A Preoperative Nutritional Index for Predicting Cancer-Specific and Overall Survival in Chinese Patients With Laryngeal Cancer

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ABSTRACT: Pinato prognostic nutritional index (PNI) adequately predicts long-term outcomes of various malignancies. However, its value in predicting outcomes in laryngeal squamous cell carcinoma (LSCC) is unknown.

All patients newly diagnosed with LSCC presenting to the Department of Head and Neck Oncology at Sun Yat-sen University Cancer Center between January 1, 1990 and July 31, 2010 were eligible. The PNI was calculated as serum albumin (g/L) + 5 x total lymphocyte count/L. The cutoff finder software program was used to classify the patients into 3 groups for which the PNI score was at least 70% sensitive, at least 70% specific, or equivocal. Cancer-specific survival was estimated using the Kaplan–Meier method, and predictors were assessed with Cox regression analysis.

Median time between surgery and PNI administration for the 975 eligible patients was 83 months. Index score groups were significantly associated with age, T stage, TNM stage, and type of surgery. Five-year CSS and OS were 57.3% and 56.6% in patients with PNI scores below 48.65 (low-probability of survival), 72.8% and 71.3% with scores between 48.65 and 56.93 (moderate-probability of survival), and 77.6% and 75.3% with scores above 56.93 (high-probability of survival); 10-year CSS and OS were 44.2% and 42.7%, 61.6% and 55.6%, 68.3% and 63.5%, respectively. The PNI score groups significantly predicted CSS and OS (P < 0.001).

The PNI is an inexpensive and readily available score that predicted survival in patients with LSCC after curative laryngectomy.

METHODS

The institutional review board of the Sun Yat-sen University Cancer Center approved the study. All data were kept anonymous and confidential and were aggregated for analysis.

Patient Selection

We retrospectively analyzed patients who underwent laryngectomy as a 1st curative treatment option for LSCC between January 1, 1990 and July 31, 2010 at the Sun Yat-sen University Cancer Center, Guangzhou, China. All patients had histopathologically proven LSCC without distant metastasis and underwent curative laryngectomy. None had a history of adjuvant or...
Table 1. Frequency of Clinicopathological Characteristics in 975 Patients With Laryngeal Squamous Cell Carcinoma, by Preoperative Nutritional Index Group

