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Original Article

# Pretreatment risk stratification for non-metastatic head and neck squamous cell carcinoma in a high-prevalence area

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**Abstract**

*Background*: This retrospective study was to establish a prognostic scoring system for patients with non-metastatic head and neck squamous cell carcinoma (HNSCC).
*Methods*: The medical records of 151 patients with HNSCC were evaluated. Clinical data were collected and statistical analyses were performed to determine the prognostic value of pretreatment variables and to build a risk stratification system. Analysis of the data for 94 additional patients validated the risk stratification system.
*Results*: Three independent adverse prognostic factors were identified: Age <65 years, LDH ≥ upper normal limit and performance status. The risk stratification was defined as two or more adverse factors presented at diagnosis versus one adverse factor or no adverse factors. Patients with two or more adverse factors had a shorter survival regardless of treatment. This was confirmed in both the training set and the validation set.
*Conclusion*: This risk stratification provides additional information to the current tumor staging system, which could be useful in making decisions for individual patients and selecting more homogenous patients when designing clinical trials.


*Keywords:* albumin; head and neck squamous cell carcinoma; lactate dehydrogenase; prognosis

## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the major cancers in Taiwan, where its incidence is the most increased among all cancers. It ranks fourth in cancer incidence and cancer-related deaths among men.[1] This is most likely the result of habitual chewing of betel nuts by middle-aged men.[2] A multi-disciplinary approach, including surgery, radiotherapy, and chemotherapy, is the mainstay for treating patients with HNSCC. Some pretreatment factors had been reported to predict poor prognosis, such as co-morbidity index determined by the Adult Comorbidity Evaluation-27 (ACE-27) score,[3] hypercalcemia,[4–7] pre-treatment hematologic profile, or prolonged facial edema.[8,9] Other factors have also been shown to be associated with a poor prognosis in various kinds of cancer other than HNSCC, such as tumor-related leukocytosis,[10] pretreatment anemia,[11–15] pretreatment thrombocytosis,[16–23] levels of pretreatment serum albumin[24,25] and serum lactate dehydrogenase (LDH),[26–28] and hypercalcemia.[29] Some molecular prognostic factors, such as, human papilloma virus 16 (HPV-16),[30–33] vascular endothelial growth factor (VEGF),[31] and epidermal growth factor receptor (EGFR)[31,33] were also recently reported to influence the prognosis of HNSCC.

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However, a pretreatment risk-stratification system to predict the prognosis of patients with advanced HNSCC is still lacking.

Risk stratification is important in cancer treatment because it provides information that may be used to select the most appropriate therapeutic approach. Several well-known risk stratification systems are applied worldwide today.[26,27,29] Other risk stratification systems based on prognostic factors also assist physicians to more confidently select treatment strategies; furthermore, they facilitate the selection of more homogenous patient groups for clinical trials.[34–37] Given the predictive efficacy demonstrated for the factors described above, we elected to apply a similar model to locally advanced HNSCC. We focused on pretreatment clinical factors as they are easily obtained and reproducibly measured.

## 2. Methods

### 2.1. Training set of the risk stratification

We retrospectively reviewed the charts of 158 patients with primary HNSCC diagnosed by pathology in the Taipei Veterans General Hospital from December 2002 to May 2006. All patients' personal profiles were de-linked during statistical analyses. Patients with nasopharyngeal carcinoma were excluded. Patients with medical conditions associated with reactive leukocytosis or thrombocytosis, such as acute or chronic inflammatory diseases, or anemia related to acute blood loss were excluded.[8] Patients with distant metastases at the time of diagnosis, or metastatic squamous cell carcinoma other than the head and neck were also excluded, as our goal was to establish a risk-scoring model for nonmetastatic HNSCC only. We ultimately enrolled 152 patients. Pretreatment clinical data, such as age, sex, site of primary tumor, TNM staging of tumor according to the American Joint Committee on Cancer (AJCC) staging system sixth edition,[38] concentrations of LDH and serum calcium, ECOG performance status (ECOG PS),[39] ACE-27 score,[3] and hematologic profile (white blood cell count, differential count, hemoglobin level, and platelet count) were collected. All 152 patients underwent definitive treatment for HNSCC. Overall survival (OS) was estimated from the day of diagnosis to the last follow-up date or death. The median follow-up time was 24.3 months (range 0.2 months to 83.2 months).

