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# Prognostic Value of the Lymphocyte-to-Monocyte Ratio in Patients with Parotid Gland Carcinoma

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**Objective:** Previous studies have evaluated various markers as prognostic predictors in patients with many types of cancers. However, the influence of such factors on the outcomes of patients with parotid gland carcinoma (PGC) is unknown. This study investigated the roles of alternative markers in the prognoses of patients with PGC.

**Methods:** Overall, 101 patients who underwent curative treatment for PGC were retrospectively evaluated, and their 5-year overall and disease-free survival rates were calculated. The prognostic values of clinical and pathologic factors were determined.

**Results:** The 5-year overall and disease-free survival rates were 73.1% and 62.8%, respectively. Multivariate analysis revealed that a low lymphocyte-to-monocyte ratio (LMR), high T classification, high N classification, and perineural invasion were independent predictors of poor prognosis.

**Conclusions:** Thus, we identified LMR as an independent prognostic factor for patients with PGC. Patients with low LMRs who are amenable to treatment may require adjuvant treatment to improve their prognoses.

**Key Words:** Disease free survival, lymphocyte-to-monocyte ratio, overall survival, parotid gland carcinoma, prognostic factor..

**Level of Evidence:** 4

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## INTRODUCTION

Parotid gland carcinoma (PGC) represents 0.3% of all cancers and 1% to 3% of all head and neck cancers, and has different malignant phenotypes and prognoses.[1,2] Owing to its low incidence and histological diversity, the prognoses of patients with PGC remain unclear. Previous studies have revealed that prognostic factors for such patients include age,[3] TNM classification,[1,4] preoperative facial paralysis,[5] high-risk histology,[6] perineural invasion,[5] lymphovascular invasion,[4] and surgical margin.[5]

Recent studies have demonstrated the relevance of inflammatory, nutritional, and immunological markers as predictors of prognosis in patients with various cancers.[7–13] These markers include the modified Glasgow prognostic score (mGPS),[11] C-reactive protein (CRP)-to-albumin ratio (CAR),[14,15] neutrophil-to-lymphocyte ratio (NLR),[12] platelet-to-lymphocyte ratio (PLR),[13] and lymphocyte-to-monocyte ratio (LMR).[7–9] Previous investigations have explored the prognostic value of the NLR in pediatric patients with PGC[16] as well as of the mGPS, CRP, and NLR in patients with salivary duct carcinoma.[17] However, the importance of these prognostic markers in patients with PGC overall (ie, not specific subgroups) has not been fully established.

In the present study, we investigated the role of blood test–derived inflammatory, nutritional, and immunological markers as predictors of prognoses in patients with PGC who underwent curative treatment.

## MATERIALS AND METHODS

### *Patient Characteristics*

One hundred eighteen patients with PGC who underwent curative treatment at the Department of Otolaryngology, Head and Neck Surgery, Keio University School of Medicine between January 1991 and December 2018 were included in this retrospective study. Fourteen patients were subsequently excluded



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All authors contributed to patient diagnosis and treatment. T.M. and Y.W. contributed to data analysis, collection, and interpretation. T.M. prepared the draft of the paper, and T.M. and H.O. were responsible for writing the paper. T.M., H.O., and Y.W. collected the findings and drafted the manuscript. All authors revised the paper and approved the final manuscript.

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because they lacked blood test data acquired within 1 month prior to surgery. Two patients with distant metastasis at diagnosis and one with clinical evidence of acute infection were also excluded. Finally, 101 patients were included in this study. Their characteristics (age, sex, TNM classification, surgical findings, pathologic characteristics, any pretreatment for facial nerve paralysis, and follow-up examinations) were collected from their medical records. The TNM classification was based on the eighth edition of the American Joint Committee on Cancer staging manual.[18] The patients were histologically diagnosed using the World Health Organization (WHO) criteria.[19] The high-risk histology was defined based on the description of WHO criteria; if not described, we did not define as high-risk histology. Postoperative follow-up was performed at regular intervals (1- to 3-month intervals during the first 3 postoperative years, 3- to 6-month intervals during the fourth and fifth years, and 6- to 12-month intervals from the sixth year onward). Computed tomography or magnetic resonance imaging was performed every 3–6 months in year one and every 6–12 months from year two onward.