| Variables               | Number, % | Low-Probability of Survival PNI: <48.65 n, % | Mid-Probability of Survival PNI: 48.65–56.93 n, % | High-Probability of Survival PNI: >56.93 n, % | P Value |
|-------------------------|-----------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------|
| Sample size             | 975 (100) | 203 (20.8)                                | 515 (52.8)                                    | 257 (26.4)                                    | <0.001 |
| Age, years (range, 22–87 years) |           |                                           |                                               |                                               |         |
| <60                     | 479 (49.1)| 58 (28.6)                                 | 261 (50.7)                                    | 160 (62.3)                                    |         |
| ≥60                     | 496 (50.9)| 145 (71.4)                                | 254 (49.3)                                    | 97 (37.7)                                     |         |
| Gender                  |           |                                           |                                               |                                               | 0.289   |
| Male                    | 948 (97.2)| 198 (97.5)                                | 497 (96.5)                                    | 253 (98.4)                                    |         |
| Female                  | 27 (2.8)  | 5 (2.5)                                   | 18 (3.5)                                      | 4 (1.6)                                       |         |
| Smoking status          |           |                                           |                                               |                                               | 0.274   |
| Never smoker            | 103 (10.6)| 19 (9.4)                                  | 62 (12.0)                                     | 22 (8.6)                                      |         |
| Ever smoker             | 872 (89.4)| 184 (90.6)                                | 453 (88.0)                                    | 235 (91.4)                                    |         |
| Drinking status         |           |                                           |                                               |                                               | 0.495   |
| Never drinker           | 625 (64.1)| 123 (60.6)                                | 336 (65.2)                                    | 166 (64.6)                                    |         |
| Ever drinker            | 350 (35.9)| 80 (39.4)                                 | 179 (34.8)                                    | 91 (35.4)                                     |         |
| T stage                 |           |                                           |                                               |                                               | 0.466   |
| Supraglottic            | 289 (29.6)| 65 (32.0)                                 | 159 (30.9)                                    | 65 (25.3)                                     |         |
| Glottic                 | 668 (68.5)| 135 (66.5)                                | 347 (67.4)                                    | 186 (72.4)                                    |         |
| Subglottic              | 18 (1.8)  | 3 (1.5)                                   | 9 (1.7)                                       | 6 (2.3)                                       |         |
| T1 and 2                |           |                                           |                                               |                                               | 0.020   |
| T3 and 4                | 484 (49.6)| 114 (56.2)                                | 259 (50.3)                                    | 111 (43.2)                                    |         |
| N stage                 |           |                                           |                                               |                                               | 0.650   |
| N0                      | 792 (81.2)| 166 (81.8)                                | 413 (80.2)                                    | 213 (82.9)                                    |         |
| N1, 2 and 3             | 183 (18.8)| 37 (18.2)                                 | 102 (19.8)                                    | 44 (17.1)                                     |         |
| TNM stage               |           |                                           |                                               |                                               | 0.006   |
| I and II                | 454 (46.6)| 80 (39.4)                                 | 235 (45.6)                                    | 139 (54.1)                                    |         |
| III and IV              | 521 (53.4)| 123 (60.6)                                | 280 (54.4)                                    | 118 (45.9)                                    |         |
| Tumor differentiation   |           |                                           |                                               |                                               | 0.134   |
| High                    | 409 (41.9)| 94 (46.3)                                 | 215 (41.7)                                    | 100 (38.9)                                    |         |
| Moderate                | 407 (41.7)| 73 (36.0)                                 | 227 (44.1)                                    | 107 (41.6)                                    |         |
| Poor                    | 159 (16.3)| 36 (17.7)                                 | 73 (14.2)                                     | 50 (19.5)                                     |         |
| Neck dissection         |           |                                           |                                               |                                               | 0.157   |
| No                      | 716 (73.4)| 158 (77.8)                                | 366 (71.1)                                    | 192 (74.7)                                    |         |
| Yes                     | 259 (26.6)| 45 (22.2)                                 | 149 (28.9)                                    | 65 (25.3)                                     |         |
| Type of laryngectomy    |           |                                           |                                               |                                               | 0.020   |
| Partial                 | 560 (57.4)| 101 (49.8)                                | 298 (57.9)                                    | 161 (62.6)                                    |         |
| Total                   | 415 (42.6)| 102 (50.2)                                | 217 (42.1)                                    | 96 (37.4)                                     |         |

M = metastasis, N = node, PNI = prognostic nutritional index, T = tumor.

* According to the 7th American Joint Committee on Cancer staging system.

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Cancer-specific survival (CSS) was defined as the time in months from the date of the surgery until death from cancer-related causes. Overall survival (OS) was defined as the time in months from the date of the surgery until death from any cause during the follow-up period.

**Statistical Methods**

The optimal cut-off PNI scores were determined with the Cutoff Finder software program, an R software-engineered,
A web-based system designed by Budczies et al.13 (http://molpath.charite.de/cutoff/) was used to analyze the data. The PNI cut-off value for 2 groups was 44.25, which had a specificity of only 10.4%. We then divided the patients into 3 groups based on their PNI scores: patients in whom the test was 70% sensitive (the high-probability of survival group), patients in whom the test was 70% specific (the low-probability of survival group), and patients in whom the test was equivocal (the mid-probability of survival group).

Categorical variables are reported as counts and percentages and were compared using Chi-square or Fisher exact tests. Univariate and multivariate analyses for survival difference were performed using Cox proportional hazards models and were expressed as hazard ratios and 95% confidence intervals. The variables that were shown to be associated with CSS and OS in the univariate analysis were evaluated in the multivariate Cox proportional hazard model. The likelihood ratios forward stepwise method was used for the multivariate Cox proportional analysis. Survival curves were calculated using the Kaplan–Meier method and compared using the log-rank test. All analyses were performed using IBM SPSS statistics software, version 20.0 (SPSS, Inc., Chicago, IL). Two-tailed P values < 0.05 were considered significant.

RESULTS

Patient Characteristics

Of 1010 patients identified in the records, 35 with incomplete preoperative laboratory data were excluded, leaving 975 patients (948 men) in the analysis (Table 1). Median follow-up (from the day of surgery to death or final follow-up call) was 83 months (range 0.3–300 months). Median (range) age was 60 (22–87) years. Almost 90% of patients were smokers, and 36% had a history of alcohol intake. Of primary tumors, two-thirds were in the glottis larynx and one-third was in the supraglottic larynx. About half the tumors were T1–2 and half in T3–4. About 20% of patients had lymph node metastasis. For cancer stage, about half the patients were initially diagnosed as early stage and about half as advanced stage.

