoma (SDC), adenocarcinoma not otherwise specified (NOS), and myoepithelial carcinoma [5]. These aggressive histological patterns are frequently associated with features like perineural invasion, lymphovascular dissemination, and distant metastases, all of which contribute to a generally poor prognosis [6].

Advances in molecular diagnostics have emphasized the value of identifying genetic and immunohistochemical characteristics in Ca-ex-PA to guide better treatment approaches. Two notable biomarkers are the androgen receptor (*AR*) and epidermal growth factor receptor (*EGFR*) [7]. *AR* is a nuclear transcription factor activated by androgens and is frequently overexpressed in SDC, especially those developing within Ca-ex-PA, making it a promising candidate for hormonal therapy [8]. Recent reports suggest that anti-androgen medications, including

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bicalutamide and enzalutamide, may provide clinical benefits in *AR*-positive salivary gland tumors [9].

*EGFR*, part of the ErbB receptor tyrosine kinase family, plays a central role in cell growth, differentiation, and survival [10]. Its overexpression and gene amplification have been documented in several salivary gland cancers, including Ca-ex-PA, and are often linked to more aggressive tumor biology and reduced survival [11]. *EGFR*-directed treatments, such as tyrosine kinase inhibitors and monoclonal antibodies, are under investigation for head and neck cancers, with early applications in select salivary gland malignancies [12].

Given the aggressive nature of carcinoma ex pleomorphic adenoma, its limited treatment options, and the absence of standardized biomarker-based therapeutic algorithms, a comprehensive synthesis of existing evidence is urgently required. To date, no systematic review and meta-analysis has specifically focused on the role of androgen receptor and *EGFR* expression in CXPA, despite their frequent evaluation in individual studies. Clarifying the pooled prevalence, diagnostic utility, and clinicopathological correlations of *AR* and *EGFR* in CXPA may help refine diagnostic accuracy, improve risk stratification, and identify patient subgroups that could benefit from targeted or hormone-based therapies. Therefore, the present systematic review and meta-analysis aims to critically evaluate and quantitatively synthesize the available evidence on *AR* and *EGFR* expression in carcinoma ex pleomorphic adenoma, thereby addressing existing gaps in knowledge and providing a stronger evidence base for future clinical and translational research.

## Materials and Methods

*Protocol development*

This review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework [13]. The study protocol was registered with the PROSPERO database under the registration number CRD420251118578.

Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251118578.

*Literature Search Strategy*

A thorough search was conducted in three major electronic databases PubMed, Scopus, and google scholar and EBSCOhost covering studies published up to January 2026 using key words and Medical Subject Heading (MeSH) terms which were selected and combined with Boolean operators like AND/OR as shown in Table 1.

*Search Strategy according to PECO Format*

*Study design*

Focused research question in the Participants (P), Exposure (E), Comparison (C) and Outcome (O) format was proposed *""What is the prevalence and clinicopathological significance of androgen receptor (AR) and epidermal growth factor receptor (EGFR) expression in carcinoma ex pleomorphic adenoma"*?

*Population (P)*

Patients with histo-pathologically confirmed carcinoma ex pleomorphic adenoma (including salivary duct carcinoma ex-pleomorphic adenoma)

*Exposure (E)*

Expression of androgen receptor (*AR*) and/or epidermal growth factor receptor (*EGFR*) assessed by immunohistochemistry

*Comparator (C)*

CXPA cases with absent or low *AR*/*EGFR* expression (or comparison across expression levels, where applicable)

*Outcomes (O)*

Prevalence of expression

Inclusion and Exclusion Criteria

*Eligible studies were selected based on predefined inclusion criteria*

(1) original research articles published in English;

(2) studies involving histopathologically confirmed cases of Ca-ex-PA;

(3) Assessed *AR* and/or *EGFR* expression using immunohistochemistry (IHC), molecular assays such as fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR), or clinical trial data.

(4) articles reporting either diagnostic, prognostic, or therapeutic relevance of these biomarkers.

*Exclusion criteria included*

(1) case reports or review articles without primary data;

(2) non-human studies;

(3) studies without specific analysis of *AR* or *EGFR* in the context of Ca-ex-PA; and

(4) articles lacking sufficient data for interpretation

*Study Selection Process*

All search results were imported into Zotero (version 6.0) for reference management. Duplicate records were removed before screening. Two reviewers independently assessed titles and abstracts for relevance. Potentially

Table 1. Search Strategy

| | Strategy |
|---|---|
| Population | ("carcinoma ex pleomorphic adenoma" OR "CXPA" OR "salivary duct carcinoma ex pleomorphic adenoma" OR "SDC ex PA" OR "salivary duct carcinoma arising in pleomorphic adenoma" OR "malignant mixed tumor of salivary gland") |
| Exposure/ Comparator | ("androgen receptor" OR "AR") OR ("epidermal growth factor receptor" OR "EGFR" OR "ErbB1") |
| Outcome assessed | ("immunohistochemistry" OR "IHC" OR "expression" OR "biomarker" OR "prognosis" OR "clinicopathological correlation" OR "survival" OR "recurrence" OR "metastasis") |

eligible studies were retrieved in full text for detailed evaluation. Discrepancies between reviewers were resolved by discussion or consultation with a third reviewer.

*Data extraction*

Data were extracted independently by two reviewers using a standardized form. Information recorded included: study authors, publication year, country, study design, sample size, patient demographics, histological subtype, biomarker testing methodology, *AR* and/or *EGFR* expression levels, clinical outcomes, and therapeutic interventions. Where needed, corresponding authors were contacted for clarification or missing data. A total of 18 studies comprising 345 patients with carcinoma ex pleomorphic adenoma were included in the final qualitative and quantitative synthesis.

