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Nucleus YAP expression as a prognostic biomarker for local recurrence in eyelid sebaceous carcinoma

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Eyelid sebaceous carcinoma (SbC) is a rare malignancy characterized by potentially aggressive behavior and a high local recurrence rate. This study aims to investigate the expression of nuclear YAP and its clinicopathological correlation in eyelid SbC. In the patients with eyelid SbC who had available tumor specimens, nuclear YAP and androgen receptor (AR) expression were assessed using immunohistochemistry staining, quantified by histochemical scoring (H-score). The primary outcome was local recurrence-free survival (LRFS). Additionally, distant recurrence-free survival, recurrence-free survival, and overall survival were evaluated. Among 47 patients, local recurrence occurred in 10 cases (21.3%), and distant recurrence was observed in 4 cases (8.5%) over a median follow-up period of 39.5 months. All local recurrence events were observed in the low nuclear YAP group (H-score ≤ 90), with a 5-year LRFS of 66.2% among 36 patients. Additionally, lower AR expression (H-score ≤ 50) was linked to a decreased 5-year LRFS of 59.4%, compared to 82.6% in the high AR expression group (Hazard ratio, 3.43; 95% CI, 0.96–12.20; $p = 0.043$). Lower nuclear YAP and AR expression appear to be associated with high local recurrence rates. Nuclear YAP expression may serve as a promising biomarker for prognosticating local recurrence in eyelid SbC.

Keywords Eyelid sebaceous carcinoma, Nuclear YAP, Androgen receptor, Local recurrence, Immunohistochemistry

Sebaceous carcinoma (SbC) is a cutaneous malignancy that arises from any sebaceous gland. Due to the specialized sebaceous glands found in the eyelid, such as the meibomian glands within the eyelid tarsal plate and the Zeiss glands surrounding the lash follicles, the eyelid is the most frequent anatomical site, composing up to 40% of all cutaneous SbC[1,2].

Among malignant eyelid tumors, SbC of the eyelid has a relatively low incidence. However, eyelid SbC exhibits potentially aggressive behavior characterized by vascular and perineural invasion. According to previous literature, the local recurrence rate was 5–25%, and regional lymph node or distant recurrence comprised 7–21%.[3–8] Historically, routine conjunctival map biopsies were essential for controlling local tumor lesions and reducing local recurrence. However, these days, targeted map biopsies are recommended for cases with a high risk of local recurrence[3]. Additionally, approaches to targeted treatment and immunotherapies are being developed based on tumor profiling, such as epidermal growth factor receptor, androgen receptor (AR), retinoic acid receptor-β, PD-1, and mTOR[4–10]. However, no standardized systemic management exists for advanced stages[11]. The pathologic mechanisms of SbC are not fully understood, necessitating further research to identify high-risk patients for recurrence and develop targeted therapies.

Yes-associated protein (YAP) is one of the final effectors of the Hippo pathway. Nuclear-localized YAP acts as a transcriptional coactivator regulating cell growth, cell proliferation, tumorigenesis, and cancer progression[12–15]. Contrary to its familiar role as an oncoprotein, emerging evidence has demonstrated that YAP has a tumor-suppressive function in a context-dependent manner[16]. Specifically, in hormone-associated tumors, such as estrogen receptor-positive breast cancer and AR-positive prostate cancer, YAP disrupted the transcriptional

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program of crucial oncogenic factors[17,18]. As a tumor expressing the AR[19]it is essential to delineate the role of YAP in SbC to enhance our understanding of its pathologic mechanisms and to guide future directions for YAP-based targeted therapies.

In this study, we analyzed nuclear YAP expression using immunohistochemistry (IHC) to determine its prognostic significance, as well as assessed AR expression and its association with clinical features.

Results

Patient characteristics

A total of 47 were included in this study, and demographic details are summarized in Table 1. The median age of the patients was 66 years, ranging from 20 to 89 years, with 68.1% being female and 31.9% male. Of the tissue samples analyzed, 31 (66.0%) were from the upper eyelid, 14 (29.8%) from the lower eyelid, and 2 (4.3%) from the medial canthus. Pathologically, 23 samples (48.9%) were classified as well/moderately differentiated tumors, while 24 samples (51.1%) were poorly differentiated. Intraepithelial spread was observed in 14 samples (29.8%). Local recurrence occurred in 10 cases (21.3%), and distant recurrence was observed in 4 cases (8.5%) with a median follow-up of 39.5 months (interquartile range [IQR], 27.2–92.5) as of January 31, 2024.

Nuclear YAP expression

Figure 1 illustrates YAP expression in eyelid SbC tissues, with a specific focus on nuclear YAP expression. Nuclear YAP expression was observed in all patients. Since there is no established standard cutoff for nuclear YAP expression in patients with eyelid SbC, a maximally selected rank test was performed. As a result, based on an H-score of 90, 11 patients were classified into the high-expression group, while 36 were categorized in the low-expression group. Table 2 shows the clinicopathologic characteristics of these dichotomized groups. The high nuclear YAP group showed a tendency for a higher incidence of microscopic residual tumors at the resection margin ($p = 0.076$). However, Kaplan-Meier analysis revealed that lower nuclear YAP expression was associated with a worse 5-year local recurrence-free survival (LRFS) of 66.2% compared to 100% in the high group ($p = 0.047$, Fig. 2A). All local recurrence events were observed in the lower nuclear YAP group. No significant differences were observed between the groups in terms of distant recurrence-free survival (DRFS), recurrence-free survival (RFS), or overall survival (OS) (Fig. 2B–D).

