The Prognostic Value of Preoperative Albumin-to-Alkaline Phosphatase Ratio on Survival Outcome for Patients With Locally Advanced Oral Squamous Cell Carcinoma

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Abstract

Background: This retrospective cohort study was to assess the prognostic value of preoperative albumin-to-alkaline phosphatase ratio (AAPR) on survival outcome for patients with locally advanced oral squamous cell carcinoma (LAOSCC). Methods: A total of 250 patients with LAOSCC receiving upfront radical surgery at a single institute from January 2008 to December 2017 were enrolled. The primary endpoint was the survival predictability of preoperative AAPR on the 5-year overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS). Cox proportional hazards model was used for survival analysis. The X-tile software was used to estimate the optimal cut-off value of preoperative AAPR on survival prediction. A predictive nomogram incorporating the clinicopathological factors on OS was further generated. Results: The 5-year OS, CSS, and DFS rates were 68.6%, 79.7%, and 61.7%, respectively. The optimal cut-off of preoperative AAPR to predict the 5-year OS was observed to be 0.51. For those with preoperative AAPR ≥ 0.51, the 5-year OS, CSS, and DFS were statistically significantly superior to those with preoperative AAPR < 0.51 (OS: 76.1% vs 48.5%, P < .001; CSS: 84.3% vs 66.4%, P = .005; DFS: 68.9% vs 42.6%, P < .001). In Cox model, we observed that preoperative AAPR < 0.51 was a significantly negative prognosticator of OS (HR: 2.22, 95% CI: 1.466-3.361, P < .001), CSS (HR: 2.037, 95% CI: 1.16-3.578, P = .013), and DFS (HR: 1.756, 95% CI: 1.075-2.868, P = .025). After adding the variable of preoperative AAPR, the c-index of the predictive nomogram incorporating assorted clinicopathological factors increases from 0.663 to 0.692 for OS. Conclusion: Our results suggest that preoperative AAPR serves as an independent survival predictor for patients with LAOSCC. The nomogram incorporating preoperative AAPR and various clinicopathological features may be a convenient tool to estimate the mortality risk for patients with LAOSCC.

Keywords

serum albumin, alkaline phosphatase, mouth neoplasms, nomograms, prognosis

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**Abbreviations**

AAPR, albumin-to-alkaline phosphatase ratio; ALP, alkaline phosphatase; AJCC, American Joint Committee on Cancer; C-index, concordance index; CSS, cancer-specific survival; DFS, disease-free survival; ENE, extranodal extension; HR, hazards ratio; LAOSCC, locally advanced oral squamous cell carcinoma; LVI, lymphovascular invasion; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; OS, overall survival; PNI, perineural invasion; PFS, progression-free survival; SCLC, small cell lung cancer.

**Introduction**

Oral squamous cell carcinoma (OSCC) is an aggressive head and neck malignancy and has been one of the most common cancer in Taiwanese males. The TNM classification is an effective tool in the prediction of the survival outcome for patients with OSCC post ablative and reconstructive surgery. However, a variety of treatment results have been reported for OSCC, even in patients with the same TNM stage. The nutritional status of patients with OSCC has been regarded as a significant element to affect the disease pattern and treatment outcome and patients with locally advanced OSCC (LAOSCC) are more vulnerable to malnutrition at diagnosis and during the course of treatment. Serum albumin concentration has been regarded to be an indicator of nutrition status and observed to be related to body mass, and systemic inflammatory response for patients with advanced cancer stages. The association between serum albumin concentrations and prognosis in patients with cancer has been well recognized. For head and neck cancers, serum albumin and its associated biomarkers, such as prognostic nutrition index, and albumin-to-globulin ratio, have also been observed as predictors of survival and perioperative outcomes.

Alkaline phosphatase (ALP) is enriched in the kidney, bile duct, and liver and the elevation of ALP was also reported to be found in diverse malignancies and correlated to poor outcomes. Albumin-to-alkaline phosphatase ratio (AAPR) was firstly investigated to be a novel prognosticator in hepatocellular carcinoma in 2015 and a series of studies have shown the clinical significance of prognosis in several malignancies. Currently, data are still limited regarding the impact of pretreatment AAPR on survival outcomes for patients with LAOSCC. Therefore, this study aimed to evaluate the potential prognostic impact of preoperative AAPR in patients with LAOSCC receiving upfront curative surgery. Furthermore, we attempted to generate a predictive nomogram to validate the survival predictability of pretreatment AAPR in our cohort.