### 2.2. Definition of pre-treatment parameters used in univariate analysis

To facilitate the statistical analysis, we further assigned patients to different categories: age (<65 years of age vs. ≥65 years of age), ECOG PS (0–1 vs. ≥2), ACE-27 (score 0 vs. score 1–3), definitive treatment (surgical vs. non-surgical), T stage (T3 + T4 vs. T1 + T2), N stage (N0 vs. N+, i.e., N1–3) and overall stage (stage I–III vs. stage IV, since there was no significance between stage I to III in the individual log-rank test). We defined hypoalbuminemia as serum albumin ≤3.5 g/dL.[24,25] Hypercalcemia was defined as a corrected serum calcium concentration >10 mg/dL.[29] Elevated serum LDH was defined as a serum LDH concentration > the upper limit of normal range (ULN).[26,27] Tumor-related leukocytosis was defined as a pretreatment white blood cell count (WBC) $> 10 \times 10^9$ cells/L in the absence of known inflammatory or infectious diseases. Tumor-related thrombocytosis was defined as a pretreatment platelet count of $>400 \times 10^9$ cells/L in the absence of known inflammatory conditions.[10,16,17] Monocytosis was defined as a monocyte count $>1 \times 10^9$ cells/L as reported in a recent study published by our group.[8] A hemoglobin concentration of <11 g/dL in the absence of acute blood loss was defined as tumor-related anemia.[12,13]

### 2.3. Validation set for the scoring system

We applied the prognostic scoring system among patients with nonmetastatic HNSCC diagnosed from July 2006 to December 2008. A total of 94 patients were evaluated according to this scoring system.

### 2.4. Statistical analysis

The Kaplan-Meier method was used for survival analysis, and the log-rank test was used for univariate analysis of prognostic factors. A $p$ value <0.05 by the two-tailed test was considered to indicate statistical significance. To test the independent prognostic effect of variables that showed significance in univariate analysis by the log-rank test, the Cox proportional hazards model was applied. The relative risk of survival analysis indicates the risk of death with reference to the first item of each analysis. The correlations of variables were analyzed by Chi-square test or Fischer's exact test, as appropriate. The survival endpoint was OS and was measured from the date of diagnosis to the date of death or last follow-up. All statistical analyses were performed by SPSS software (version 13.00, SPSS Inc, Chicago, IL, USA).

## 3. Results

### 3.1. Patient characteristics and univariate analyses of prognostic factors

The pretreatment clinical characteristics of 151 patients with HNSCC are shown in Table 1. Only one patient with a diagnosis of salivary gland squamous cell carcinoma was excluded from analysis because of limited numbers ($n = 1$). The median follow-up time was 24.5 months (0.5 months to 83.2 months). Fourteen variables were analyzed, and 11 variables showed adverse prognostic effects on survival. These adverse prognostic factors were enrolled into the multivariate analysis. Sex, hypercalcemia, and site of primary tumor did not exhibit any impact on survival.

### 3.2. Multivariate analysis for independent prognostic factors

The eleven variables that showed $p$ values <0.05 in the log-rank test were tested with multivariate Cox regression analysis

Table 1
Patient characteristics and univariate analysis of prognostic factors in 151 patients with non-metastatic head and neck squamous cell carcinoma.