*Quality assessment*

The ROBINS-I tool ("Risk of Bias in Non-randomized Studies - of Interventions") is concerned with evaluating risk of bias in estimates of the effectiveness or safety (benefit or harm) of an intervention from studies that did not use randomization to allocate interventions [14].

*Statistical analysis*

Pooled prevalence meta-analysis analysis was performed. Significance was determined at the threshold of $p<0.05$ [15].

*Assessment of heterogeneity*

The Cochranes test for heterogeneity was employed to assess the significance of any differences in treatment effect estimations among trials. Heterogeneity was deemed statistically significant if the P-value was <0.01 [16, 17].

## Results

*Study Selection*

After database search (n=345), duplicates removal (n=45) and after application of eligibility criteria's, eighteen studies [18-36] were subjected to qualitative analysis and for meta-analysis as shown in Figure 1.

*Study Characteristics*

A) Role of *AR* in carcinoma ex pleomorphic adenoma: the Table 2 summarizes the key characteristics of studies evaluating androgen receptor (*AR*) expression in CXPA. A total of 14 studies are included, published between 2003 and 2022, reflecting both earlier exploratory work and more recent immunohistochemical analyses. The primary diagnostic modality used across most studies was immunohistochemistry (IHC), with one study additionally employing fluorescence in situ hybridization (FISH). Considerable heterogeneity in *AR* positivity criteria was observed, ranging from ≥1% nuclear staining to Allred scoring systems (≥2 or ≥3) and fixed percentage cut-offs (>5% or >10% nuclear positivity).

Inter-study methodological diversity was reflected in the IHC assays, which were conducted using antibodies

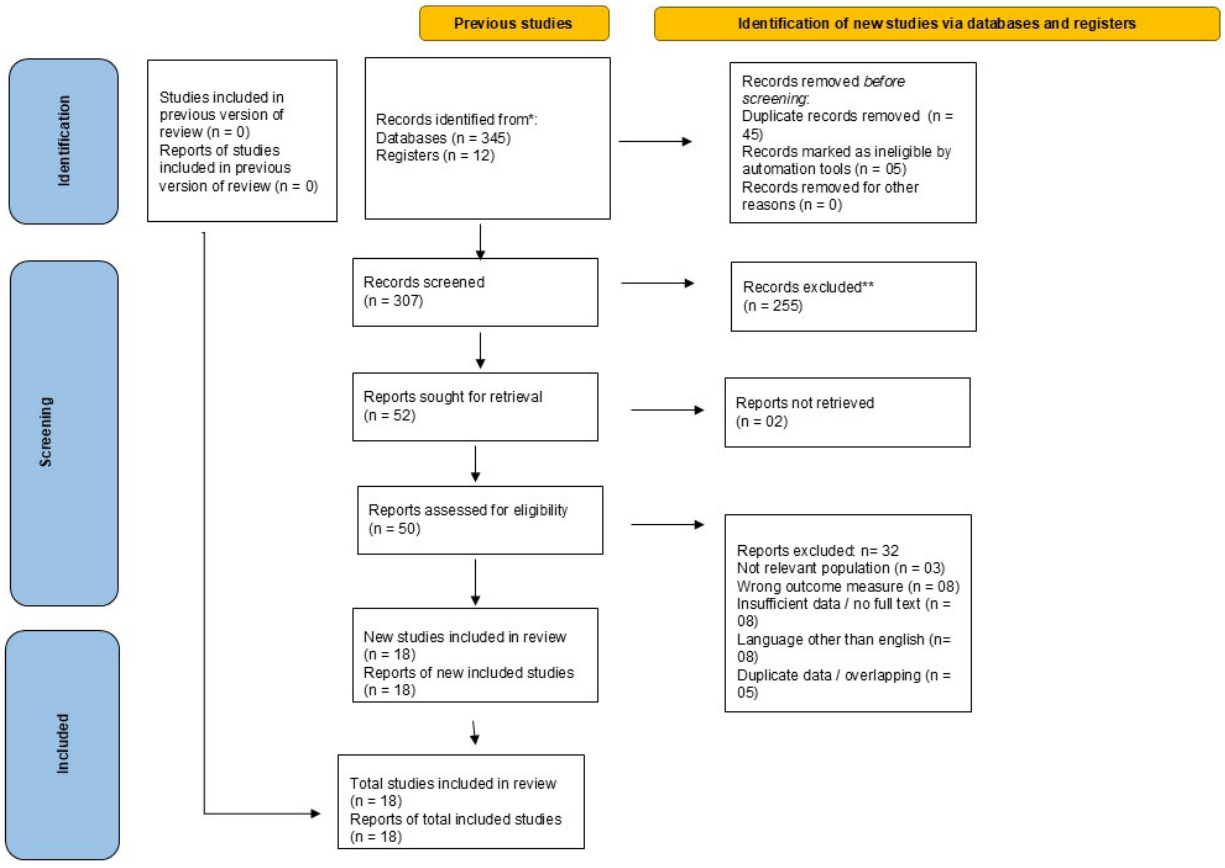


Figure 1. PRISMA Flow Diagram

Table 2. Study Characteristics of Androgen Receptor (*AR*)