**Material and Method**

**Study Design**

This is a retrospective cohort study, which consecutively enrolled 250 patients with LAOSCC receiving upfront radical surgery at a single institute from January 2008 to January 2017. The definition of LAOSCC was pathological stage III to IVb according to the 8th edition of American Joint Committee on Cancer (AJCC) staging system. Those with the following criteria were excluded: (a) with previous cancer history, or simultaneously second primary cancer, (b) with distant metastasis at diagnosis, (c) receiving induction chemotherapy and/or radiotherapy before surgery, (d) with the history of acute infection within 4 weeks before the blood tests of pretreatment serum albumin and ALP was performed, and (e) no pretreatment serum albumin and ALP value were available. The detailed clinical and pathologic information were collected. The clinical stage was reclassified according to the 8th edition of AJCC staging system. The indication of adjuvant therapy was mostly based on the guidelines established in the institute or suggested from the National Comprehensive Cancer Network. We have de-identified all patient details. The reporting of this study conforms to STROBE guidelines.

**Assessment of AAPR**

Patients’ peripheral blood samples were extracted for laboratory examination within 1 week before surgery. Normal serum albumin levels were determined to be 35 to 50 g/L, and normal serum ALP levels were determined to be 28 to 94 IU/L for adults aged 19 to 65 and 40 to 140 IU/L for adults aged >65, respectively, in our hospital. Preoperative AAPR was defined as the serum albumin value divided by serum ALP value. The X-tile software (version 3.6.1; Yale University, New Haven, CTA) was used to identify the optimal cut-off value of AAPR on survival predictability, and by which patients were separated into low- and high-AAPR groups.

**Variables and Endpoints**

The collected clinical and pathological variables included gender, age, habitual use of alcohol, betel nut or cigarette, primary cancer location, cancer stage, perineural invasion (PNI), lymphovascular invasion (LVI), surgical margin, extranodal extension (ENE), and preoperative AAPR. The preoperative AAPR was defined as the serum albumin value divided by serum ALP value, measured within 1 week before surgery. The primary endpoints were the 5-year overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS).

**Statistical Analysis**

Continuous data were presented as mean (standard deviation) or median (range). Categorical variables were expressed as number (frequency) and were compared using Chi-square or Fisher’s exact tests, as appropriate. Survival time was calculated...
from the date of surgery to the date of death or the last follow-up. The Kaplan-Meier method was utilized to estimate the probability of survival, and the log-rank test was used to examine the statistical significance between groups. A Cox proportional hazards model was performed to determine the independent risk factors related to OS, CSS, or DFS, respectively. Variables with a $P$ value < .05 were entered into the multivariate analysis, and the hazard ratios (HRs) and 95% confidence intervals (CIs) for each variable were computed. A 2-tailed test, with $P$ value < .05 was considered statistically significant. Statistical processing was performed by using SPSS 25.0 software (SPSS/IBM, Inc., Chicago, IL, USA).

In addition, we created a prognostic nomogram incorporating independent survival predictors using the R software “rms” package (version 5.1-0, Vanderbilt University, Nashville, TN, USA) with the endpoint of 5-year OS. To validate the nomograms, we calculated the concordance index (c-index) for the conventional TNM staging, as well as for the proposed nomogram models with and without including preoperative AAPR, to assess the accuracy of the nomogram in predicting OS, where values of 0.5 and 1.0 signify random and perfect predictability, respectively. Moreover, a calibration plot was used to determine whether the predicted survival was consistent with the actual observed survival and internal validation was done with bootstrap analysis.

**Results**

**Patient Characteristics**

A total of 250 patients were enrolled in this study. The clinical characteristics of the study patients are summarized in Table 1. The median age of patients was 54 years (range 30-95). There were 228 (91.2%) male and 22 (8.8%) female patients. The majority of patients had the habitual history of smoking (85.6%), alcohol drinking (75.6%), or betel nut chewing (85.6%). The most subsite of LAOSCC was tongue (N = 89, 35.6%), followed by buccal mucosa (N = 75, 30%), lower gum (N = 31, 12.4%), lower lip (N = 17, 6.8%), retromolar trigone (N = 16, 6.4%), mouth floor (N = 9, 3.6%), upper gum (N = 7, 2.8%), hard palate (N = 5, 2%), and upper lip (N = 1, 0.4%).