| Variables | Patients (%) | Overall survival | | $p$ (log rank) |
|---|---|---|---|---|
| | | Median (mo) | 3-y (%) | |
| Age (y) | | | | |
| ≥65 | 50 (33.1%) | Not reached | 80.2 | 0.018[a] |
| <65 | 101 (66.9%) | Not reached | 57.6 | |
| Gender | | | | |
| Male | 136 (90.1) | Not reached | 64.3 | 0.593 |
| Female | 15 (9.9) | Not reached | 72.7 | |
| LDH (U/L) | | | | |
| Normal | 115 (76.2) | Not reached | 72.1 | <0.001[a] |
| >ULN | 34 (22.5) | 16 | 42.5 | |
| Unknown | 2 (1.3) | | | |
| Albumin (g/dL) | | | | |
| >3.5 | 135 (89.4) | Not reached | 67.5 | 0.002[a] |
| ≥3.5 | 14 (9.3) | 8.8 | 45.8 | |
| Unknown | 2 (1.3) | | | |
| Calcium (mg/dL) | | | | |
| Normal | 131 (86.8) | Not reached | 66.2 | 0.234 |
| >10 | 18 (11.6) | Not reached | 57.8 | |
| Unknown | 2 (1.3) | | | |
| ECOG PS | | | | |
| <2 | 126 (83.4) | Not reached | 73.2 | <0.001[a] |
| ≥2 | 24 (15.9) | 9.0 | 13.4 | |
| Unknown | 1 (0.7) | | | |
| ACE-27 score | | | | |
| 0 | 90 (59.6) | Not reached | 71.1 | 0.017[a] |
| 1–3 | 61 (40.4) | Not reached | 56.5 | |
| Site [b] | | | | |
| Oral | 57 (37.7) | Not reached | 70.5 | 0.127 |
| Oropharynx | 16 (10.6) | Not reached | 80.0 | |
| Hypopharynx | 49 (32.5) | Not reached | 50.6 | |
| Larynx | 29 (19.2) | Not reached | 69.9 | |
| T stage | | | | |
| T1 + T2 | 61 (40.4) | Not reached | 78.1 | 0.015[a] |
| T3 + T4 | 90 (59.6) | Not reached | 56.2 | |
| Lymph node | | | | |
| Negative | 71 (47.0) | Not reached | 80.0 | <0.001[a] |
| Positive | 80 (53.0) | 29.0 | 50.3 | |
| Stage | | | | |
| I | 6 (4.0) | Not reached | 83.3 | 0.006[a] |
| II | 32 (21.2) | Not reached | 79.9 | |
| III | 35 (23.2) | Not reached | 72.9 | |
| IV | 78 (51.6) | 26.4 | 49.4 | |
| Stage | | | | |
| I+II+III | 73 (48.4) | Not reached | 76.4 | 0.001[a] |
| IV | 78 (51.6) | 26.4 | 49.4 | |
| WBC ($\times 10^9$ cells/L) | | | | |
| <10 | 134 (88.7) | Not reached | 67.6 | 0.014[a] |
| ≥10 | 17 (11.3) | 18.0 | 45.6 | |
| Monocytes ($\times 10^9$ cells/L) | | | | |
| <1 | 135 (89.4) | Not reached | 69.4 | 0.001[a] |
| ≥1 | 10 (6.6) | 9.1 | 26.7 | |
| Unknown | 6 (4.0) | | | |
| Hemoglobin (g/dL) | | | | |
| ≥11.0 | 130 (86.1) | Not reached | 67.6 | 0.041[a] |
| <11.0 | 21 (13.9) | 23.1 | 49.9 | |
| Platelets ($\times 10^9$ cells/L) | | | | |
| <400 | 135 (89.4) | Not reached | 68.8 | 0.001[a] |
| ≥400 | 11 (7.3) | 9.7 | 17.0 | |
| Unknown | 5 (3.3) | | | |

ACE-27 score = adult comorbidity evaluation-27 score; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; T stage = tumor spread or tumor size; ULN = upper limit of normal range; WBC = white blood cell count.

[a] $p$ value <0.05.

[b] Only one patient was diagnosed with salivary gland squamous cell carcinoma and was excluded from analysis due to limited numbers ($n = 1$).

to determine the independence of the prognostic factors (Table 2). Three factors independently showed significant adverse impacts on survival: age <65 years ($p < 0.001$, 95% CI 2.197–16.290), serum LDH > ULN ($p = 0.004$, 95% CI 1.48–6.838), and ECOG PS 2 or greater ($p < 0.001$, 95% CI 2.257–11.993).