Androgen receptor expression

Similary, IHC staining was performed for AR (Fig. 3). AR expression was evident in 87.2% (41 out of 47 patients). Using an H-score threshold of 50, determined by a maximally selected rank test, patients were categorized into two groups: 33 patients with high AR expression and 14 patients with low AR expression. The clinicopathological features of these groups revealed a tendency of poor differentiation in the low AR expression group ($p = 0.069$) (Table 3). Survival analysis using the Kaplan-Meier plot demonstrated a significantly worse 5-year LRFS of 59.4% in the low AR expression group compared to 82.6% in the high AR expression group (Hazard ratio (HR), 3.43; 95% CI, 0.96–12.21; $p = 0.043$) (Fig. 4A). No statistical differences were observed in DRFS, RFS, or OS (Fig. 4B–D).

Nuclear YAP and androgen receptor expression

We performed a subgroup analysis based on both nuclear YAP and AR expressions. A statistical difference was observed in LRFS only ($p = 0.043$) (Fig. 5A). The low YAP and low AR group had the worst 5-year LRFS of 49.9%, with an HR of 11.07 compred to the high nuclear YAP groups ($p = 0.02$). There were no significant differences in DRFS, RFS, or OS (Fig. 5B–D).

Discussion

Local recurrence of eyelid SbC often necessitates repeated surgical excisions, leading to significant cosmetic issues and an increased risk of distant recurrence. Understanding which risk groups are more prone to local recurrence remains insufficient. This study demonstrated that low nuclear YAP and AR expressions are associated with worse LRFS. These findings may assist in surgical planning, such as determining the necessity for map biopsies and recommending the optimal follow-up period for each risk group.

In our cohort, at the beginning of the initial local wide excision, only one patient had regional lymph node invasion, and none had distant metastasis. During follow-up, local recurrence occurred in 21.3% of cases, and distant recurrence occurred in 8.5%, consistent with previous reports[20–25]. Due to the limited number of patients with distant recurrence (4, 8.5%) or those who died (7, 14.9%), achieving statistical significance in the survival analysis was restricted. Additionally, the number of patients with LVI or PNI was also low, with four (8.5%) and one (2.1%), respectively. Notably, all of these patients experienced local or distant recurrence, suggesting that the presence of LVI and PNI must be carefully considered.

Among the eyelid carcinomas, SbC has been reported to have higher local recurrence rates after wide surgical excision compared to other types[26,27]. Given the anatomical and functional constraints of the eyelids, achieving negative margins and performing reconstruction can be challenging. Consequently, further resections following local recurrence can pose significant aesthetic concerns. Of the four cases with distant recurrences, excluding the two cases that underwent primary exenteration, the remaining two cases experienced distant metastasis secondary to local recurrence, suggesting that controlling local recurrences is crucial.

Several studies have identified risk factors for local recurrences of eyelid SbC. A higher T stage by AJCC, representing larger tumor size and specific tumor locations, is significantly related to a higher recurrence risk, particularly when the tumor size exceeds 20 mm[22,24,28]. Multicentric origin, diffuse growth pattern, and especially pagetoid spread- a characteristic of SbC spreading through the intraepithelium such as the eyelid epidermis and

	Number of patients	Percentage (%)
Total	47	
Age, median, years (range)	66 (20–89)	
Sex		
Male	15	31.9
Female	32	68.1
Laterality		
Right	24	51.1
Left	23	48.9
Location		
Upper lid	31	66.0
Lower lid	14	29.8
Medial canthus	2	4.3
Primary tumor		
T1	36	76.6
T2	5	10.6
T3	2	4.3
T4	4	8.5
Regional lymph nodes		
N0	46	97.9
N1	1	2.1
Distant metastasis (M)		
M0	47	100
M1	0	0
Differentiation		
Well/Moderate differentiation	23	48.9
Poor differentiation	24	51.1
Perineural invasion		
No	34	72.3
Yes	1	2.1
Not evaluable	12	25.6
Lymphovascular invasion		
No	32	68.1
Yes	4	8.5
Not evaluable	11	23.4
Intraepithelial neoplasia		
No	33	70.2
Yes	14	29.8
Initial treatment		
Local excision with reconstruction	42	89.4
Exenteration	5	10.6
Margin clearance		
Free from tumor	42	89.4
Involved by tumor	5	10.6
Total follow up duration, median, months (range)	39.5 (0.8-134.7)	
Local recurrence during follow up	10	21.3
Distant recurrence during follow up	4	8.5
Outcome		
Alive with disease	8	17.0
Alive without disease	32	68.1
Dead due to disease	1	2.1
Dead due to causes other than disease	6	12.8

Table 1. Clinical characteristics of patients.