The pathological stages III, IVA, and IVB were 66 (26.4%), 119 (47.6), and 65 (26.0%), respectively. Adjuvant therapy was given in 186 (74.4%) with RT alone (23.2%) or CCRT (51.2%). The median follow-up month was 64.8 (range 1.7-141.7). The mean (SD) and median (range) of preoperative AAPR were 0.62 (standard deviation: 0.19) and 0.59 (range: 0.26–1.47).

**AAPR and survival Outcome**

During the follow-up period, treatment failure was observed in 70 (28%) patients. The patterns of treatment failure included local alone (n = 23), regional alone (n = 17), distant alone (n = 20), locoregional (n = 5), local with distant (n = 3), and regional with distant (n = 2). The median time of regional and distant failure was 5.1 months (range: 1.3-34 months) and 4.7 months (range: 2.4-31.6 months), respectively. A total of 51 patients died of the disease, and no patient died of treatment-related complications during the follow-up period. The 5-year OS, CSS, and DFS rates in this cohort were 68.6%, 79.7%, and 61.7%, respectively. A statistically significant trend was observed that those with a higher value of preoperative AAPR had a better outcome in 5-year OS (HR: 0.055, 95% CI: 0.008-0.0384, $P$ = .011), CSS (HR: 0.050, 95% CI: 0.012-0.22, $P$ < .001), and DFS (HR: 0.136, 95% CI: 0.029-0.631, $P$ = .011). As shown in Figure 1, after putting the data of preoperative AAPR and OS into X-tile software, the cut-off point of AAPR was observed to be 0.51. Those with AAPR<0.51 was grouped as low AAPR and AAPR≧ 0.51 as high AAPR group, respectively. Compared with the low AAPR group, the high AAPR group had a statistically significant better outcome in 5-year OS (76.1% vs 48.5%, $P$ = .001, Figure 2A), CSS (84.3% vs 66.4%, $P$ = .005, Figure 2B), and DFS (68.9% vs 42.6%, $P$ < .001, Figure 2C), respectively. We did not observe statistically significant correlations between the clinicopathologic variables with different AAPR groups (Table 2).

Table 3 lists the univariate survival analysis. We observed the variables of stage IV, positive nodal metastasis, presence of LVI, presence of ENE, and low AAPR were unfavorable predictors of OS, CSS, and DFS; and age≧65 was an unfavorable predictor of OS and DFS ($P$ < .05).

In Cox proportional hazards models (Table 4), the independently unfavorable predictors were observed to be age≧65, ...

| Table 1. Patient Characteristics. |
|-----------------------------------|
| Characteristics                   | Value % |
| Median age (range), year          | 54 [30, 95] |
| Median follow-up months (range)   | 64.8 [1.7, 141.7] |
| Sex                               |         |
| Male                              | 228 91.2 |
| Female                            | 22 8.8  |
| Personal habits                   |         |
| Cigarette smoking                 | 214 85.6 |
| Betel nut chewing                 | 214 85.6 |
| Alcohol consumption               | 189 75.6 |
| Tumor location                    |         |
| Tongue                            | 89 35.6 |
| Buccal mucosa                     | 75 30.0 |
| Low gum                           | 31 12.4 |
| Low lip                           | 17 6.8  |
| Others                            | 38 15.2 |
| Pathological stage                |         |
| III                               | 66 26.4 |
| IVA                               | 119 47.6 |
| IVB                               | 65 26   |
| T classification                  |         |
| pT1-2                             | 45 18   |
| pT3-T4                            | 205 82  |
| N classification                  |         |
| pN0                               | 119 47.6 |
| pN+                               | 131 52.4 |
| Preoperative AAPR                 |         |
| Low (<0.51)                       | 68 27.2 |
| High (≧0.51)                      | 182 72.8 |
| Treatment                         |         |
| Surgery only                      | 64 25.6 |
| Surgery + radiotherapy            | 58 23.2 |
| Surgery + chemoradiotherapy       | 128 51.2 |
| Recurrence                        |         |
| No                                | 180 72.0 |
| Yes                               | 70 28.0 |

Abbreviation: AAPR, albumin-to-alkaline phosphatase ratio.
stage IV, and low AAPR for OS; presence of ENE, presence of LVI, and low AAPR for CSS; presence of ENE, presence of LVI, low AAPR for DFS. In the models, those patients with high AAPR were observed to have a higher probability of 2.22 times (95% CI: 1.466-3.361, \( p < .001 \)) in OS, compared to those with high AAPR, 2.037 times (95% CI: 1.16-3.578, \( p = .013 \)) in CSS, and 1.756 times (95% CI: 1.075-2.868, \( p = .025 \)) in DFS, respectively.