### 3.3. Risk stratification based on prognostic factors

We then categorized the 151 patients into two groups according to their independent adverse factors. Patients with two or more adverse factors were categorized into the high-risk group. All other patients were categorized into the low-risk group. Two patients with missing values for these clinical characteristics were excluded from the analysis. Patients with two or more adverse factors had significantly shorter rates of survival (Fig. 1, low-risk groups vs. high-risk groups, $p < 0.001$). The 3-year OS rates in the low- and high-risk groups were 75.4% and 17.8%, respectively. The median survival was not reached in the low-risk group and was 9.1 months in the high-risk group. We then analyzed survival according to the treatment administrated. Among patients who received definitive surgical intervention, those with two or more adverse factors had a significantly shorter survival rate than those without any adverse factors or with only one adverse factor (Fig. 2A, low-risk group vs. high-risk group, $p < 0.001$). The 3-year OS rates in the low-risk and high-risk groups were 79.7% and 23.1%, respectively. Among patients who received nonsurgical definitive intervention, this stratification also predicted a better survival rate for patients without any adverse factors or with only one adverse factor (Fig. 2B, low-risk vs. high-risk group, $p < 0.001$). The 3-year OS in the low-risk and high-risk groups were 77.1% and 14.3%, respectively. In subgroup analysis based on patients in the same stage, this risk stratification model significantly predicted worse survival among patients with stage III and stage IV HNSCC (3-year OS in the low-risk and high-risk groups 83.8% vs. 40.0%, respectively, $p = 0.003$; 69.7% vs. 5.9%, respectively, $p < 0.001$; Figs. 3A and 3B). In patients with stage II HNSCC, there was a strong trend for better 3-year OS in the low-risk group versus the high-risk group (82.6% vs. 50.0%, respectively, $p = 0.087$, data not shown). There were too few patients with stage I HNSCC (total $n = 6$) for statistical analysis to be performed.

Table 2
Multivariate analysis of prognostic factors by Cox's proportional hazards method in 151 patients with non-metastatic head and neck squamous cell carcinoma.

| Factors | Relative risk | 95% CI | *p* |
|---|---|---|---|
| Age (y) | | | |
| ≥65 | 1.000 | 2.197–16.290 | <0.001[a] |
| <65 | 5.983 | | |
| LDH (U/L) | | | |
| Normal | 1.000 | 1.448–6.838 | 0.004[a] |
| >UNL | 3.146 | | |
| Serum albumin (g/dL) | | | |
| >3.5 | 1.000 | 0.917–6.656 | 0.074 |
| ≤3.5 | 2.470 | | |
| ECOG PS | | | |
| <2 | 1.000 | 2.257–11.993 | < 0.001[a] |
| ≥2 | 5.203 | | |
| ACE-27 score | | | |
| 0 | 1.000 | 0.974–3.945 | 0.059 |
| 1–3 | 1.961 | | |
| T stage | | | |
| T1 + T2 | 1.000 | 0.792–3.720 | 0.171 |
| T3 + T4 | 1.716 | | |
| Lymph node | | | |
| Negative | 1.000 | 0.739–3.989 | 0.208 |
| Positive | 1.718 | | |
| Stage | | | |
| Stage I+II+III | 1.000 | 0.576–3.112 | 0.498 |
| Stage IV | 1.339 | | |
| WBC ($\times 10^9$ cells/L) | | | |
| <10 | 1.000 | 0.391–2.982 | 0.882 |
| ≤10 | 1.080 | | |
| Monocytes ($\times 10^9$ cells/L) | | | |
| <1 | 1.000 | 0.423–4.362 | 0.607 |
| ≥1 | 1.359 | | |
| Hemoglobin (g/dL) | | | |
| ≥11.0 | 1.000 | 0.463–2.504 | 0.865 |
| <11.0 | 1.076 | | |
| Platelets ($\times 10^9$ cells/L) | | | |
| <400 | 1.000 | 0.202–1.942 | 0.417 |
| ≥400 | 0.626 | | |

ACE-27 score = adult comorbidity evaluation-27 score; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; T stage = tumor spread or tumor size; UNL = upper normal limit; WBC = white blood cell counts.
[a] *p* value <0.05.

### 3.4. Validation test

In order to test our scoring system for risk stratification, we further applied it among patients diagnosed with nonmetastatic HNSCC from July 2006 to December 2008. A total of 94 patients were enrolled in the validation set. The median follow-up time in this set was 27.9 months (range 0.8 months to 43.6 months). This stratification predicted a better rate of survival among patients in the low-risk group (low-risk vs. high-risk groups, $p = 0.003$). The 3-year survival rates were 83.5% and 60.6%, respectively. Again, among patients who received definitive surgical intervention, the low-risk group had a significantly longer survival rate than the high-risk group (low-risk vs. high-risk groups, $p = 0.039$). Among patients who received nonsurgical definitive intervention, this scoring system also predicted a better rate of survival for low-risk patients (low-risk vs. high-risk groups, $p = 0.028$). In subgroup analysis, there were only 14 patients with stage III HNSCC. Patients in the low-risk group still showed better 3-year OS than patients in the high-risk group (100% vs. 50.0%, respectively, $p = 0.016$). Patients with low-risk stage IV HNSCC showed a longer survival than patients in the high-risk group (3-year OS in the low-risk and high-risk groups, 78.4% vs. 61.4%, respectively, $p = 0.029$). Since there were only 4 patients with stage I or II HNSCC, statistical analysis was not performed.