Preoperative Nutritional Index Diagnostic Cut-Off Scores

The optimal cut-off PNI scores for predicting survival were determined to be 48.65 and 56.93 (Figure 1). The level of 48.65 and 56.93 were defined as the cut-off values for CSS and OS in our study. Thus, we classified the patients into 3 groups: those with PNI scores of up to 48.65 (n = 203; 20.8%) indicated a low probability of cancer-specific survival, scores between 48.65 and 56.93 (n = 515; 52.8%), a moderate probability of cancer-specific survival; and scores greater than 56.93 (n = 257; 26.4%), a high probability of cancer-specific survival.
TABLE 2. Results of Cox Regression Analysis for Predictors of Cancer-Specific Survival Among 975 Patients With Laryngeal Squamous Cell Carcinoma

| Characteristics               | Univariate HR (95% CI) | P Value | Multivariate HR (95% CI) | P Value |
|-------------------------------|------------------------|---------|--------------------------|---------|
| Age, years                    |                        |         |                          |         |
| <60                           | 1.00                   | <0.001  | 1.00                     | 0.001   |
| ≥60                           | 1.56 (1.27–1.92)       |         | 1.41 (1.14–1.75)         |         |
| Gender                        |                        |         |                          |         |
| Male                          | 1.00                   | 0.093   | ND                       | ND      |
| Female                        | 0.50 (0.22–1.12)       |         | ND                       | ND      |
| Smoking                       |                        |         |                          |         |
| Never smoker                  | 1.00                   | 0.186   | ND                       | ND      |
| Ever smoker                   | 1.27 (0.89–1.82)       |         | ND                       | ND      |
| Drinking                      |                        |         |                          |         |
| Never drinker                 | 1.00                   | <0.001  | 1.00                     | <0.001  |
| Ever drinker                  | 1.48 (1.21–1.82)       |         | 1.46 (1.19–1.79)         |         |
| Tumor subsite                |                        |         |                          |         |
| Supraglottic                  | 1.00                   | <0.001  | NS                       |         |
| Glottic                       | 0.57 (0.46–0.71)       |         | NS                       |         |
| Subglottic                    | 0.60 (0.26–1.36)       |         | NS                       |         |
| T stage*                      |                        |         |                          |         |
| T1 and 2                      | 1.00                   | <0.001  | 1.00                     | <0.001  |
| T3 and 4                      | 2.16 (1.75–2.66)       |         | 1.70 (1.36–2.12)         |         |
| N stage*                      |                        |         |                          |         |
| N0                            | 1.00                   | <0.001  | 1.00                     | <0.001  |
| N1, 2, and 3                  | 2.71 (2.17–3.40)       |         | 2.35 (1.85–2.98)         |         |
| TNM stage*                    |                        |         |                          |         |
| I and II                      | 1.00                   | <0.001  | NS                       |         |
| III and IV                    | 2.34 (1.89–2.91)       |         | NS                       |         |
| Tumor differentiation        |                        |         |                          |         |
| High                          | 1.00                   | <0.001  | NS                       |         |
| Moderate                      | 1.29 (1.03–1.62)       |         | NS                       |         |
| Poor                          | 1.75 (1.32–2.31)       |         | NS                       |         |
| Neck dissection               |                        |         |                          |         |
| No                            | 1.00                   | <0.001  | NS                       |         |
| Yes                           | 2.02 (1.62–2.51)       |         | NS                       |         |
| Type of laryngectomy          |                        |         |                          |         |
| Partial                       | 1.00                   | <0.001  | NS                       |         |
| Total                         | 1.83 (1.50–2.25)       |         | NS                       |         |
| PNI                            |                        |         |                          |         |
| <48.65 (low)                  | 1.00                   | <0.001  | 1.00                     | <0.001  |
| 48.65–56.93 (mid)             | 0.59 (0.47–0.75)       |         | 0.65 (0.51–0.83)         |         |
| >56.93 (high)                 | 0.47 (0.35–0.63)       |         | 0.54 (0.40–0.73)         |         |

CI = confidence interval, HR = hazard ratio, M = metastasis, N = node, ND = not done, NS = no significance, PNI = prognostic nutritional index, T = tumor.
*According to the 7th American Joint Committee on Cancer staging system.