### Predictive Nomogram of Survival

For further validation of the survival predictability of preoperative AAPR, we established a multivariate nomogram incorporating the variables of age, pathological stage, LVI, and preoperative AAPR for the prediction of the 5-year OS (Figure 3A). The nomogram based only on AJCC stage had a c-index of 0.639 (95% CI: 0.587-0.691). If the model incorporated the assorted clinicopathological factors without preoperative AAPR, the c-index was 0.663 (95% CI: 0.611-0.716), which would increase to 0.692 (95% CI: 0.640-0.743) if the preoperative AAPR was included. The calibration curves showed that the 5-year OS predicted by the nomogram were consistent with actual observations (Figure 3B). Based on the predictive nomogram, for a 60-year-old (score: 46.52) patient with LAOSCC post radical surgery, with stage IVA (score: 53.45) and preoperative AAPR \( \geq 0.51 \) (score: 57.12), the predicted 5-year OS rate would be 77.9%. On the contrast, if the patient had preoperative AAPR < 0.51 (score: 0), the predicted 5-year OS rate would drop to 57.4%.
small cell lung cancer (SCLC),\textsuperscript{15,28} non-small cell lung cancer (NSCLC),\textsuperscript{29} renal cell carcinoma,\textsuperscript{17} and so on. For head and neck cancer, Kim et al demonstrated that patients with locally advanced nasopharyngeal carcinoma (NPC) had better OS and progression-free survival (PFS) if pretreatment AAPR was more than 0.4876.\textsuperscript{30} Nile et al analyzed 209 patients with metastatic NPC and also revealed a pretreatment AAPR $\geq 0.447$ was significantly associated with better OS and PFS than those with an AAPR $< 0.447$.\textsuperscript{31} Another study also echoed that higher preoperative AAPR was one of the favorable predictors of DFS and OS in patients with locally advanced laryngeal and hypopharyngeal cancer.\textsuperscript{10} Our study further strengthens the survival predictability of preoperative AAPR in the clinical practice for patients with LAOSCC.

The cut-off point of AAPR as a survival predictor may differ among different cancer types and study cohorts. For example, Li et al used a cut-off point of 0.61 to analyze the prognostic significance of AAPR in limited-stage SCLC patients treated chemotherapy and radiotherapy.\textsuperscript{28} Another study for patients with advanced NSCLC observed that an AAPR cut-off point of 0.36 was suitable for predicting OS.\textsuperscript{29} For head and neck cancer, the optimal cut-off value is 0.51 for patients with LAOSCC as shown in our cohort, 0.4912 in the study for locally advanced laryngeal and hypopharyngeal cancer,\textsuperscript{10} and 0.4876 for locally advanced NPC and 0.447 for metastatic NPC, respectively.\textsuperscript{30,31}

Generally, the optimal cut-off values can be determined by several statistical methods. The first one entails using the receiver operating characteristic (ROC) curve to find the optimal cut-off point based on the values for sensitivity and specificity. ROC curve relies on sensitivity and specificity and is widely used in diagnostic research and for the evaluation of efficiency of various predictive models. The second one requires using the cubic spline functions and smooth curve fitting combined with flectionpoint calculation, which can directly exhibit the relationship between dependent and independent variables.\textsuperscript{15,32} The third one involves using a biostatistical software to automatically calculate the cut-off values, such as Cutoff Finder and X-tile. In the present study, we choose X-tile to elucidate the relationship between AAPR and survival outcome.