### *Treatment*

All patients underwent partial parotidectomy, total parotidectomy, extended total parotidectomy, or parotidectomy plus neck dissection as a primary treatment. Facial nerves that were directly involved with the tumor were sacrificed; all others were preserved. Neck lymph node dissection was concurrently performed for patients with positive neck nodes. In principle, adjuvant radiotherapy or chemoradiotherapy was administered to patients with adverse features such as high histological grade, close or positive margins, perineural invasion, lymph node metastases, and/or lymphatic/vascular invasion. Patients were generally irradiated at 2.0 Gy/fraction, five times a week for a total dose of 50–60 Gy, although their performance statuses and any comorbidities were considered before treatment. Patients in whom resectable locoregional recurrences or neck metastases were detected during follow-up underwent additional resections immediately. Some patients received chemotherapy as palliative treatment for persistent disease or after the discovery of distant metastases; these included tegafur/uracil; tegafur/gimeracil/oteracil; herceptin and docetaxel; and docetaxel, cisplatin, and fluorouracil.

### *Scoring Systems*

The LMR was defined as the absolute lymphocyte count (ALC) divided by the absolute monocyte count (AMC). The NLR was defined as the absolute neutrophil count (ANC) divided by the ALC. The PLR was defined as the absolute platelet count (APC) divided by the ALC. The CAR was defined as the serum CRP level divided by the serum albumin level. The cutoff values for the LMR, NLR, PLR, CAR, ALC, AMC, ANC, APC, CRP, and albumin were calculated using receiver operator characteristic analyses as 5.54, 2.43, 209, 0.077, 1 742 μL, 231 μL, 3 741 μL, $22.5 \times 10^4$ /μL, 0.275 mg/dL, and 4.25 g/dL, respectively. The mGPS was estimated as described previously.[20] Patients with normal albumin and CRP levels (≥ 3.5 g/dL and < 0.5 mg/dL, respectively) were allocated a score of 0; patients with both low albumin (< 3.5 g/dL) and elevated CRP level (≥ 0.5 mg/dL) were allocated a score of 2, while all others were assigned a score of 1. All markers levels were obtained during blood tests performed within 1 month before surgery.

### *Statistical Analysis*

The 5-year overall survival (OS) and disease-free survival (DFS) rates were determined using the Kaplan–Meier method under various conditions. All survival periods were calculated from the date of surgery to that of the event or of the latest follow-up visit. The following variables were included: age, sex, T classification, N classification, TNM stage, existence of pretreatment facial nerve paralysis, high-risk histology, perineural invasion, surgical margin, LMR, NLR, PLR, CAR, mGPS, ALC, AMC, ANC, APC, CRP, and albumin. On univariate analysis, the OS and DFS of patients in the different subgroups were assessed using the log-rank test. Factors that were significant on univariate analysis were then analyzed using multivariate analyses, which were performed using a Cox proportional hazards model with a backward-selection procedure. To avoid multicollinearity, the correlations between variables were evaluated using Pearson's correlation coefficient. When two or more variables were strongly correlated, the most significant representative of that group was selected. The distributions of categorical variables between the two groups were compared using the chi-square or Fisher's exact test. Associations between continuous variables were assessed using the Mann–Whitney test. All statistical analyses were performed using SPSS

TABLE I.
Patient Characteristics.

| Variables | Cases (N = 101) | % |
|---|---|---|
| Age | | |
| Median (range) | 59 (13–85) | |
| Sex | | |
| Male/Female | 63/38 | 62%/38% |
| Histology | | |
| Mucoepidermoid carcinoma | 35 | 35% |
| Acinic cell carcinoma | 15 | 15% |
| Salivary duct carcinoma | 14 | 14% |
| Adenoid cystic carcinoma | 9 | 9% |
| Carcinoma ex pleomorphic adenoma | 9 | 9% |
| Adenocarcinoma, not otherwise specified | 8 | 8% |
| Basal cell adenocarcinoma | 4 | 4% |
| Squamous cell carcinoma | 3 | 3% |
| Sebaceous carcinoma | 1 | 1% |
| Carcinosarcoma | 1 | 1% |
| Lymphoepithelial carcinoma | 1 | 1% |
| Small cell carcinoma | 1 | 1% |
| Unclassified | 1 | 1% |
| T classification | | |
| T1/T2/T3/T4 | 15/31/15/40 | 15%/31%/15%/40% |
| N classification | | |
| N0/N1/N2/N3 | 74/8/18/1 | 73%/8%/18%/1% |
| TNM stage | | |
| I/II/III/IV | 13/29/15/44 | 13%/29%/15%/44% |
| Pretreatment facial nerve paralysis | | |
| Yes/No | 23/78 | 23%/77% |
| High-risk histology | | |
| Yes/No | 62/39 | 61%/39% |
| Perineural invasion | | |
| Yes/No | 38/63 | 38%/62% |
| Surgical margin | | |
| Positive/Negative | 43/58 | 43%/57% |