<48.65 [low probability]; HR, 0.66; 95% CI, 0.50–0.87; P < 0.001) remained significant independent predictors of CSS (Table 3).

Analysis of Cancer-Specific Survival and Prognostic Factors

Overall, 5- and 10-year CSS rates were 70.8% and 59.6%, respectively. The 5-year CSS rate was 57.3% in the low-probability group, 72.8% in the mid-probability group, and 77.6% in the high-probability group. The 10-year CSS rates were 44.2%, 61.6%, and 68.3%, respectively (P < 0.001; Figure 2). During follow-up, 112 patients (55.2%) in the low-probability group, 186 (36.1%) in the mid-probability group, and 78 (30.4%) in the high-probability group died of tumor-related causes (P < 0.001; Figure 3).

DISCUSSION

We used the Cutoff Finder software program to determine the optimal PNI scores for predicting cancer survival. The
preoperative PNI groups predicted long-term outcome of LSCC, independent of age, history of alcohol intake, T stage, and N stage. The low-probability group had a significantly lower CSS and OS rate and more often died of tumor-related causes than the other 2 groups.

Two important factors characterize head and neck cancer patients: malnutrition and immunosuppression. Clinically, most laboratory assessments could reflect both malnutrition and immunosuppression, but they are not ideal because they are inaccurate, insensitive, or inconvenient to perform. However, albumin is a widely used indicator of nutrition and the host’s inflammatory reaction, whereas lymphocytes are key elements of the immune system. The PNI, a prognostic score based on lymphocyte count and albumin levels, was first used to assess the immunological and nutritional aspects of patients undergoing surgery of the gastrointestinal tract, predominantly as an indicator of the nutritional status of any given patient. Nutritional status has recently been linked to the prognosis of various cancer types. A low PNI indicates lower in albumin concentrations, lymphocyte counts, or both. The presence of cancer cachexia, partly reflected by a lower albumin concentration, is driven by a sustained inflammatory response, either from the tumor itself or as a host reaction.

Table 3: Univariate and Multivariate Analyses for Predictors of Overall Survival Among 975 Laryngeal Squamous Cell Carcinoma

| Characteristics | Univariate | | Multivariate | |
|-----------------|------------|------------|--------------|------------|------------|------------|------------|-------------|
|                 | HR (95% CI) | P Value    | HR (95% CI)  | P Value    |
| Age, years      |            |            |              |            |            |
| <60             | 1.00       | <0.001     | 1.00         | <0.001     |
| ≥60             | 1.89 (1.56–2.28) | <0.001 | 1.78 (1.46–2.16) | <0.001 |
| Smoking         |            |            |              |            |            |
| Never smoker    | 1.00       | 0.163      | ND           | ND         |
| Ever smoker     | 1.25 (0.91–1.72) | <0.001 | ND           | ND         |
| Drinking        |            |            |              |            |            |
| Never drinker   | 1.00       | <0.001     | 1.00         | <0.001     |
| Ever drinker    | 1.46 (1.21–1.76) | <0.001 | 1.46 (1.21–1.76) | <0.001 |
| Tumor subsite   |            |            |              |            |            |
| Supraglottic    | 1.00       | <0.001     | NS           |            |
| Glottic         | 0.61 (0.50–0.74) | <0.001 | NS           |            |
| Subglottic      | 0.63 (0.30–1.34) | <0.001 | NS           |            |
| T stage         |            |            |              |            |            |
| T1 and 2        | 1.00       | <0.001     | 1.00         | <0.001     |
| T3 and 4        | 2.03 (1.68–2.45) | <0.001 | 1.63 (1.34–1.99) | <0.001 |
| N stage         |            |            |              |            |            |
| N0              | 1.00       | <0.001     | 1.00         | <0.001     |
| N1, 2, and 3    | 2.56 (2.07–3.17) | <0.001 | 2.28 (1.82–2.86) | <0.001 |
| TNM stage       |            |            |              |            |            |
| I and II        | 1.00       | <0.001     | NS           |            |
| III and IV      | 2.20 (1.81–2.67) | <0.001 | NS           |            |
| Tumor differentiation |      |            |              |            |            |
| High            | 1.00       | 0.001      | NS           |            |
| Moderate        | 1.30 (1.06–1.59) | 0.001 | NS           |            |
| Poor            | 1.61 (1.24–2.09) | 0.001 | NS           |            |
| Neck dissection |            |            |              |            |            |
| No              | 1.00       | <0.001     | NS           |            |
| Yes             | 1.99 (1.62–2.44) | <0.001 | NS           |            |
| Type of laryngectomy |    |            |              |            |            |
| Partial         | 1.00       | <0.001     | NS           |            |
| Total           | 1.80 (1.50–2.16) | <0.001 | NS           |            |
| PNI             |            |            |              |            |            |
| <48.65 (low)    | 1.00       | <0.001     | 1.00         | 0.010      |
| 48.65–56.93 (mid) | 0.68 (0.54–0.84) | <0.001 | 0.78 (0.63–0.97) |      |
| >56.93 (high)   | 0.53 (0.41–0.69) | <0.001 | 0.66 (0.50–0.87) |      |