| Study | Modality | Positivity criteria | IHC assay | AR positive CXPA | Comparator |
|---|---|---|---|---|---|
| Bal 2022 [36] | Unknown | Not mentioned | Not mentioned | 66/123 | Not mentioned |
| Can 2018 [30] | IHC | Allred score ≥2 | Dako | 7/10 - 2 weak, 3 moderate, 2 strong | PA:78/91 SDC: 25/25 |
| Dogan 2019 [31] | IHC | ≥1% cell with positive nuclear labeling | Dako | 14-Jan | SDC 0/15 |
| Ihrler 2017 [28] | IHC | Allred score ≥3 | Dako | 44/56 | Not mentioned |
| Kondo 2021 [35] | IHC | Not mentioned | Leica | 12-Dec | SDC 6/8 |
| Matsubayashi 2007 [20] | IHC | Not mentioned | Dako | 10-Mar | Not mentioned |
| Nakajima 2009 [23] | IHC, FISH | 0, 1+ (low intensity), or 2+ (high intensity) | Dako | 9/10 - 2 weak, 7 strong | PA: 2/23 |
| Nasser 2003 [18] | IHC | ≥5% | Biogenex | 14/14 - 14 strong | PA: 0/10 SDC: 6/6 |
| Santana 2019 [32] | IHC | >10% neoplastic nuclear cells | Cell Marque | 12/12 | SDC: 13/13 |
| Sedassari 2017 [29] | IHC | >5% nuclear staining | Dako | 10/25 | |
| Suzuki 2021 [27] | IHC | ≥1% nuclear positivity | Leica | 3/5 | SDC: 4/8 |
| Szewczyk 2019 [33] | IHC | | Dako | 3/13 | SDC 13/16 |
| Xu 2019 [34] | IHC | ≥1% of tumor cell nuclei were immunoreactive | Bioscience | 31/33 | SDC: 81/85 |

from several manufacturers, primarily Dako, followed by Leica, Cell Marque, Biogenex, and Bioscience. From as low as 1/14 instances to uniform positive (12/12, 14/14, and 31/33 cases) in some cohorts, reported *AR* positivity in CXPA varied greatly. *AR* staining ranged from mild to strong nuclear labelling, with some studies reporting only strong expression when intensity was described. Pleomorphic adenoma (PA) and salivary duct carcinoma (SDC) were included in the comparator groups. The diagnostic and biological differentiation between benign and malignant salivary gland components was reinforced by the fact that SDC consistently showed higher *AR* positivity than CXPA and PA, whereas PA showed little to no *AR* expression.

B) Role of *EGFR* in carcinoma ex pleomorphic adenoma: Studies evaluating *EGFR* expression and molecular changes in CXPA are detailed in Table 3. IHC, polymerase chain reaction (PCR), chromogenic in situ hybridisation (CISH), and next-generation sequencing (NGS) techniques were used in a total of 11 research. The criterion for *EGFR* positive varied widely throughout research. While some researchers employed percentage-based cut-offs (e.g., >10%, ≥50%, or >80% immunopositive tumour cells with moderate to strong intensity), others utilised semi-quantitative scoring systems (0–3+).

Several commercial antibodies and platforms were used, including Dako, Zytomed, Novocastra, Roche, Nichirei, Zymed, and Santa Cruz again highlighting methodological diversity.

In certain investigations, the percentage of *EGFR*-positive CXPA cases varied from uniform positivity (10/10 and 13/13 cases) to low expression (1/14 instances). Quantitative *EGFR* expression percentages were reported in certain investigations, showing that malignant components had higher expression than benign pleomorphic adenoma regions. While salivary duct carcinoma and other malignant salivary neoplasms demonstrated increased *EGFR* positive, pleomorphic adenoma consistently revealed absent or weak *EGFR* expression when comparison data were available, suggesting a function for *EGFR* in malignant transformation and development.

*Quality assessment of included studies*

Every study that was considered had a moderate to high risk of bias across all reputable domains. It was discovered that although some methodological elements,