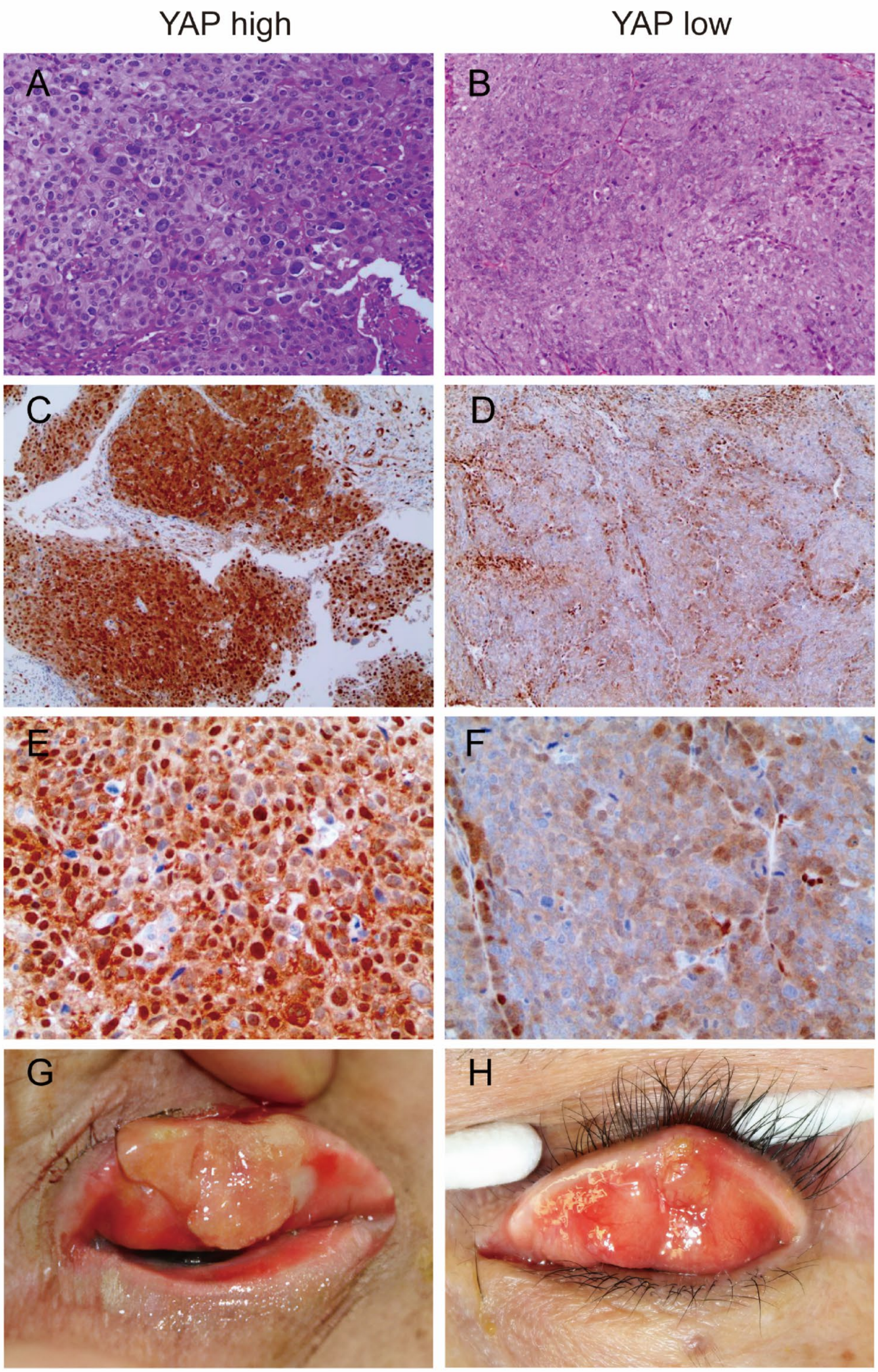

Fig. 1. Representative images of YAP expression in eyelid sebaceous carcinoma, stratified by nuclear YAP level. In the high nuclear YAP expression group, images include (**A**) H&E staining (x 200), YAP immunohistochemical staining (**C**) at low magnification (x 200), and (**E**) at high magnification (x 400). In the low nuclear YAP expression group, images include (**B**) H&E staining (x 200), YAP immunohistochemical staining (**D**) at low magnification (x 200), and (**F**) at high magnification (x 400). Clinical photographs of representative lesions are also shown: (**G**) high nuclear YAP case; (**H**) low nuclear YAP case.

	High nuclear YAP (*N* = 11)	Low nuclear YAP (*N* = 36)	*p*-value
Age, mean ± standard deviation, years	70.5 ± 14.7	62.5 ± 14.6	0.123
Sex			1.000
Male	3	12	
Female	8	24	
Primary tumor (pT)			0.249
T1	7	29	
T2	1	4	
T3	1	1	
T4	2	2	
Differentiation			0.792
Well/Moderate differentiation	5	18	
Poor differentiation	6	18	
Perineural invasion			1.000*
No	8	26	
Yes	0	1	
Not evaluable	3	9	
Lymphovascular invasion			0.255*
No	7	25	
Yes	2	2	
Not evaluable	2	9	
Intraepithelial neoplasia			1.000
No	8	25	
Yes	3	11	
Initial treatment			0.578
Local excision with reconstruction	9	33	
Exenteration	2	3	
Margin clearance			0.076
Free from tumor	8	34	
Involved by tumor	3	2	

Table 2. The relationships between clinicopathological features and YAP expression. *A Fisher's exact test was performed excluding the 'not evaluable' category.

conjunctival epithelium- have also been associated with local, distant recurrence and increased tumor-related mortality (HR = 2.95)[23,28–30]. Additionally, elevated p53 protein expression has been linked to poor prognosis, including higher rates of recurrence[31–33].