TABLE II.
Univariate Analyses of Prognostic Factors for OS and DFS in PGC Patients.

| Variables | Cases | 5-year OS (%) | *P*-value | 5-year DFS (%) | *P*-value |
|---|---|---|---|---|---|
| Overall | 101 | 73.1% | | 62.8% | |
| Age | | | | | |
| < 60 | 55 | 86.8% | **0.001** | 75.9% | **0.002** |
| ≥ 60 | 46 | 56.4% | | 47.5% | |
| Sex | | | | | |
| Male | 63 | 63.0% | **0.018** | 61.7% | 0.394 |
| Female | 38 | 90.7% | | 65.0% | |
| T classification | | | | | |
| 1,2 | 46 | 91.8% | **< 0.001** | 81.4% | **< 0.001** |
| 3,4 | 55 | 59.4% | | 48.7% | |
| N classification | | | | | |
| 0 | 74 | 89.4% | **< 0.001** | 78.5% | **< 0.001** |
| 1,2,3 | 27 | 27.3% | | 19.0% | |
| TNM stage | | | | | |
| I, II | 42 | 96.9% | **< 0.001** | 85.9% | **< 0.001** |
| III, IV | 59 | 57.7% | | 47.8% | |
| Pretreatment facial nerve paralysis | | | | | |
| Yes | 23 | 29.2% | **< 0.001** | 21.9% | **< 0.001** |
| No | 78 | 86.2% | | 75.9% | |
| High-risk histology | | | | | |
| Yes | 62 | 59.2% | **< 0.001** | 50.6% | **0.001** |
| No | 39 | 97.2% | | 82.9% | |
| Perineural invasion | | | | | |
| Yes | 38 | 49.7% | **< 0.001** | 35.1% | **< 0.001** |
| No | 63 | 88.2% | | 80.8% | |
| Surgical margin | | | | | |
| Positive | 43 | 61.4% | **0.011** | 49.0% | **0.010** |
| Negative | 58 | 83.3% | | 74.2% | |
| LMR | | | | | |
| ≥5.54 | 58 | 89.5% | **<0.001** | 79.5% | **<0.001** |
| <5.54 | 41 | 52.1% | | 42.6% | |
| NLR | | | | | |
| <2.43 | 59 | 84.6% | **0.004** | 74.7% | **0.004** |
| ≥2.43 | 40 | 54.7% | | 47.8% | |
| PLR | | | | | |
| <209 | 86 | 76.1% | **0.013** | 66.8% | 0.106 |
| ≥209 | 13 | 43.1% | | 26.4% | |
| CAR | | | | | |
| <0.077 | 75 | 76.9% | **0.001** | 68.1% | **0.021** |
| ≥0.077 | 18 | 41.2% | | 37.7% | |
| mGPS | | | | | |
| 0 | 76 | 74.8% | **0.024** | 66.2% | 0.208 |
| 1,2 | 16 | 45.6% | | 39.7% | |
| ALC | | | | | |
| ≥1742 | 47 | 83.5% | **0.019** | 78.5% | **0.010** |
| <1742 | 52 | 62.7% | | 49.9% | |
| AMC | | | | | |
| <231 | 26 | 95.2% | **0.004** | 86.4% | **0.029** |
| ≥231 | 73 | 65.0% | | 55.9% | |
| ANC | | | | | |
| <3741 | 52 | 74.7% | 0.938 | 62.3% | 0.845 |
| ≥3741 | 47 | 70.4% | | 64.9% | |
| APC | | | | | |
| $<22.5 \times 10^4$ | 41 | 68.5% | 0.127 | 52.8% | 0.135 |
| $\geq 22.5 \times 10^4$ | 60 | 75.8% | | 70.8% | |
| CRP | | | | | |
| <0.275 | 72 | 81.0% | **<0.001** | 67.0% | **0.014** |
| ≥0.275 | 23 | 39.0% | | 45.7% | |
| Albumin | | | | | |
| ≥4.25 | 49 | 82.1% | 0.057 | 74.8% | 0.091 |
| <4.25 | 51 | 64.0% | | 53.9% | |