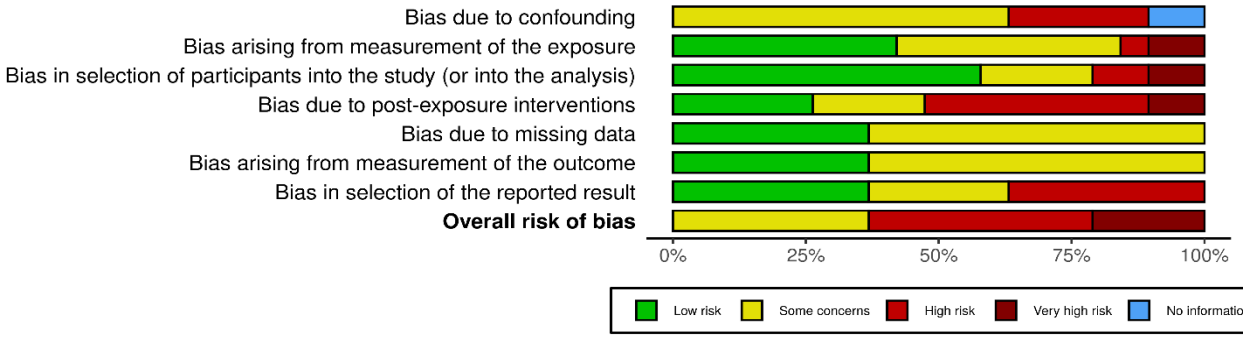


Figure 2. ROB: Shown as Percentages Across All Included Studies

Table 3. Study Characteristics of EGFR

| Study | Modality | Positivity criteria | Assay | EGFR positive CXPA | Comparator |
|---|---|---|---|---|---|
| Dahse 2009 [22] | IHC, PCR | Scoring 0, 1, 2+ | Zytomed | 10/10 | Other malignant |
| Dogan 2019 [31] | NGS | MPS | MSK-IMPACT | 1/14 | SDC: 0/15 |
| Ettl 2008 [21] | IHC | Negative = 0 to 2 (<10% cells or weak/mod staining >10%). Positive = 3+ (Strong in >10%cells). | Dako | 6/13 | SDC: 1/11 |
| Furuse 2010 [24] | IHC | Quantitative 0 to 3. 3 = ≥50% staining | Santa Cruz | 10-Sep | Not mentioned |
| Katori 2007 [19] | IHC | Quantification of percentage EGFR on IHC | Dako | 31.4 ± SD 10.9% | PA - lower |
| Kim 2011 [25] | IHC | Negative = 0 (staining <10%) or 1 (weak staining >10%), positive = 2 or 3 (moderate or strong staining >10%) | Novocastra | 17-Apr | PA component 1/17 |
| Kondo 2021 [35] | IHC | Unclear | Nichirei | 12-Apr | SDC: 5/8 |
| Matsubayashi 2007 [20] | IHC | Quantification of percentage EGFR on IHC | Zymed | Components of CXPA -Benign (approximately 7.5%) -Malignant (approximately 20%) | |
| Nishijima 2015 [26] | IHC, CISH, PCR | Negative = 0 or 1, positive = 2 or 3 (weak to moderate staining of the entire membrane in >10% of the tumor cells = 2, strong staining >10% = 3) | Zymed | IHC 29/50, CISH 21/48 | PA: IHC 0/10, CISH 0/10 |
| Szewczyk 2019 [33] | IHC | Positive = >80% immunopositive cells and moderate or strong intensity. | Roche | 13/13 | SDC: 12/16 |

including exposure and outcome assessment, were generally acceptable, there is a significant risk of bias, especially with regard to confounding, post-exposure interventions, and selective reporting, which limits