Pearson et al.[34] proposed binary pan-cancer classes, YAP-on and YAP-off, based on pro- or anti-cancer YAP/TEAD activity. YAP-on cancers are defined by the activation of proliferative genes mediated by YAP, promoting cell division and tumor growth. Conversely, YAP-off cancers are characterized by the activation of YAP-targeted integrin/ECM/adhesion genes. While YAP-on cancers depend on YAP for proliferation, YAP-off cancers are driven by high MYC activity to sustain cell divisions. Examples of YAP-off solid cancers include neuroendocrine cancers and frequently RB1-/- cancers, such as retinoblastoma, small cell lung cancer, and neuroendocrine prostate cancer. Previously, in ocular adnexal sebaceous carcinoma, RB1 mutation was frequently reported in next-generation sequencing, and MYC proteins were highly expressed[35]. Additionally, MYC overactivation, regulated by the AR/p53 axis, contributes to the oncogenesis of sebaceous gland carcinomas[36].

In YAP-off cancers, YAP drives cytostasis and cell-matrix adhesion, mediated by integrins[34]. Low nuclear YAP expression could lead to decreased integrin expression, thereby reducing cell adhesion and increasing the propensity for cancer cells to disseminate into adjacent tissues. In our study, the R0 resection rate was numerically higher in the low nuclear YAP group (94.4%) compared to the high nuclear YAP group (72.7%). Although this difference is not statistically significant, it shows marginal significance ($p = 0.076$). Despite the marginally higher R0 resection rate, the low nuclear YAP group demonstrated a higher risk of local recurrence. Our findings support the concept that YAP exhibits anti-cancer activity, suggesting that eyelid SbC could be classified as YAP-off solid cancer. However, further analysis of the underlying molecular mechanisms is necessary to explain why lower nuclear YAP expression correlates with worse LRFS. Based on our study results, assessing nuclear YAP expression prior to wide excision could provide valuable information on the need for further map biopsies and may help reduce local recurrences.

SbC is notorious for masquerading clinically and histologically[37]and AR is recognized as a specialized marker for differentiating between various inflammatory lesions or other malignant eyelid tumors, such as basal cell carcinoma and squamous cell carcinoma[19,38,39]. However, the role of AR in prognosis and tumor characteristics remains controversial. A high AR score has been associated with greater local recurrence (Odds ratio, 7.0)

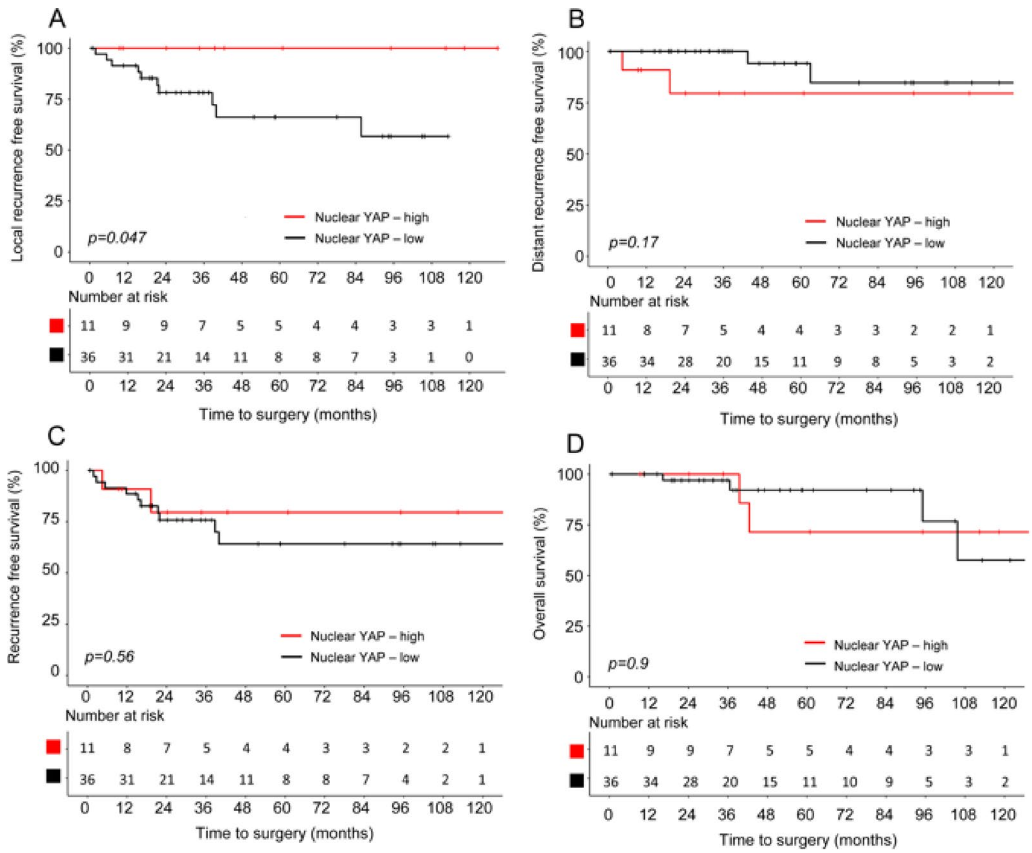

Fig. 2. Kaplan-Meier curves stratified by nuclear YAP expression status comparing (**A**) local recurrence-free survival, (**B**) distant recurrence-free survival, (**C**) relapse-free survival, and (**D**) overall survival.