Statistically significant values are marked in bold.

ALC = absolute lymphocyte count; AMC = absolute monocyte count; ANC = absolute neutrophil count; APC = absolute platelet count; CAR = C-reactive protein-to-albumin ratio; CRP = C-reactive protein; DFS = disease-free survival; LMR = lymphocyte-to-monocyte ratio; mGPS = modified Glasgow prognostic score; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PLR = platelet-to-lymphocyte ratio.

version 25 for Mac (IBM, Armonk, NY, USA). A *P*-value of <0.05 was considered statistically significant.

## RESULTS

Table I shows the characteristics of the 101 patients with PGC who were evaluated in this study. The median age was 59 years, while the male-to-female ratio was almost 3:2. Pathological diagnosis revealed that a plurality of patients (35) had mucoepidermoid carcinoma. On pathological grading, 62 patients had PGC with high-risk histology, 59 had advanced T-stage disease (T3–4), 27 had cervical lymph node metastasis, and 59 were at an advanced TNM stage (III–IV). Twenty-three patients had facial nerve paralysis before treatment. The median follow-up time was 65 months (range, 0.5–325 months).

The patients' 5-year OS and DFS rates were 73.1% and 62.8%, respectively; results of the univariate analyses for OS and DFS are summarized in Table II. An age ≥ 60 years, male sex, higher T classification, higher N classification, higher TNM stage, presence of pretreatment facial nerve paralysis, presence of high-risk histology, presence of perineural invasion, positive surgical margin, low LMR, high NLR, high PLR, high CAR, high mGPS, low ALC, high AMC, and high CRP were all significantly associated with poorer OS. Age ≥ 60 years, high T classification, high N classification, high TNM stage, presence of pretreatment facial nerve paralysis, presence of high-risk histology, presence of perineural invasion, positive surgical margin, low LMR, high NLR, high CAR, low ALC, high AMC, and high CRP were also significantly associated with DFS.

The results of the multivariate analyses of factors potentially associated with OS and DFS are shown in Table III. N classification (hazard ratio [HR] 0.214, $P = 0.001$), perineural invasion (HR 0.286, $P = 0.011$), and LMR (HR 3.658, $P = 0.015$) were independently associated

TABLE III.
Multivariate Analyses of Prognostic Factors for OS and DFS in PGC Patients.

| | OS | | | DFS | | |
|---|---|---|---|---|---|---|
| Variables | HR | 95% CI | *P*-value | HR | 95% CI | *P*-value |
| Age | 0.569 | 0.200–1.615 | .289 | 0.507 | 0.243–1.058 | .07 |
| Sex | 0.409 | 0.108–1.555 | .190 | - | - | - |
| T classification | 0.799 | 0.174–3.663 | .772 | 0.317 | 0.113–0.892 | **.030** |
| N classification | 0.214 | 0.085–0.540 | **.001** | 0.266 | 0.122–0.581 | **.001** |
| Pretreatment facial nerve paralysis | 0.417 | 0.155–1.123 | .084 | 0.592 | 0.243–1.438 | .247 |
| High-risk histology | 0.133 | 0.017–1.065 | .057 | 0.620 | 0.190–2.019 | .427 |
| Perineural invasion | 0.286 | 0.109–0.754 | **.011** | 0.428 | 0.188–0.977 | **.044** |
| Surgical margin | 0.658 | 0.147–2.936 | .583 | 0.948 | 0.319–2.816 | .923 |
| LMR | 3.658 | 1.286–10.403 | **.015** | 3.005 | 1.306–6.912 | **.010** |
| NLR | 1.643 | 0.415–6.502 | .479 | 1.773 | 0.609–5.156 | .293 |
| PLR | 0.531 | 0.123–2.281 | .394 | - | - | - |
| mGPS | 2.252 | 0.806–6.293 | .122 | - | - | - |
| ALC | 0.353 | 0.097–1.286 | .114 | 2.065 | 0.764–5.581 | .153 |
| AMC | 0.377 | 0.043–3.333 | .380 | 1.108 | 0.327–3.756 | .869 |
| CRP | 0.549 | 0.228–1.317 | .179 | 1.130 | 0.475–2.687 | .783 |