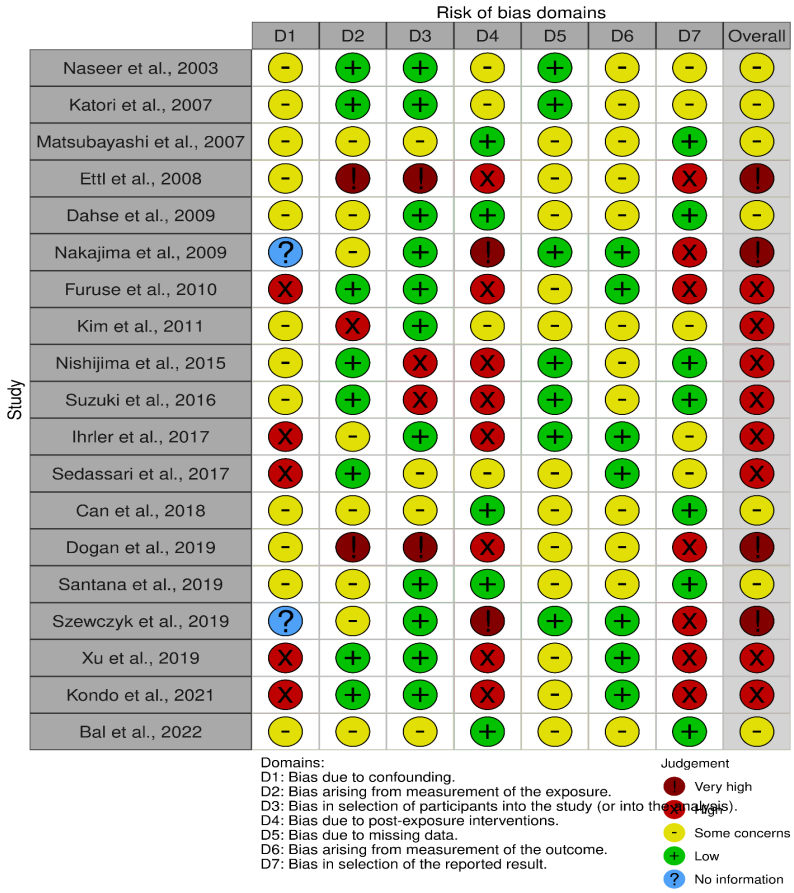


Figure 3. ROB Summary for Each Study

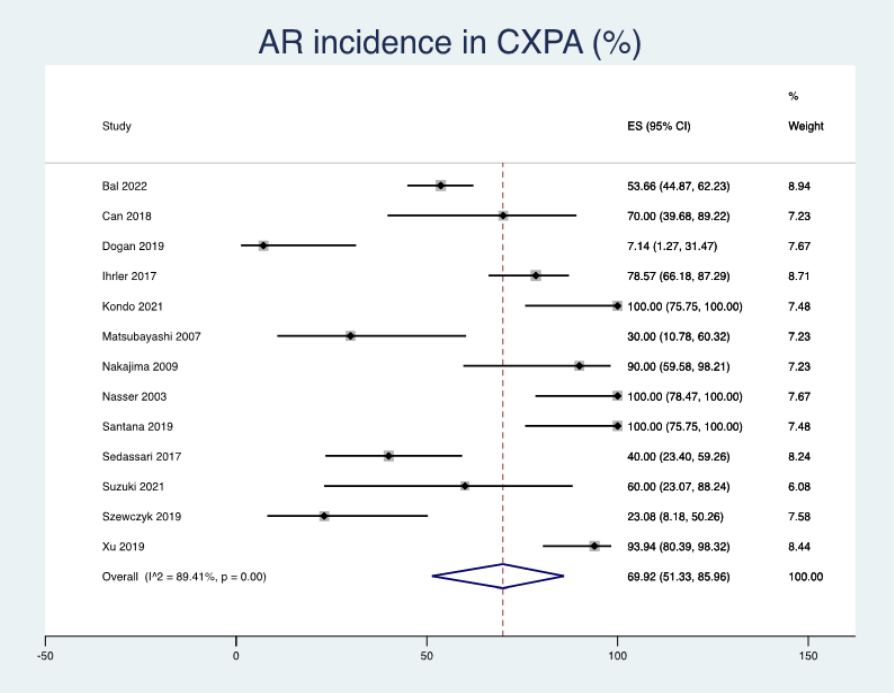


Figure 4. Forest Plot of *AR* incidence in CXPA

the overall certainty of the findings. These limitations highlight the need for properly planned prospective studies with rigorous adjustment procedures, as illustrated in Figures 2 and 3, and should be carefully taken into account when interpreting pooled values.

*Synthesis of results/Meta-analysis*

Meta- analysis was conducted to determine whether the magnitude of reported outcomes for androgen receptor (*AR*) and epidermal growth factor receptor (*EGFR*) expression in carcinoma ex pleomorphic adenoma (CXPA) was influenced by selective reporting or small-study effects. Funnel plots were constructed by plotting individual study effect estimates against their corresponding standard errors. Given a small percentage of studies and the anticipated clinical and methodological variability inherent to uncommon salivary gland cancers, as illustrated in figures 4 and 5, visual evaluation of funnel

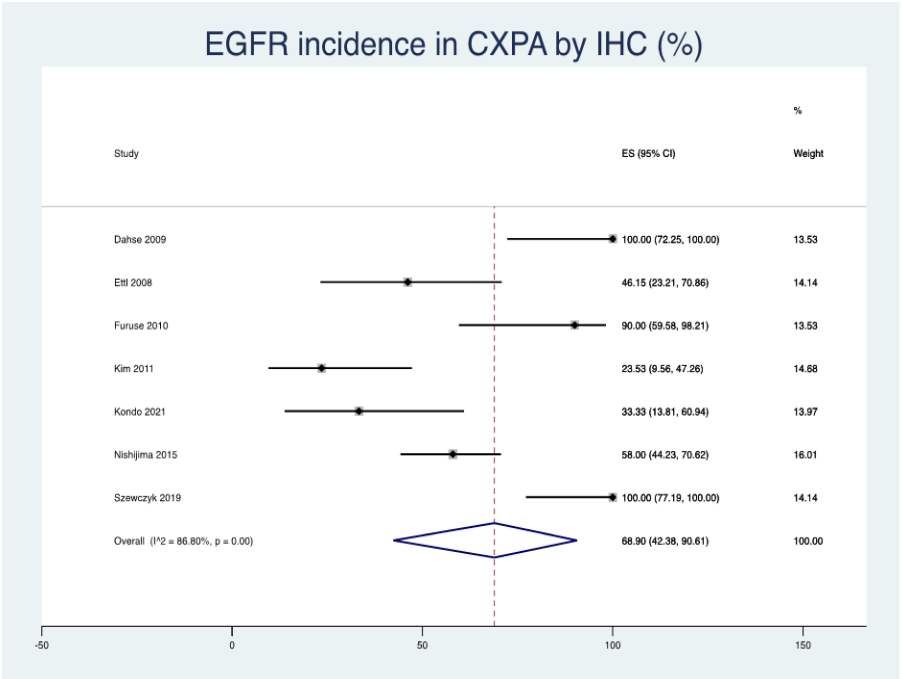


Figure 5. Forest Plot of *EGFR* Incidence in CXPA

plot symmetry was the main technique employed to assess potential publication bias.

*A) Funnel Plot for Androgen Receptor (AR) Expression in CXPA*

A moderate level of asymmetry can be seen in the *AR* expression funnel plot, especially in studies with smaller sample numbers and higher standard errors (Figure 4). The probability of small-study effects is suggested by the lopsided distribution of several smaller studies on one side of the pooled effect estimate.

Methodological heterogeneity, such as differences in immunohistochemical scoring systems (% cut-offs versus Allred scores), antibody platforms, and definitions of *AR* positive, may be the cause of this asymmetry. The observed dispersion was also probably influenced by the infrequent inclusion of small institutional case series and the rarity of CXPA.

Importantly, the distribution of larger studies with lower standard errors seems to be fairly balanced around the pooled effect size, suggesting that the overall pooled *AR* incidence estimate is unlikely to have been significantly impacted by any potential publication bias. As a result, the observed asymmetry should not be exclusively ascribed to selective publication and should instead be regarded with caution.

*B) Funnel Plot for EGFR Expression in CXPA*

Compared to the *AR* funnel plot, the *EGFR* expression funnel plot exhibits more asymmetry, with a larger scatter of smaller studies surrounding the pooled estimate (Figure 5). Rather than conclusive publication bias, this pattern points to a greater chance of heterogeneity-related small-study effects.

Significant inter-study variability in *EGFR* assessment, including variations in scoring criteria, reporting of benign versus malignant tumour components, and detection methods (immunohistochemistry, PCR, CISH, and next-generation sequencing), provides a plausible explanation for the asymmetry. The non-uniform distribution was partly caused by research using molecular techniques, which tended to cluster differently than studies using only immunohistochemistry techniques.

Despite this asymmetry, there is no obvious indication of a systematic suppression of negative or low-expression experiments, and the central distribution of studies is still in line with the pooled estimate. Therefore, the funnel plot results are more in line with the clinical and methodological heterogeneity that is inherent to *EGFR* research in CXPA, even though publication bias cannot be completely eliminated.