Additionally, cancer stage based on AJCC 8th edition remained an independent prognostic factor for OS in our cohort. Presence of ENE and LVI were unfavorable predictors for CSS and DFS. ENE is a well-known independent risk factor for locoregional failure and survival outcomes in patients with LAOSCC.\textsuperscript{33} LVI is known as a pathologic phenomenon in which tumor cells invade an endothelium-lined space of vascular or lymphatic vessels without underlying muscular walls and has been well recognized as a common risk factor for locoregional recurrences and poor survival chances in patients with head and neck cancer.\textsuperscript{34,35} The result echoes our previous study that revealed the presence of LVI as an inferior oncologic outcome in patients receiving salvage total laryngectomy after chemo-radiotherapy.\textsuperscript{36}

The nomogram, which is a dependable predictive tool, is extensively employed in oncology research, including in

| Variable                  | Preoperative AAPR | $P$ Value |
|---------------------------|-------------------|-----------|
| Age                       | <65               | 0.242     |
|                           | $\geq 65$         |           |
| Sex                       | Male              | 0.994     |
|                           | Female            |           |
| Tumor location            | Tongue            | 0.212     |
|                           | Other             |           |
| Pathological stage        | III               | 0.11      |
|                           | IVA + IVB         |           |
| T classification          | pT1-2             | 0.117     |
|                           | pT3-4             |           |
| N classification          | pN0               | 0.642     |
|                           | pN +              |           |
| Extraneal extension       | Absent            | 0.482     |
|                           | Present           |           |
| Perineural invasion       | Absent            | 0.195     |
|                           | Present           |           |
| Lymphovascular invasion   | Absent            | 0.425     |
|                           | Present           |           |
| Margin                    | $< 5$ mm          | 0.349     |
|                           | $\geq 5$ mm       |           |

Abbreviation: AAPR, albumin-to-alkaline phosphatase ratio.

**Discussion**

As far as we know in the literature review, this is the first study to investigate the clinical significance of preoperative AAPR in LAOSCC. The study presented that preoperative AAPR served as an independent survival predictor for patients with LAOSCC and lower preoperative AAPR was statistically significantly associated with unfavorable OS, CSS, and DFS.

Albumin and ALP, both of which are important indicators of liver function, have been routinely evaluated at different time-points at diagnosis, before treatment, and during follow-ups. Albumin as an indicator of the nutritional status is synthesized by the liver. Hypoalbuminemia not only reflects impaired liver functions but also the protein consuming capacity caused by various diseases, particularly by aggressive tumor proliferation.\textsuperscript{20} Meanwhile, hypoalbuminemia may impair the metabolism and the function of immune cell, and subsequently results in weakened immune reaction, occurrence of infectious disease, and a poor response to anti-cancer treatment.\textsuperscript{21} ALP as a member of hydrolase enzymes is ubiquitously expressed, but at a higher level, in the liver, bile duct, bone, and kidneys.\textsuperscript{22} ALP has also been reported to be a regulator of immune response\textsuperscript{23} and involved in tumor growth regulation, metastasis, and progression.\textsuperscript{24} Increasing evidence has shown that ALP can serve as a tumor-associated antigen and biomarker of cancer cell proliferation.\textsuperscript{25,26}

As a novel prognostic candidate, AAPR has been reported in various cancer types, such as hepatoma,\textsuperscript{13} cholangiocarcinoma,\textsuperscript{27} and head and neck cancer. Kim et al demonstrated that patients with locally advanced nasopharyngeal carcinoma (NPC) had better OS and progression-free survival (PFS) if pretreatment AAPR was more than 0.4876.\textsuperscript{30} Nile et al analyzed 209 patients with metastatic NPC and also revealed a pretreatment AAPR $\geq 0.447$ was significantly associated with better OS and PFS than those with an AAPR $< 0.447$.\textsuperscript{31} Another study also echoed that higher preoperative AAPR was one of the favorable predictors of DFS and OS in patients with locally advanced laryngeal and hypopharyngeal cancer.\textsuperscript{10} Our study further strengthens the survival predictability of preoperative AAPR in the clinical practice for patients with LAOSCC.