Statistically significant values are marked in bold.

ALC = absolute lymphocyte count; AMC = absolute monocyte count; CRP = C-reactive protein; DFS = disease-free survival; LMR = lymphocyte-to-monocyte ratio; mGPS = modified Glasgow prognostic score; NLR = Neutrophil-to-lymphocyte ratio; OS = Overall survival; PLR = Platelet-to-lymphocyte ratio.

with OS. In addition, T classification (HR 0.317, $P = 0.030$), N classification (HR 0.266, $P = 0.001$), perineural invasion (HR 0.428, $P = 0.044$), and LMR (HR 3.005, $P = 0.010$) were independently associated with DFS. Since there were strong correlations between T classification and TNM stage, as well as between CAR and CRP, only the T classification and CRP were selected as prognostic factors. The Kaplan–Meier curves for OS and DFS divided by significant prognostic factors are shown in Figures 1 and 2.

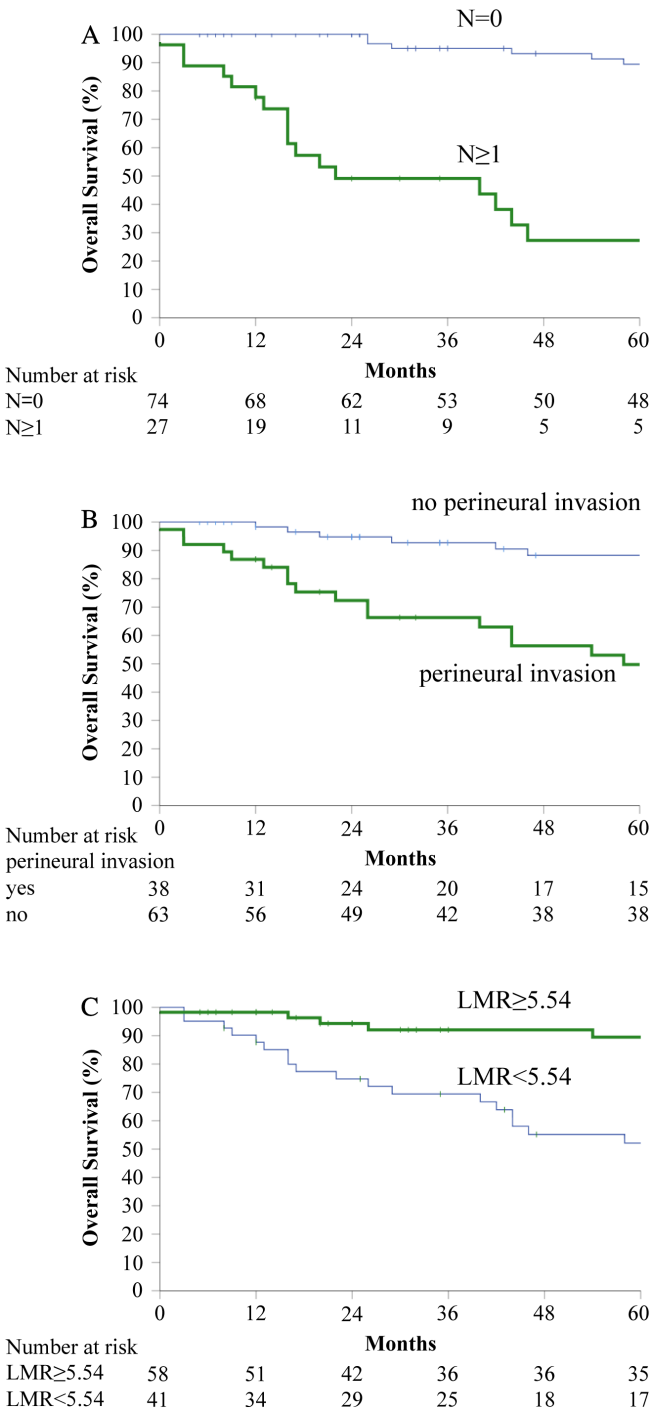


Fig. 1. Kaplan–Meier survival curves for OS according to N classification (A), perineural invasion (B), and LMR (C).