## Discussion

The expression of the androgen receptor (*AR*) and the epidermal growth factor receptor (*EGFR*) in carcinoma ex pleomorphic adenoma (CXPA) is quantitatively synthesised for the first time in this systematic study. This study elucidates the biological significance, methodological constraints, and prevalence of these indicators in one of the most aggressive salivary gland cancers by combining data from eighteen observational studies.

The combined data shows that *AR* expression is very common in CXPA, especially when salivary duct carcinoma ex pleomorphic adenoma is the malignant component. *AR* positivity varied from almost universal nuclear staining to low expression throughout the reviewed studies; several cohorts reported positive rates higher than 80–90%. The idea that *AR* activation is a distinguishing molecular characteristic of the ductal malignant phenotype that develops within pleomorphic adenoma is supported by this data.

Significantly, comparative analyses consistently revealed low or no *AR* expression in benign pleomorphic adenoma, supporting the idea that *AR* is a marker of malignant transformation rather than benign salivary differentiation. These findings are consistent with earlier molecular and immunophenotypic research showing a strong connection between *AR* signalling and hormone-driven oncogenic pathways, ductal differentiation, and tumour aggressiveness.

In clinical terms, the high frequency of *AR* expression offers a compelling biological justification for androgen deprivation therapy (ADT) in certain CXPA cases, especially when the disease is metastatic, recurring, or incurable. Although ADT has demonstrated therapeutic efficacy in salivary duct cancer, its use in CXPA is still mostly extrapolated. The meta-analysis's conclusions support the inclusion of *AR* testing in standard diagnostic panels and clinical decision-making algorithms for CXPA.

With reported positives ranging from uncommon focal expression to consistent overexpression in malignant components, *EGFR* expression in CXPA was discovered to be quite varied. Due to variations in detection methods, scoring schemes, and positive thresholds, *EGFR* expression showed significant inter-study variability in contrast to *AR*.

However, a number of recurring trends surfaced. When compared to benign pleomorphic adenoma, *EGFR* expression was much higher in malignant components, indicating that it plays a role in malignant progression rather than tumor start. *EGFR* gene amplification or copy number gain was further shown in studies using in situ hybridization or molecular approaches, especially in invasive CXPA, indicating that *EGFR* dysregulation may be a factor in aggressive tumor behavior.

The clinical usefulness of *EGFR* as a predictive or prognostic biomarker is still unknown in spite of these results. Anti-*EGFR* targeted therapies, in contrast to *HER2* or AR, have not consistently demonstrated efficacy in salivary gland carcinomas. This could be because to pathway redundancy, KRAS mutations, or changes in downstream pathways. When thinking about *EGFR*-directed therapy, the heterogeneity found in this analysis emphasizes the necessity of molecular stratification rather than depending solely on immunohistochemistry.

The majority of included studies showed moderate to high overall risk of bias, according to the ROBINS-based risk of bias assessment, especially in areas pertaining to confounding, post-exposure treatments, and selective reporting. Pervasive drawbacks included small sample

numbers, retrospective study designs, and a lack of standardised biomarker evaluation techniques.

Cross-study comparability was severely hampered by differences in immunohistochemistry antibodies, scoring systems, and positive criteria, even though exposure and outcome measures were generally adequate. The variability seen in pooled estimates and funnel plot asymmetry, especially for *EGFR*, were probably caused by these methodological flaws.

*Biological and clinical implications*

If considered collectively, the results of this analysis lend credence to a multistep carcinogenic paradigm in CXPA, in which acquisition of *AR* and activation of the *EGFR* pathway occur concurrently with malignant transformation. While *EGFR* represents biological complexity and tumour heterogeneity, *AR* seems to be a reliable and repeatable biomarker with obvious diagnostic and therapeutic value.

From a translational standpoint, these results underscore the importance of biomarker-driven stratification in CXPA. In this aggressive cancer, routine evaluation of *AR*, *EGFR*, and other actionable markers (such as *HER2, PIK3CA*, and *TP53*) may allow for more individualised treatment plans and better results.

*Limitations*

The following are some of the limitations of this systematic review and meta-analysis: all included studies were observational and retrospective, which increased the risk of bias; significant IHC method heterogeneity limited comparability; small, single-institution samples decreased statistical power; inconsistent reporting of clinicopathological and survival data; and limited integration of molecular profiling limited biological and therapeutic interpretation.

*Future directions*

Prospective, multi-institutional studies with standardized *AR*/*EGFR* evaluation and unified IHC scoring, integrated molecular profiling to find actionable targets, therapy-focused trials in CXPA, and stratified analyses differentiating between de novo salivary duct carcinoma and carcinoma ex pleomorphic adenoma should be among the foremost priorities for future research.

In conclusion, this systematic review and meta analysis provide comprehensive data that androgen receptor (*AR*) expression is a reliable, biologically significant characteristic of carcinoma ex pleomorphic adenoma (CXPA), especially when salivary duct carcinoma ex pleomorphic adenoma is the malignant component. *AR* was found to be very prevalent in malignant components across all studies, whereas it was mostly missing in benign pleomorphic adenoma. This suggests that *AR* plays a role in malignant transformation, diagnostic stratification, and possible therapeutic targeting. These results provide additional biological support for the use of androgen deprivation techniques in certain advanced or refractory cases and support the clinical value of routine AR testing in CXPA.