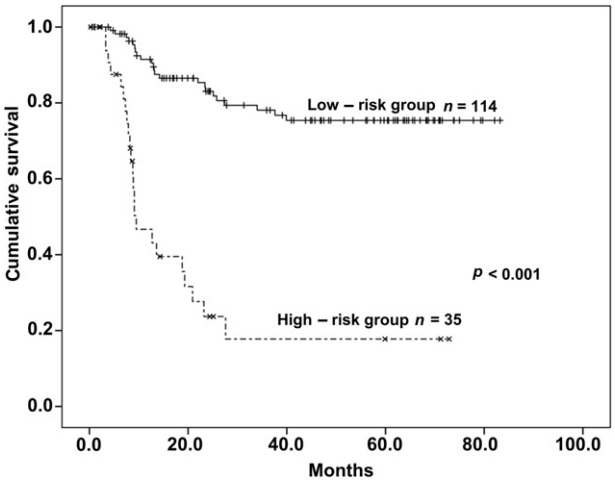


Fig. 1. Kaplan-Meier-estimated overall survival curves for the two risk groups, as derived from analysis of data for 151 patients with locally invasive head and neck squamous cell carcinoma ($p < 0.001$, log-rank test).

## 4. Discussion

In this study, we attempted to create a model based on prognostic factors for the stratification of patients with non-metastatic HNSCC into more homogenous groups, facilitating a more accurate prediction of the outcome and the selection of more homogenous patient groups for clinical trials. The two major primary cancer sites of our patients were the oral cavity and the hypopharynx, which are consistent with our nationwide population data.[1] Firstly, we identified 11 prognostic factors with clinical effects on survival. Most of the identified factors were in accordance with previous reports, with the exception of hypercalcemia.[3,8,28] Hypercalcemia has been reported to be a poor prognostic factor but showed no prognostic effect in our univariate analysis.[4–7] However, if we analyzed the original 158 patients regardless of distant metastases, the results were statistically significant ($p = 0.013$, data not shown). Furthermore, among the 7 patients with metastatic HNSCC, 5 (71.4%) presented initially with hypercalcemia. This result suggests that the patients with HNSCC who presented with hypercalcemia were likely to have distant metastases. In addition, we demonstrated four novel prognostic factors that have never been reported for HNSCC: age <65 years, LDH greater than ULN, hypoalbuminemia, and ECOG PS 2 or greater.

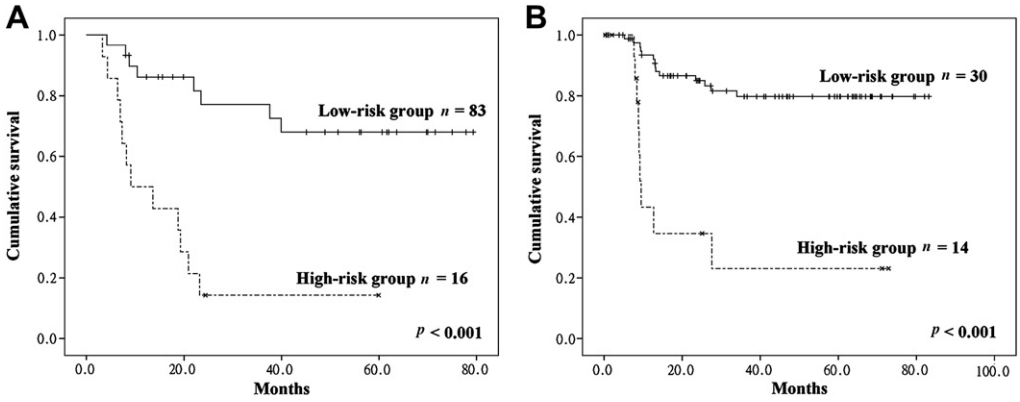


Fig. 2. Survival analysis for two risk groups according to the primary treatment modalities, showing the adverse impact on survival in high-risk patients whether the patient had received definitive surgical intervention (A) or not (B) (both $p < 0.001$).