## DISCUSSION

Our study demonstrated that the 5-year OS and DFS among patients with PGC who underwent curative treatment were 73.1% and 62.8%, respectively. These rates were previously reported to be 46% to 82.9%[1,3-6,21–24] and 60.2% to 74.4%,[3–5,25] respectively; our results are consistent with those of previous studies, given that the treatment protocol at our institution is based on the National Comprehensive Cancer Network guidelines for head and neck cancers.[26]

Multivariate analysis revealed that N classification, perineural invasion, and LMR were significant predictors of OS and DFS in our study; moreover, T classification was a significant predictor of DFS. In previous studies, TNM classification[1,3,21,23,24] and perineural invasion[21,24] were also found to be significant prognostic factors; however, in contrast to such studies, in our study age,[3,6,23] high-risk histology,[3,21] preoperative facial paralysis[21,23] and surgical margin[5] showed no consistent association with survival. The *P*-values of high-risk histology and preoperative facial paralysis were close to significant ($P = 0.057$ and 0.084 for OS, respectively); therefore, these factors may be found to be statistically significant in a larger case series. It has also been reported that age,[1] high-risk histology,[6] preoperative facial paralysis,[1]

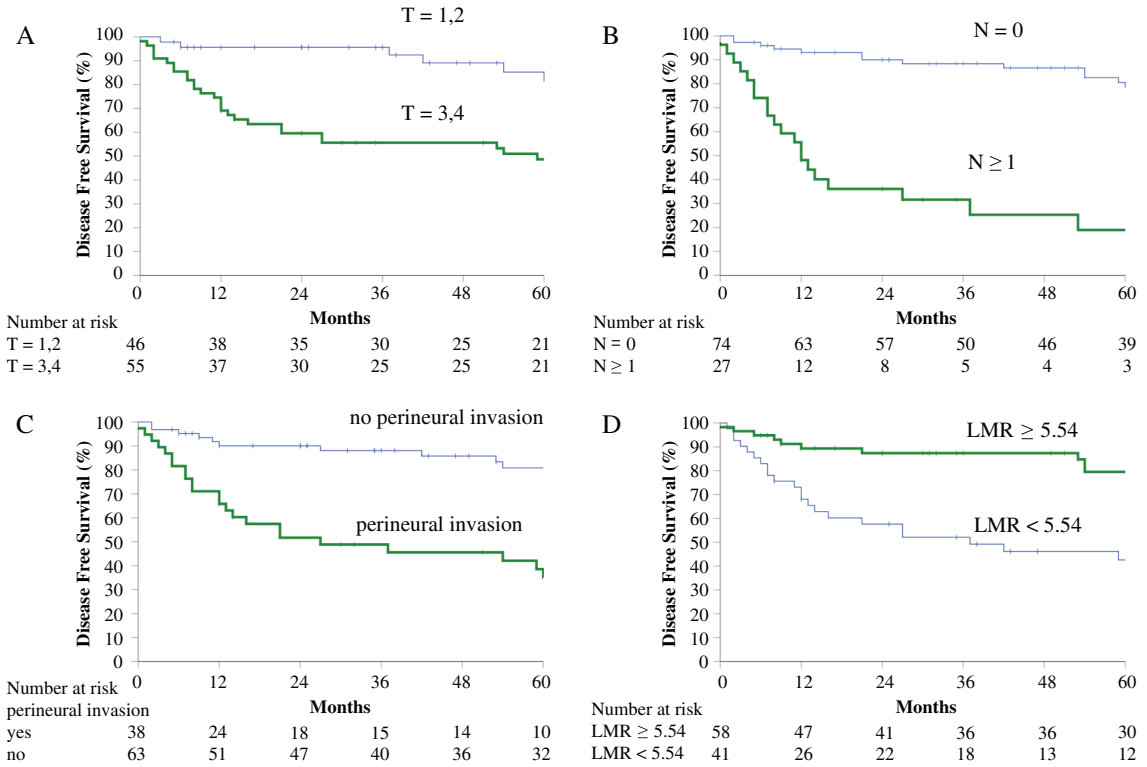


Fig. 2. Kaplan–Meier survival curves for DFS according to T classification (A), N classification (B), perineural invasion (C), and LMR (D).