The cut-off point of AAPR as a survival predictor may differ among different cancer types and study cohorts. For example, Li et al used a cut-off point of 0.61 to analyze the prognostic significance of AAPR in limited-stage SCLC patients treated chemotherapy and radiotherapy.\textsuperscript{28} Another study for patients with advanced NSCLC observed that an AAPR cut-off point of 0.36 was suitable for predicting OS.\textsuperscript{29} For head and neck cancer, the optimal cut-off value is 0.51 for patients with LAOSCC as shown in our cohort, 0.4912 in the study for locally advanced laryngeal and hypopharyngeal cancer,\textsuperscript{10} and 0.4876 for locally advanced NPC and 0.447 for metastatic NPC, respectively.\textsuperscript{30,31}

Generally, the optimal cut-off values can be determined by several statistical methods. The first one entails using the receiver operating characteristic (ROC) curve to find the optimal cut-off point based on the values for sensitivity and specificity. ROC curve relies on sensitivity and specificity and is widely used in diagnostic research and for the evaluation of efficiency of various predictive models. The second one requires using the cubic spline functions and smooth curve fitting combined with flectionpoint calculation, which can directly exhibit the relationship between dependent and independent variables.\textsuperscript{15,32} The third one involves using a biostatistical software to automatically calculate the cut-off values, such as Cutoff Finder and X-tile. In the present study, we choose X-tile to elucidate the relationship between AAPR and survival outcome.

Additionally, cancer stage based on AJCC 8th edition remained an independent prognostic factor for OS in our cohort. Presence of ENE and LVI were unfavorable predictors for CSS and DFS. ENE is a well-known independent risk factor for locoregional failure and survival outcomes in patients with LAOSCC.\textsuperscript{33} LVI is known as a pathologic phenomenon in which tumor cells invade an endothelium-lined space of vascular or lymphatic vessels without underlying muscular walls and has been well recognized as a common risk factor for locoregional recurrences and poor survival chances in patients with head and neck cancer.\textsuperscript{34,35} The result echoes our previous study that revealed the presence of LVI as an inferior oncologic outcome in patients receiving salvage total laryngectomy after chemo-radiotherapy.\textsuperscript{36}

The nomogram, which is a dependable predictive tool, is extensively employed in oncology research, including in
The nomogram integrates the clinical and pathological information with better patient stratification to estimate individualized treatment outcomes. The study for the first time constructed an AAPR-based nomogram to predict OS for patients with LAOSCC. We applied the C-index and calibration plots to validate the nomogram and demonstrated a reliable predictive accuracy and discriminative ability of model. Under the scenario, the nomogram based on the AAPR and various clinicopathological features could be used as a convenient tool to help clinicians execute an individualized estimation of the risk of mortality for patients with LAOSCC.

Admittedly, some limitations exist in this study. First, only those with available preoperative AAPR data were included and some physiological or pathological status that might inherently affect the levels of AAPR could not be strictly evaluated in our cohort, thus, a selection bias might exist in the retrospective study. Second, our cohort focused on patients’ upfront surgery with/without adjuvant therapy, which was the main treatment option for patients with LAOSCC; thus, the results might fail to extend to the patient’s upfront definitive chemoradiotherapy. Thirdly, the study’s results were not validated using an independent dataset, by which the survival predictability of