in periocular SbC[5]. Conversely, marked decreases in AR expression have been linked to poor differentiation and higher T staging, suggesting a poor prognosis[36,40,41]. Additionally, AR negativity has been associated with shorter disease-free survival[42]. Previous studies have highlighted the role of androgens in the development and differentiation of sebaceous glands. AR is involved in sebaceous differentiation, showing peak expression and downregulated activity at the onset and final stages of sebocyte maturation respectively[36]. A decrease in AR expression may indicate a deficiency in tumor differentiation[43]. Our study supports these findings, demonstrating that low AR expression is associated with poor LRFS (HR, 3.43; 95% CI, 0.96–12.20; $p = 0.043$) and shows a non-significant but borderline association with poor differentiation histology ($p = 0.069$).

Additionally, with regard to the tumor-suppressive roles of YAP, previous studies have linked hormone receptors, such as estrogen receptor (ER) and AR, with YAP. In breast and prostate cancers, YAP functions as a TEAD-mediated antagonist in ER- or AR-associated transcription of downstream genes, thereby inhibiting hormone receptor-induced signaling and tumor cell growth[17,18]. We further analyzed the correlation between nuclear YAP and AR expression (Supplementary Figure S1) and found no significant association between them (Spearman's ρ = -0.06, $p = 0.68$). In a subgroup analysis stratified by both nuclear YAP and AR expression, we compared LRFS (Fig. 5A) and found that high YAP expression was associated with no local recurrence, regardless of AR expression. Notably, high YAP expression correlated with a lower rate of local recurrence, particularly when AR expression was low (HR 11.07, $p = 0.02$). Further studies are warranted to validate the relationship between YAP and AR as a prognostic factor in eyelid SbC.

Our study has several limitations. First, its retrospective, single-institution design and relatively small cohort (47 cases, 36 of which were pathologic T1 tumors $\leq$ 10 mm) may limit generalizability and statistical power. Second, YAP expression was assessed solely by IHC; quantitative qPCR validation was precluded by insufficient RNA yield per FFPE block and reduced tumor purity following macrodissection. These limitations will be addressed in future studies in larger, multi-institutional cohorts. Third, no consensus standard exists for evaluating YAP and AR expression, so we derived the cut-off points using a maximally selected rank test; although the resulting nuclear YAP threshold (H-score of 90) aligns with the highest tertile, suggesting it may represent a natural and clinically meaningful point, these criteria will need independent validation in future studies. Finally, further elucidation of the molecular mechanisms in SbC is essential to understand the clinical implications of YAP/TAZ-based tumor treatment and to guide the development of targeted therapies.

Despite these limitations, it is significant that the surgical treatments were performed by a limited number of highly skilled surgeons at a single institution, suggesting that the surgical methods related to local recurrence were relatively well-controlled. Given the high rate of local recurrence of eyelid SbC, this study provides valuable