CI = confidence interval, HR = hazard ratio, M = metastasis, N = node, ND = not done, NS = no significance, PNI = prognostic nutritional index, T = tumor.
observational studies suggest that low serum albumin concentration is associated with higher mortality from cancer. Albumin is important in assessing malnutrition, indicating that these nutritional assessments identify different at-risk groups. On the other hand, malnutrition impairs host immunity. Patients with tumors have decreased host immunity that nearly always worsens coexisting malnutrition, and the outcomes of decreased host immunity maybe more dangerous in a malnourished host than in a well-nourished one.

On the other hand, lymphocytes are involved in cytotoxic cell death and cytokine production, which inhibit the proliferation and metastatic capacity of tumor cells by starting an immune response against the tumor. Cytotoxic T Lymphocytes (CTL) induce apoptosis of cancer cells and inhibit tumor growth, whereas CD8+ T lymphocyte infiltration is associated with better overall patient outcomes. Furthermore, immunologic mediators (such as IL-10 and transforming growth factor-b) are released, which can have a marked immunosuppressive effect with consequent impaired lymphocyte function and reduced lymphocyte counts. Thus, a low lymphocyte count is associated with an immunosuppressed condition, suggesting that the host has an insufficient antitumor immunological reaction. Thus, albumin concentrations and lymphocyte counts, taken together, may indicate chronic inflammation, immunity, and nutritional status, all of which are of prognostic value.
Malnutrition and immunosuppression are often problems in elderly surgical patients. Among our patients, 71.4% (145/203) of those with a low-probability of survival (PNI scores < 48.65) were 60 years old or older, whereas only 37.7% (97/257) of those with a high-probability of survival (PNI scores > 56.93) were 60 years old or older. Thus, the overall prevalence of malnutrition and immunosuppression was indeed higher among our elderly patients.

We found that PNI score was also related to T stage and TNM stage. Further, advanced T stage (T3–4) and advanced TNM stage (TNM III–IV) patients were preferentially treated with total laryngectomy. The TNM stage comprises the effects of T and N stages, which generally reflects the prominent impact of local invasion of LSCC and cervical lymph node metastasis on prognosis. More than 60% of our patients with TNM III–IV stage disease were in the low-probability-of-survival group. These patients were also more likely to experience malnutrition and immunosuppression.

Various PNI cut-off scores selected with different methods have been used in different cancers. The cut-off score is usually set at 45, which is defined as moderate-to-severe malnutrition. However, the optimal PNI cut-off score for predicting the long-term outcomes of LSCC remains unclear. In the present study, the optimal PNI cut-off scores were determined to be 48.65 and 56.93 by the Cutoff Finder software program. Based on these cut-off values, we classified the patients into 3 groups according to their PNI scores: below 48.65, between 48.65 and 56.93, and above 56.93. CSS was lower in patients with PNI scores less than 48.65 than it was in those with PNI scores between 48.65 and 56.93, and in those with PNI greater than 56.93 (5-year OS, 56.6% vs 71.3% and 75.3%, respectively; 10-year OS, 42.7% vs 55.6% and 63.5%, respectively; log-rank test, P < 0.001).

**Limitations of the Study**

It is a retrospective, single-institution observational study based on only 975 patients. A prospective study would provide a better evaluation of prognostic factors and would allow serial PNI scores to be obtained so that they could be correlated with declines in other clinical variables. Hence, these analyses need to be validated in a larger cohort of patients.

**CONCLUSIONS**

Although our results warrant further validation in independent prospective studies, we found that the PNI is a simple, reproducible, inexpensive, and reliable measure of systemic inflammation response. In our study, the PNI score significantly predicted CSS and OS. Therefore, we suggest that the PNI should be included in the routine assessment of LSCC patients.

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