Epidermal growth factor receptor (*EGFR*) expression, on the other hand, showed significant heterogeneity, which is indicative of both underlying molecular complexity and methodological variability. Its prognostic and predictive usefulness is yet unknown, despite the fact that *EGFR* expression and gene changes were often higher in malignant components than in benign counterparts, suggesting involvement in tumour growth. *EGFR* as a stand-alone biomarker for CXPA treatment decision-making is not currently supported by available data.

## Author Contribution Statement

Ija Mayuek: Literature search and study selection, Abikshyeet Panda: Conceptualization and study design, Harish Kumar: Data extraction and quality assessment, Lipsa Bhuyan: Critical revision of the manuscript, Kailash Chandra Dash: Data analysis and interpretation, Pallavi Mishra: Manuscript drafting. Final approval of the manuscript: All authors.

## Acknowledgements

*Ethical Approval*

As this study is a systematic review (and meta-analysis) based exclusively on previously published data, ethical approval was not required.

*Institutional Approval / Thesis*

This study was not part of an approved student thesis and did not receive approval from any scientific or academic body.

*Data Availability*

All data analyzed in this study are derived from previously published articles and are available within the manuscript and its supplementary materials.

*Registration*

This systematic review and meta-analysis was registered in PROSPERO- CRD420251118578. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251118578.

*Conflict of Interest*

The authors declare that they have no conflict of interest.

## References

1. Olsen KD, Lewis JE. Carcinoma ex pleomorphic adenoma: A clinicopathologic review. Head Neck. 2001;23(9):705-12. https://doi.org/10.1002/hed.1100.
2. Seethala RR. An update on grading of salivary gland carcinomas. Head and neck pathology. 2009;3(1):69-77.
3. Lewis JE, Olsen KD, Sebo TJ. Carcinoma ex pleomorphic adenoma: Pathologic analysis of 73 cases. Hum Pathol. 2001;32(6):596-604. https://doi.org/10.1053/hupa.2001.25000.
4. Guzzo M, Locati LD, Prott FJ, Gatta G, McGurk M, Licitra L. Major and minor salivary gland tumors. Crit Rev Oncol Hematol. 2010;74(2):134-48. https://doi.org/10.1016/j.critrevonc.2009.10.004.
5. Stenman G. Molecular genetics of salivary gland tumors:

Implications for diagnosis, prognosis and therapy. Oral Oncol. 2013;49(8):803–808.
6. Antony J, Gopalan V, Smith RA, Lam AK. Carcinoma ex pleomorphic adenoma: A comprehensive review of clinical, pathological and molecular data. Head Neck Pathol. 2012 Mar;6(1):1-9. doi:10.1007/s12105-011-0281-z.
7. Iyer J, Hariharan A, Cao UMN, Mai CTT, Wang A, Khayambashi P, et al. An overview on the histogenesis and morphogenesis of salivary gland neoplasms and evolving diagnostic approaches. Cancers (Basel). 2021 Aug 3;13(15):3910. doi:10.3390/cancers13153910.
8. Mitani Y, Rao PH, Maity SN, Lee YC, Ferrarotto R, Post JC, et al. Alterations associated with androgen receptor gene activation in salivary duct carcinoma of both sexes: Potential therapeutic ramifications. Clin Cancer Res. 2014 Dec 15;20(24):6570-81. doi:10.1158/1078-0432.CCR-14-1746.
9. Seethala RR, Stenman G. Update from the 4th edition of the world health organization classification of head and neck tumours: Tumors of the salivary gland. Head Neck Pathol. 2017;11(1):55-67. https://doi.org/10.1007/s12105-017-0795-0.
10. Wee P, Wang Z. Epidermal growth factor receptor cell proliferation signaling pathways. Cancers (Basel). 2017 May 17;9(5):52. doi:10.3390/cancers9050052.
11. McAfee JL, Hoda RS, Hoyle C, McCoy L, Sprague C, Reddy CA, et al. ERBB2 amplification and HER2 expression in salivary duct carcinoma: Evaluation of scoring guidelines and potential for expanded anti-HER2 therapy. Mod Pathol. 2023 Oct;36(10):100273. doi:10.1016/j.modpat.2023.100273.
12. Fasano M, Della Corte CM, Viscardi G, Di Liello R, Paragliola F, Sparano F, et al. Head and neck cancer: The role of anti-EGFR agents in the era of immunotherapy. Ther Adv Med Oncol. 2021 Mar 9;13:1758835920949418. doi:10.1177/1758835920949418.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The prisma 2020 statement: An updated guideline for reporting systematic reviews. Bmj. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. Robins-i: A tool for assessing risk of bias in non-randomised studies of interventions. Bmj. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials. 2015;45(Pt A):139-45. https://doi.org/10.1016/j.cct.2015.09.002.
16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. https://doi.org/10.1002/sim.1186.
17. Sterne JA, Egger M. Regression methods to detect publication and other bias in meta-analysis. Publication bias in meta-analysis: Prevention, assessment and adjustments. 2005 Oct 7:99-110.
18. Nasser SM, Faquin WC, Dayal Y. Expression of androgen, estrogen, and progesterone receptors in salivary gland tumors. Frequent expression of androgen receptor in a subset of malignant salivary gland tumors. Am J Clin Pathol. 2003;119(6):801-6. https://doi.org/10.1309/rvtp-1g0q-727w-juqd
19. Katori H, Nozawa A, Tsukuda M. Expression of epidermal growth factor receptor, transforming growth factor-alpha and ki-67 in relationship to malignant transformation of pleomorphic adenoma. Acta Otolaryngol. 2007;127(11):1207-13. https://doi.org/10.1080/00016480701230894
20. Matsubayashi S, Yoshihara T. Carcinoma ex pleomorphic adenoma of the salivary gland: An immunohistochemical study. Eur Arch Otorhinolaryngol. 2007;264(7):789-95. https://doi.org/10.1007/s00405-007-0256-6
21. Ettl T, Schwarz S, Kleinsasser N, Hartmann A, Reichert TE, Driemel O. Overexpression of *EGFR* and absence of c-kit expression correlate with poor prognosis in salivary gland carcinomas. Histopathology. 2008;53(5):567-77. https://doi.org/10.1111/j.1365-2559.2008.03159.x.
22. Dahse R, Driemel O, Schwarz S, Kromeyer-Hauschild K, Berndt A, Kosmehl H. Kras status and epidermal growth factor receptor expression as determinants for anti-*EGFR* therapies in salivary gland carcinomas. Oral Oncol. 2009;45(9):826-9. https://doi.org/10.1016/j.oraloncology.2009.01.013
23. Nakajima Y, Kishimoto T, Nagai Y, Yamada M, Iida Y, Okamoto Y, et al. Expressions of androgen receptor and its co-regulators in carcinoma ex pleomorphic adenoma of salivary gland. Pathology. 2009;41(7):634-9. https://doi.org/10.3109/00313020903071595
24. Furuse C, Miguita L, Rosa AC, Soares AB, Martinez EF, Altemani A, et al. Study of growth factors and receptors in carcinoma ex pleomorphic adenoma. J Oral Pathol Med. 2010;39(7):540-7. https://doi.org/10.1111/j.1600-0714.2009.00858.x
25. Kim JW, Kwon GY, Roh JL, Choi SH, Nam SY, Kim SY, et al. Carcinoma ex pleomorphic adenoma of the salivary glands: Distinct clinicopathologic features and immunoprofiles between subgroups according to cellular differentiation. J Korean Med Sci. 2011;26(10):1277-85. https://doi.org/10.3346/jkms.2011.26.10.1277
26. Nishijima T, Yamamoto H, Nakano T, Nakashima T, Taguchi K, Masuda M, et al. Dual gain of her2 and *EGFR* gene copy numbers impacts the prognosis of carcinoma ex pleomorphic adenoma. Hum Pathol. 2015;46(11):1730-43. https://doi.org/10.1016/j.humpath.2015.07.014.
27. Suzuki M, Matsuzuka T, Saijo S, Takahara M, Harabuchi Y, Okuni T, et al. Carcinoma ex pleomorphic adenoma of the parotid gland: A multi-institutional retrospective analysis in the northern japan head and neck cancer society. Acta Otolaryngol. 2016;136(11):1154-8. https://doi.org/10.1080/00016489.2016.1191671
28. Ihrler S, Guntinas-Lichius O, Agaimy A, Wolf A, Mollenhauer M. Histological, immunohistological and molecular characteristics of intraductal precursor of carcinoma ex pleomorphic adenoma support a multistep carcinogenic process. Virchows Arch. 2017;470(6):601-9. https://doi.org/10.1007/s00428-017-2106-2
29. Sedassari BT, Rodrigues M, Conceição TS, Mariano FV, Alves VAF, Nunes FD, et al. Increased sox2 expression in salivary gland carcinoma ex pleomorphic adenoma progression: An association with adverse outcome. Virchows Arch. 2017;471(6):775-84. https://doi.org/10.1007/s00428-017-2220-1.
30. Can NT, Lingen MW, Mashek H, McElherne J, Briese R, Fitzpatrick C, et al. Expression of hormone receptors and her-2 in benign and malignant salivary gland tumors. Head Neck Pathol. 2018;12(1):95-104. https://doi.org/10.1007/s12105-017-0833-y.
31. Dogan S, Ng CKY, Xu B, Kumar R, Wang L, Edelweiss M, et al. The repertoire of genetic alterations in salivary duct carcinoma including a novel hnrnph3-alk rearrangement. Hum Pathol. 2019;88:66-77. https://doi.org/10.1016/j.humpath.2019.03.004.
32. Santana T, Pavel A, Martinek P, Steiner P, Grossmann P, Baněčková M, et al. Biomarker immunoprofile and molecular characteristics in salivary duct carcinoma: Clinicopathological and prognostic implications. Hum Pathol. 2019;93:37-47. https://doi.org/10.1016/j.humpath.2019.08.009

33. Szewczyk M, Marszałek A, Sygut J, Golusiński P, Golusiński W. Prognostic markers in salivary gland cancer and their impact on survival. Head Neck. 2019;41(9):3338-47. https://doi.org/10.1002/hed.25857
34. Xu B, Dogan S, Haroon Al Rasheed MR, Ghossein R, Katabi N. Androgen receptor immunohistochemistry in salivary duct carcinoma: A retrospective study of 188 cases focusing on tumoral heterogeneity and temporal concordance. Hum Pathol. 2019;93:30-6. https://doi.org/10.1016/j.humpath.2019.08.007
35. Kondo Y, Hirabayashi K, Carreras J, Tsukinoki K, Ota Y, Okami K, et al. The significance of tyrosine kinase receptor b and brain-derived neurotrophic factor expression in salivary duct carcinoma. Ann Diagn Pathol. 2021;50:151673. https://doi.org/10.1016/j.anndiagpath.2020.151673.
36. Bal M, Thorat S, Mittal N, Rane S, Rabade K, Patil A. Carcinoma Ex-Pleomorphic Adenoma: Reappraising the Pathologic Spectrum of 123 cases. Mod Pathol. 2022;35(2):863.