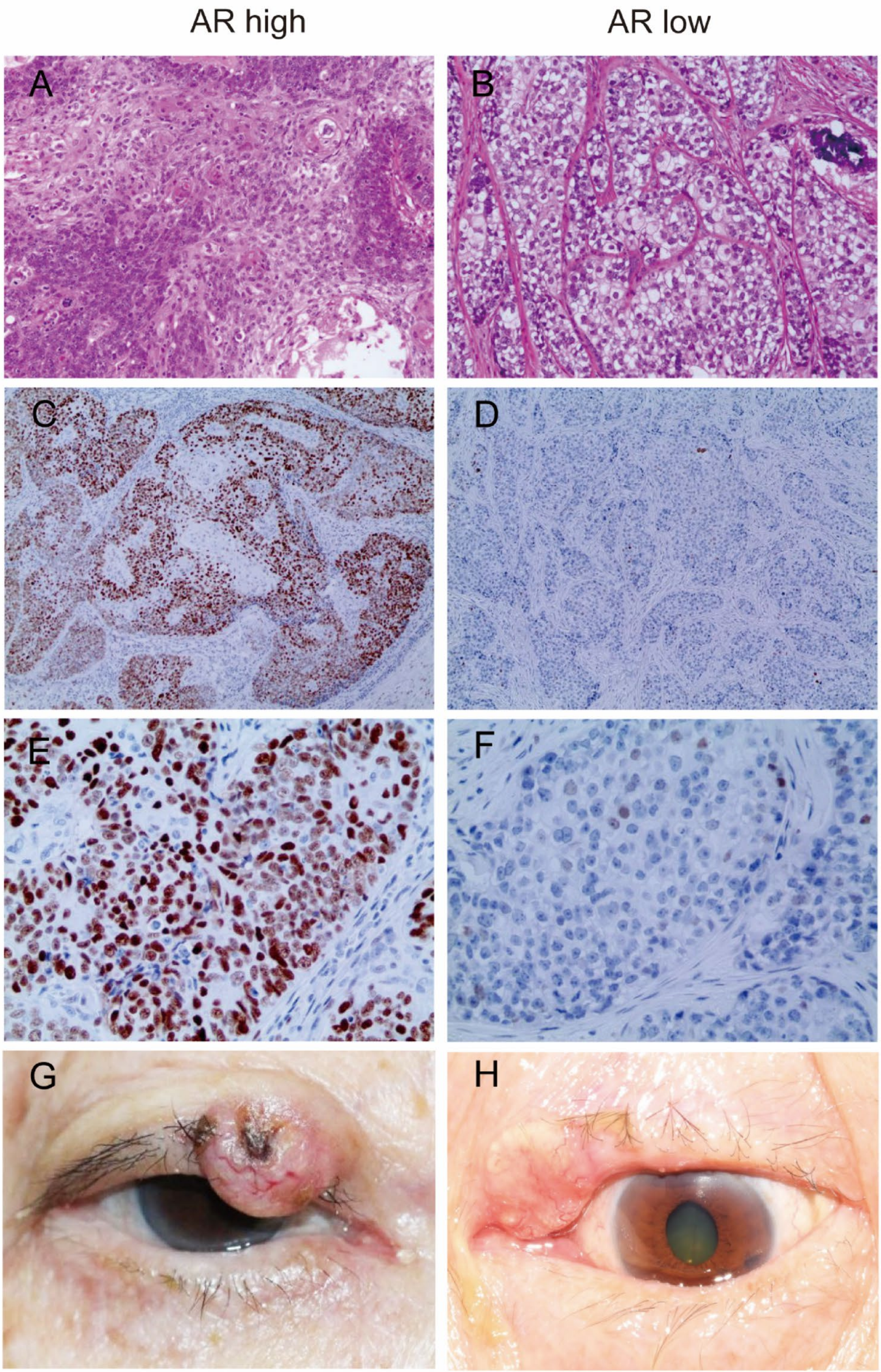

Fig. 3. Representative images of AR expression in eyelid sebaceous carcinoma, stratified by AR level. In the high nuclear AR expression group, images include (**A**) H&E staining (x 200), AR immunohistochemical staining (**C**) at low magnification (x 200), and (**E**) at high magnification (x 400). In the low AR expression group, images include (**B**) H&E staining (x 200), AR immunohistochemical staining (**D**) at low magnification (x 200), and (**F**) at high magnification (x 400). Clinical photographs of representative lesions are also shown: (**G**) high AR case; (**H**) low AR case.

	High AR (*N* = 33)	Low AR (*N* = 14)	*p*-value
Age, mean ± standard deviation, years	62.76 ± 15.39	68.21 ± 13.28	0.230
Sex			1.000
Male	11	4	
Female	22	10	
Primary tumor (pT)			0.584
T1	24	12	
T2	4	1	
T3	1	1	
T4	4	0	
Differentiation			0.069
Well/Moderate differentiation	19	4	
Poor differentiation	14	10	
Perineural invasion			0.257*
No	26	8	
Yes	0	1	
Not evaluable	7	5	
Lymphovascular invasion			0.305*
No	24	8	
Yes	2	2	
Not evaluable	7	4	
Intraepithelial neoplasia			1.000
No	23	10	
Yes	10	4	
Initial treatment			0.303
Local excision with reconstruction	28	14	
Exenteration	5	0	
Margin clearance			0.303
Free from tumor	28	14	
Involved by tumor	5	0	

Table 3. The relationships between clinicopathological features and AR expression. *A Fisher's exact test was performed, excluding the 'not evaluable' category.

insights for surgeons in determining surgical planning, particularly for targeted map biopsies and postoperative follow-up periods. The proposed methods are simple, quick to verify, and can be clinically applied, potentially improving current practice.

In conclusion, lower nuclear YAP and AR expression were associated with a higher risk of local recurrence, suggesting that nuclear YAP could serve as a prognostic biomarker for local recurrence. YAP may exhibit tumor-suppressive activity, and further molecular investigations are necessary to enhance our understanding of the pathogenesis of eyelid SbC and to develop effective risk stratification and treatment strategies.

Methods

Study population and data collection

This study included patients diagnosed with eyelid SbC who underwent surgical resection at the Severance Hospital between 2009 and 2022, as performed by two authors (JSY, JK). Clinical data were extracted from electronic medical records and included patient age, sex, tumor location, local and distant recurrence status and dates, survival status, and the date of last follow-up. Pathological variables, including perineural invasion (PNI), lymphovascular invasion (LVI), margin status, and tumor differentiation, were determined based on the final pathology reports following surgical resection. TNM staging at the time of surgery was conducted according to the AJCC TNM Staging System, 8th Edition[44].

This study was approved by the institutional review board of Severance Hospital, Yonsei University College of Medicine (Seoul, Korea) (IRB number: 4-2022-0112). Written informed consent was obtained from all the subjects. For two patients who had passed away before the study began, with samples collected prior to February 2013, informed consent was obtained from the next of kin. This study adhered to the tenets of the Declaration of Helsinki.