and surgical margin[3,21] were not significant prognostic factors. As such, the prognostic values of these factors remain controversial.

We found that the LMR was a significant predictor of the OS and DFS in patients with PGC who were receiving curative treatment. To the best of our knowledge, we are the first to report a correlation between a low LMR and poor prognosis in patients with this disease. Our results are consistent with those of previous studies showing LMR to be a prognostic factor in B cell lymphoma,[7] colon cancer,[8] and renal cell carcinoma.[9] The specific mechanism underlying how LMR influences prognosis remains unclear; however, both lymphocytes and monocytes are related to the tumor microenvironment, as tumor-infiltrating lymphocytes and tumor-associated macrophages[8] play critical roles in tumor immunity. Zhu et al. reported that the preoperative peripheral LMR is correlated with the tumor-infiltrating lymphocyte-to-tumor-associated macrophage ratio in the tissues of postoperative patients with esophageal squamous cell carcinoma.[27] The presence of tumor-infiltrating lymphocytes indicates the activation of an effective anti-tumor cellular immune response[28] that includes the induction of active tolerance and apotosis.[29] Tumor-associated macrophages play a role in secreting pro-inflammatory cytokines (interleukin [IL]-1, IL-4, IL-6, IL-10, IL-13, tumor necrosis factor, and transforming growth factor-β); this promotes tumor-associated angiogenesis, invasion, and migration while suppressing anti-tumor immunity.[30,31] LMR might represent the balance of host immune status and tumor malignancy, and is an inexpensive and easily measurable marker calculated from parameters obtained during routine blood tests. Therefore, patients with PGC who have low LMRs and are amenable to treatment may be recommended to undergo adjuvant treatments such as radiotherapy to improve their prognoses after a thorough evaluation of the patients' immunological, nutritional, and performance status.

The roles of other blood test-derived inflammatory, nutritional, and immunological markers in PGC were unclear. As in previous studies of pediatric patients with PGC and patients with salivary duct carcinoma,[16,17] the NLR and mGPS were significant prognostic predictors according to our univariate analysis; however, in contrast to these studies, the NLR and mGPS were not significant prognostic predictors on multivariate analysis. These discrepancies may be attributable to the pathological variations in this study. It was previously reported that malignant bladder cancer,[32] renal cell carcinoma,[33] PGC,[34] and epithelial ovarian cancer[35] of high pathological grades exhibit higher NLR and GPS than do those with low pathological grades. Our study included PGCs of all pathological grades; as such, the ANC, ALC, CRP, and albumin might be more closely associated with the prognosis of patients with salivary duct carcinoma than are the ALC and AMC.

There were several limitations in this study. First, this was a retrospective investigation conducted at a single institution; as such, the sample size was small and may have been subject to inevitable bias. Second, we could not fully evaluate lymphovascular invasion, a potentially important prognostic factor, due to a lack of data in the records. Third, this study did not investigate

the effect of the adjusted treatment according to LMR. In the future, larger, multi-institutional prospective investigations are required to validate the findings of this study, and to investigate the effect of adjusted treatment protocols, which consider LMR as a factor, on the prognosis of patients with PGC.

## CONCLUSION

Our study revealed that the LMR, T classification, N classification, and perineural invasion status are useful for predicting the prognosis of patients with PGC who have undergone curative treatment. The LMR is an inexpensive and easily measurable marker calculated from routine blood test data before treatment. Patients with PGC who are diagnosed with low LMRs and are amenable to treatment may be recommend to receive adjuvant treatment for improving their prognoses after a thorough evaluation of the patients' immunological, nutritional, and performance status.

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