Considering age, we revealed that patients aged <65 years were predisposed toward a poor histopathology of their HNSCC (Chi-square test, $p = 0.026$, data not shown). In comparison with other factors, age <65 years was associated with a predisposition toward having a higher rate of lymph node involvement and higher platelet count (Chi-square test, $p = 0.001$; Mann-Whitney U test, $p = 0.017$, respectively, data not shown). This may explain why the survival of patients <65 years of age was worse. Although serum LDH was included in a prognostic scoring system established by Cheng et al for nasopharyngeal cancer,[28] no association has been reported for HNSCC. The situation with hypoalbuminemia is similar.[24,25]

In the multivariate analysis, only age <65 years, LDH > ULN, and ECOG PS 2 or greater were independent risk factors for nonmetastatic HNSCC. Other prognostic factors, including ACE-27 score 1–3,[3] lymph node involvement, hypoalbuminemia, T stage 3–4, tumor-related leukocytosis, anemia, thrombocytosis, or monocytosis, which have been previously reported to be associated with poor prognosis,[8] showed no significance in the multivariate analysis.

We then assigned these risk factors into two risk categories and showed the feasibility of predicting clinical outcome for patients with nonmetastatic HNSCC. Furthermore, this stratification clearly predicted a group of patients with short survival rates despite administration of definitive treatment (Figs. 2A and 2B). In the validation test, this stratification also predicted the poor outcomes of those patients with two or more adverse factors. Again the predictive ability was not influenced by the administration of definitive treatment. In the subgroup analyses based on the same stage, this risk stratification also identified a group of patients with worse survival in the same stage, especially in stage III and stage IV (Fig. 3). These results showed that our risk stratification can add information in addition to the current staging system, both in the training and the validation set.

The limitation of our study is its retrospective nature. The median survival times were not reached in the low-risk groups in either the training set or the validation set.

We have determined that combining three independent prognostic factors (age, LDH, and ECOG performance status) provides a statistically verifiable basis for risk stratification, with distinct clinical characteristics and outcomes demonstrated for each of the good- and poor-risk groups. Cheng et al has established a prognostic model for patients with nasopharyngeal cancer, but it focuses on locoregional control and was obtained for nasopharyngeal cancer only.[28] Our results proved that the scoring system established in this study was not influenced by the administered treatment and may add additional information to the current staging system.

In conclusion, this is the first study to establish a risk-stratification scoring system for predicting prognosis among patients with nonmetastatic HNSCC. This model for risk stratification based on prognostic factors may prove efficacious for the selection of more homogenous patient cohorts for clinical trials.

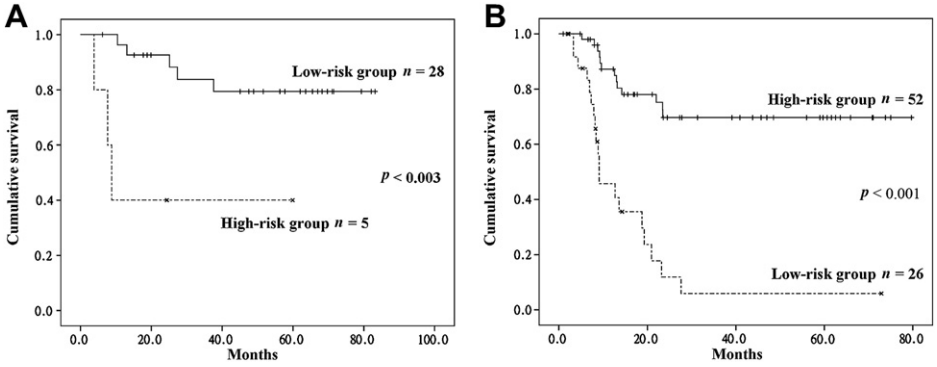


Fig. 3. Survival analysis for two risk groups according to the stage showing the adverse impact on survival in high-risk group patients with stage III (A) or stage IV (B) ($p = 0.003$, $p < 0.001$, respectively).

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