Immunohistochemistry protocols and methods

Tumor specimens were preserved in paraformaldehyde and embedded in paraffin. Formalin-fixed, paraffin-embedded tissues were sectioned into 4 μm-thick slices using a microtome and mounted on adhesive slides.

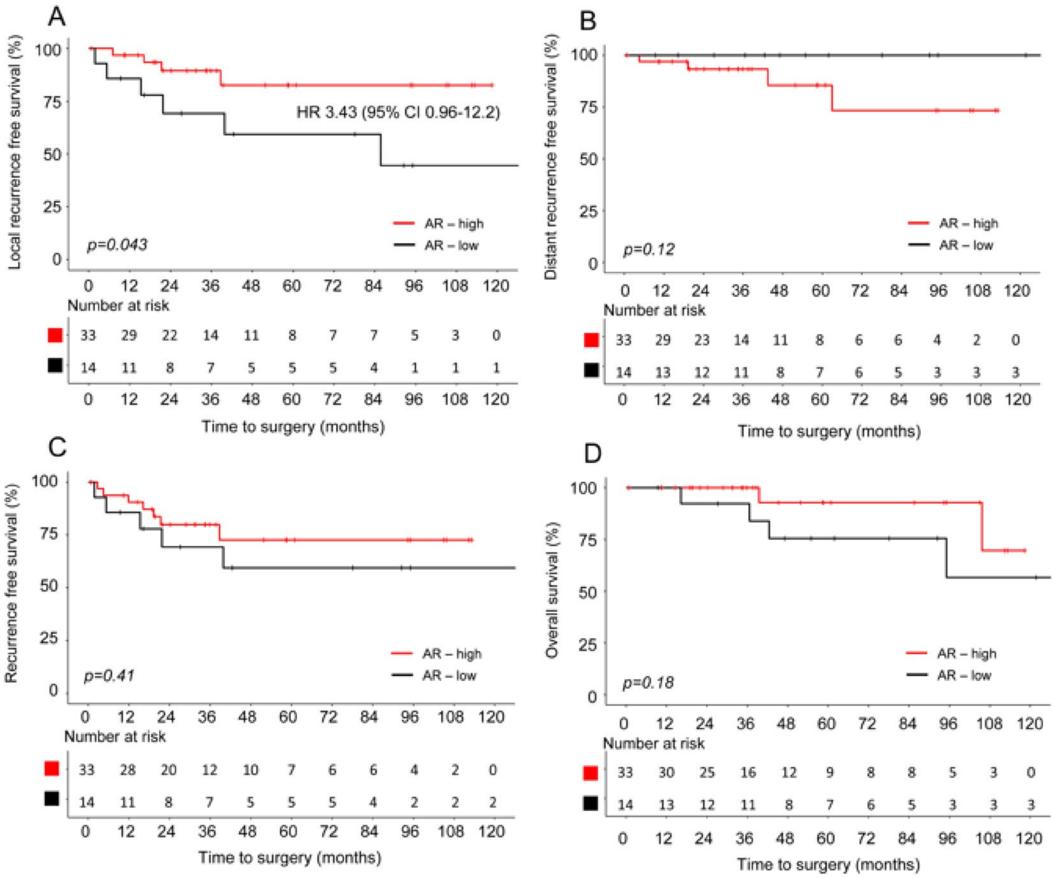

Fig. 4. Kaplan-Meier curves stratified by AR expression status comparing (**A**) local recurrence-free survival, (**B**) distant recurrence-free survival, (**C**) relapse-free survival, and (**D**) overall survival.

The slides were stained with hematoxylin and eosin (H&E) and processed for IHC using an Autostainer Link48 (Dako, Glostrup, Denmark). All slides were deparaffinized in xylene, followed by antigen retrieval using a PT LINK (Dako) in FLEX Target Retrieval Solution High-pH (Dako k8004) buffer. Primary antibodies, including anti-YAP (#14074, 1:50 dilution, Cell Signaling Technology, Danvers, MA, USA) and anti-AR (#760–4605, Ventana Medical Systems, Inc. Tucson, AZ, USA), were incubated for 60 min at room temperature. Following a 20-minute incubation with polymer, diaminobenzidine was applied as the chromogen for 5 min, with subsequent counterstaining using hematoxylin for 10 min.

Nuclear YAP and AR expression levels were evaluated under light microscopy. IHC staining was assessed using the Histoscore (H-score) system, which considers both the intensity of staining (rated on a scale from 0: nil, 1: weak, 2: moderate, to 3: strong, Supplementary Figure S2) and the percentage of labeled cells (ranging from 0 to 100%). The final score was calculated by multiplying the intensity by the percentage of labeled cells, producing a score ranging from 0 to 300.

Statistical analysis

Patient demographics, clinical characteristics, and outcomes were summarized using descriptive statistics. Clinicopathological features between the two groups were compared using the Chi-square test or Fisher's exact test. The Kaplan-Meier method was used to estimate time-to-event distributions, with survival differences assessed using the log-rank test. The HR was calculated using Cox proportional hazards regression analysis. When the sample size or event counts were limited, Firth's penalized Cox regression test was used instead.