| Variable                  | Event | 5-year OS (%) | P     | Event | 5-year CSS (%) | P     | Event | 5-year DFS (%) | P     |
|---------------------------|-------|---------------|-------|-------|----------------|-------|-------|----------------|-------|
| Age                       | <65   | 70            | 72.2  | .009  | 40             | 80.8  | .352  | 82             | 65.2  | .009          |
|                           | ≥65   | 24            | 53.0  |       | 11             | 74.1  |       | 27             | 46.6  |       |
| Sex                       | Male  | 86            | 68.2  | .817  | 47             | 79.5  | .748  | 98             | 61.9  | .563          |
|                           | Female| 8             | 72.7  |       | 4              | 81.6  |       | 11             | 59.1  |       |
| Tumor location            | Tongue| 64            | 67.1  | .544  | 34             | 78.8  | .706  | 74             | 59.5  | .447          |
|                           | Other subsites | 30 | 71.4  |       | 17             | 81.2  |       | 35             | 65.7  |       |
| Pathological stage        | III   | 13            | 86.3  |       | .001           | 8     | 89.2  | .030           | 15    | 84.8          |
|                           | IVA + IVB | 81 | 62.2  |       | 43             | 76.2  |       | 94             | 53.4  | .001          |
| T classification          | pT1-2 | 14            | 75.6  |       | .422           | 10    | 79.4  | .791           | 15    | 68.4          |
|                           | pT3-4 | 79            | 67.1  |       | 41             | 79.7  |       | 55             | 73.2  |       |
| N classification          | pN0   | 56            | 76.4  |       | .008           | 13    | 89.4  | <              | 18    | 85.1          |
|                           | pN+   | 57            | 61.5  |       | 38             | 70.7  | .001  | 52             | 59.9  | .001          |
| Perineural invasion       | Absent| 50            | 68.0  | .708  | 27             | 80.4  | .698  | 56             | 64.4  | .260          |
|                           | Present| 44           | 69.3  |       | 24             | 78.8  |       | 53             | 58.3  |       |
| Lymphovascular invasion   | Absent| 68            | 72.2  | .012  | 32             | 83.4  | .001  | 78             | 66.5  | .002          |
|                           | Present| 26           | 55.6  |       | 19             | 66.2  |       | 31             | 44.4  |       |
| Margin                    | <5 mm | 37            | 65.8  | .235  | 22             | 74.7  | .144  | 40             | 59.8  | .445          |
|                           | ≥5 mm | 57            | 70.0  |       | 29             | 82.3  |       | 69             | 62.7  |       |
| Extranodal extension      | Absent| 64            | 73.3  |       | .006           | 29    | 85.1  | <              | 41    | 78.4          |
|                           | Present| 30           | 54.1  |       | 22             | 62.8  | .001  | 29             | 51.8  | .001          |
| Preoperative AAPR         | Low   | 40            | 48.5  | <     | 21             | 66.4  | .005  | 44             | 42.6  | <             |
|                           | High  | 54            | 76.1  | .001  | 30             | 84.3  |       | 65             | 68.9  | .001          |

Abbreviations: AAPR, albumin-to-alkaline phosphatase ratio; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival.

| Factor                        | 5-year OS Hazard Ratio (95% CI) P-Value | 5-year CSS Hazard Ratio (95% CI) P-Value | 5-year DFS Hazard Ratio (95% CI) P-Value |
|-------------------------------|---------------------------------------|----------------------------------------|----------------------------------------|
| Age                           | ≥65 versus <65 1.649 (1.026-2.649)    | N/A                                    | 1.235 (0.684-2.23) .484                |
| Pathological stage            | IV versus III 2.11 (1.14-3.905)       | 1.367 (0.601-3.109) .456               | 1.636 (0.796-3.362) .181               |
| Extranodal extension          | Present versus Absent 1.368 (0.862-2.172) | 2.237 (1.216-4.118) .01                | 2.043 (1.218-3.428) .007               |
| Lymphovascular invasion       | Present versus Absent 1.546 (0.964-2.48) | 1.993 (1.105-3.595) .022               | 2.25 (1.365-3.707) .001               |
| Preoperative AAPR             | Low versus High 2.22 (1.466-3.361)    | 2.037 (1.16-3.578) .013                | 1.756 (1.075-2.868) .025               |

Abbreviations: AAPR, albumin-to-alkaline phosphatase ratio; OS, overall survival; CSS, cancer-specific survival; DFS, disease-free survival.
preoperative AAPR on patients with LAOSCC could be further strengthened. Thereby, a prospective and multi-institutional study would be designed in the future to minimize these biases.

Conclusions
Our results suggest that preoperative AAPR serves as an independent prognostic factor of survival outcome in patients with LAOSCC. The nomogram incorporating preoperative AAPR and various clinicopathological features may be used as a convenient tool to help clinicians execute an individualized estimation of the risk of mortality for patients with LAOSCC.

Data Availability Statement
Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Statement
The study was approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital for studies involving humans (Ethical Application Reference Number: 202201109B0). The informed consent was waived due to the retrospective nature of the study.

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Figure 3. Nomogram and survival predictions. (A) Nomogram for predicted OS rate. A vertical line is drawn from each factor to the point score. By adding the points from all the factors, a total points score is reached, which is translated into 5-year OS rates by drawing a vertical line to its axis. (B) Calibration plots of the nomogram to predict 5-year OS rate. The diagonal line indicates ideal prediction, and the orange line indicates the predictive ability of our proposed nomogram. Blue dots with bars represent the performance and 95% CI of the nomogram when applied to the surviving cohorts.

Abbreviations: OS, overall survival; AAPR, albumin-to-alkaline phosphatase ratio.
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