LRFS, DRFS, and RFS were defined according to RECIST 1.1 criteria. LRFS was the interval from surgical resection to local recurrence, DRFS to distant recurrence, and RFS to any recurrence. OS was defined as the time from randomization to death from any cause.

Given the absence of a validated standard cutoff for nuclear YAP and AR expression in patients with eyelid SbC, we employed maximally selected rank test using the MaxStat package in R (version 3.1.1) to determine appropriate thresholds[45–47]. Nuclear YAP expression levels were categorized as high (H-score ≥ 90) or low (H score < 90), while AR expression levels were categorized as high (H-score ≥ 50) or low (H score < 50).

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY) and R version 4.2.2 (The R Foundation, Vienna, Austria).

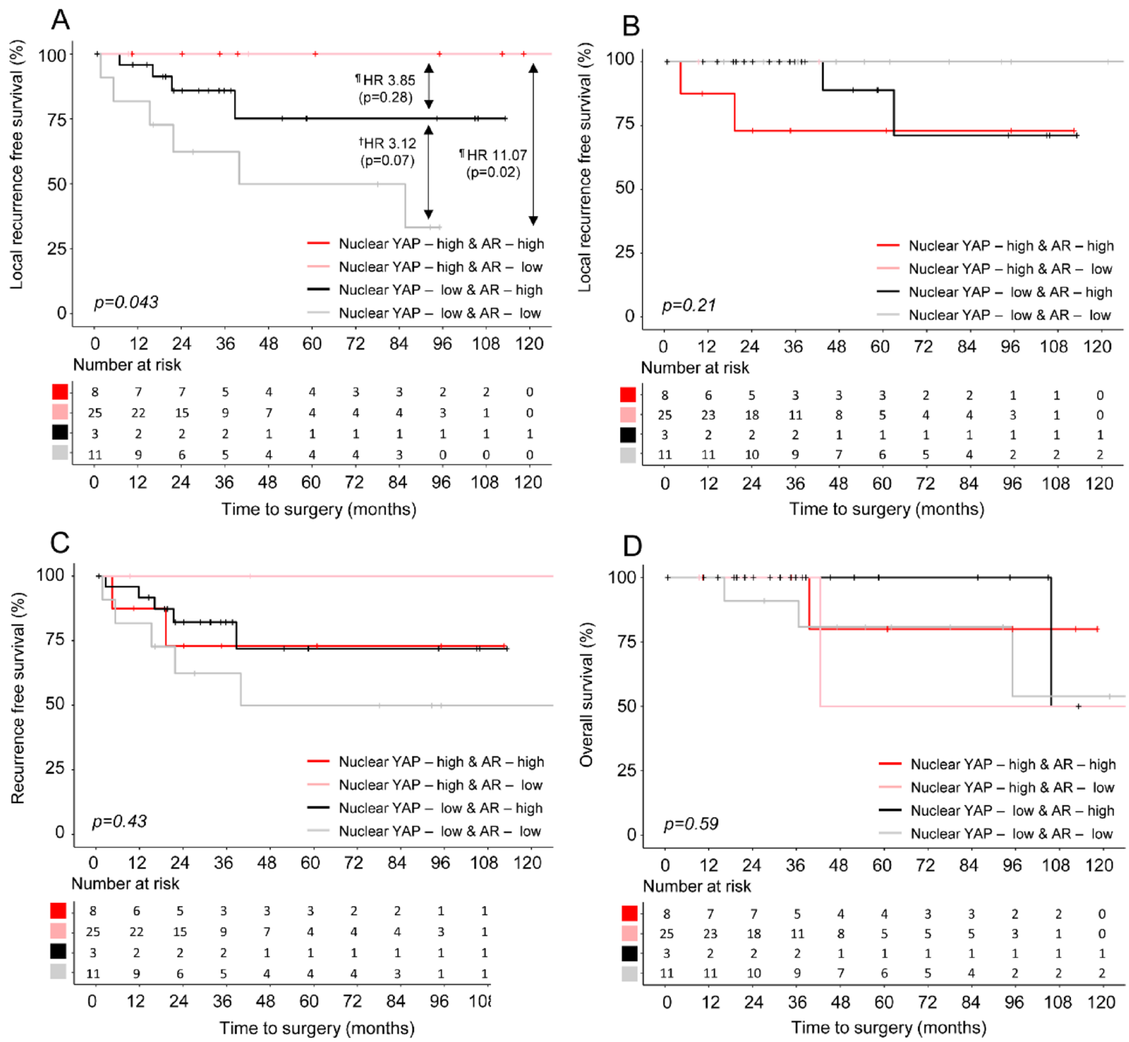

Fig. 5. Kaplan-Meier curves stratified by both nuclear YAP and AR expression status comparing (**A**) local recurrence-free survival, (**B**) distant recurrence-free survival, (**C**) relapse-free survival, and (**D**) overall survival. †Hazard ratio (HR) was calculated between the AR low and AR high expression subgroups within the low nuclear YAP expression group. ¶HR was calculated using Firth's Penalized Cox Regression to reduce bias and provide stable estimates with limited sample size or event counts.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Data is provided within the manuscript or supplementary files.

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Declarations

Competing interests

The authors declare no competing interests.

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