Baseline Low Prognostic Nutritional Index Predicts Poor Survival in Locally Advanced Nasopharyngeal Carcinomas Treated With Radical Concurrent Chemoradiotherapy

Erkan Topkan, MD1®, Nur Yucel Ekici, MD2, Yurday Ozdemir, MD1, Ali Ayberk Besen, MD3, Huseyin Mertsoylu, MD3, Ahmet Sezer, MD3, and Ugur Selek, MD4,5

Abstract

Background: To retrospectively assess the impact of prognostic nutritional index (PNI) on survival outcomes of patients with locoregionally advanced nasopharyngeal carcinoma (LA-NPC) treated with concurrent chemoradiotherapy (CCRT). Methods: This study incorporated 154 patients with LA-NPC who received exclusive cisplatinum-based CCRT. Receiver operating characteristic (ROC) curve analysis was utilized for accessibility of pretreatment PNI cutoffs influencing survival results. The primary end point was the interaction between the overall survival (OS) and PNI values, while cancer-specific survival (CSS), locoregional progression-free survival (LR-PFS), distant metastasis–free survival (DMFS), and PFS were the secondary end points. Results: A rounded PNI cutoff value of 51 was identified in ROC curve analyses to exhibit significant link with CSS, OS, DMFS, and PFS outcomes, but not LR-PFS. Patients grouping per PNI value (≥51 [N = 95] vs <51 [N = 49]) revealed that PNI < 51 group had significantly shorter median CSS (P < .001), OS (P < .001), DMFS (P < .001), and PFS (P < .001) times than the PNI ≥ 51 group, and the multivariate results confirmed the PNI < 51 as an independent predictor of poor outcomes for each end point (P < .05 for each). The unfavorable impact of the low PNI was also continued at 10-year time point with survival rates of 77.9% versus 42.4%, 73.6% versus 33.9%, 57.9% versus 27.1%, and 52.6% versus 23.7% for CSS, OS, DMFS, and PFS, respectively. Additionally, we found that PNI < 51 was significantly associated with higher rates of weight loss >5% over past 6 months (49.2% versus 11.6%; P = .002) compared to PNI ≥ 51 group. Conclusion: Low pre-CCRT PNI levels were independently associated with significantly reduced CSS, OS, DMFS, and PFS outcomes in patients with LA-NPC treated with definitive CCRT.

Keywords
nasopharyngeal carcinoma, weight loss, concurrent chemoradiotherapy, prognostic nutritional index, prognosis, survival outcomes

Introduction

Concurrent chemoradiotherapy (CCRT) is the current gold standard management option for patients presenting with locoregionally advanced nasopharyngeal carcinoma (LA-NPC).1 Significant advances in diagnostic and staging tools and implementation of intensity-modulated radiotherapy (IMRT) to the treatment algorithm of LA-NPCs enhanced the locoregional tumor control rates.2-4 But consequently, distant metastasis (DM) turned into the leading failure pattern in such patients with over 20% DM rates.4,5 Tumor (T) and node (N) components of the current tumor–node–metastasis (TNM) staging system represents for the current best quality level framework for treatment decision and outcome prediction of the patients with LA-NPC. However, this system accounts only for the local and regional tumor

1 Department of Radiation Oncology, Baskent University Medical Faculty, Adana, Turkey
2 Clinics of Otorlaryngology, Adana City Hospital, Adana, Turkey
3 Department of Medical Oncology, Baskent University Medical Faculty, Adana, Turkey
4 Department of Radiation Oncology, Koc University, School of Medicine, Istanbul, Turkey
5 Department of Radiation Oncology, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Received: April 10, 2019; revised: May 15, 2019; accepted: May 20, 2019

Corresponding Author:
Erkan Topkan, MD, Department of Radiation Oncology, Baskent University Medical Faculty, 01120, Adana, Turkey.
Email: docdretopkan@gmail.com
extent but disregards the considerable biological variations among the tumor- and host-related response factors. Moreover, the remarkably distinct treatment outcomes observed between the patients with identical TNM stages, even after the same treatment conventions, render the predictive power of TNM framework flawed and underlines the pivotal significance of the identification of additional novel biological factors for more sophisticated prognostic stratification of patients with LA-NPC.

Growing evidence suggest that cancer-related malnutrition and inflammation enhance the local/regional tumor progression and widespread DM by altering the host immunity and tumor biology in unfavorable manners. The prognostic nutritional index (PNI), a combination of the serum albumin (Alb) concentration and total lymphocyte count (TLC) in peripheral blood, has been repeatedly shown to reliably reflect the magnitude of the systemic inflammation and the immunonutritional status of patients with many tumor types, including the pancreatic-, colorectal, gastric-, hepatocellular-, and lung cancers, malignant pleural mesothelioma, and glioblastoma multiforme. However, to date, very few studies have been reported to assess the prognostic and/or predictive value of PNI in patients with LA-NPC. In these studies, variable cutoffs those determined with various methodologies were utilized for discrimination of the outcomes usually with an end goal of 1 or 2 survival results. Hence, present retrospective study was designed to investigate the prognostic worth of pre-CCRT PNI values on the multiple survival end points of patients with LA-NPC and to determine the potential covariates which may correlate with PNI.

Methods

Study Population

The medical records of patients with LA-NPC treated with definitive CCRT by the Baskent University Medical Faculty Head and Neck Cancers Group between January 2007 and December 2015 were retrospectively reviewed. The eligibility criteria were histologically proven non-keratinizing (type 2) or undifferentiated (type 3) squamous cell carcinoma, age 18 to 80 years, Karnofsky Performance Score ≥70, clinical/radiological proof of T2-4N0-3M0 or T1-4N1-3M0 disease stage according to the TNM staging system (seventh edition), body mass index ≥20.0 kg/m2, no prior chemotherapy/RT history, at least 1 cycle of platinum-based chemotherapy administered during the CCRT course, available baseline fluorodeoxyglucose-positron emission computerized tomography (PET-CT) and chest CT scans, no evidence of brain metastasis on magnetic resonance imaging (MRI) scans obtained over past 1 month, available RT and chemotherapy charts, available complete data of baseline complete blood count and biochemistry tests, and available records of pretreatment and follow-up head and neck clinical examinations, MRI and PET-CT scans.

The retrospective study protocol was designed in accordance with the guidelines outlined in the Declaration of Helsinki and approved by the institutional Ethics Committee.

Concurrent Chemoradiotherapy

All patients received definitive CCRT with the RT and chemotherapy doses as reported previously. In brief, the RT technique was 3-dimensional conformal RT (3D-CRT) between January 2007 to June 2011 and IMRT thereafter, administered in a daily fractionation basis: 5 days/week, for 7 weeks. Anti-emetic and nutritional support was provided as indicated. Prophylactic nasogastric tube or percutaneous endoscopic gastrostomy was not utilized, as our institutional treatment approach did not dictate their standard usage for such patients.

Prognostic Nutritional Index Measurements

PNI was calculated by utilizing the total blood count and biochemistry tests obtained on the first day of CCRT with using the Onodera’s original formula:

\[ PNI = 10 \times \text{serum Alb (g/dL)} + 0.005 \times \text{TLC (per mm3)} \]

As PNI reflects the nutritional and immune status of patients with cancer, patients on steroid treatment or with chronic or infectious diseases which may potentially alter the Alb and/or TLC levels were excluded from the analyses to avoid artificial alterations on outcomes.

Toxicity and Treatment Response Assessments

Acute toxicity was assessed weekly (or more frequently) during the CCRT, while patients were regularly examined every 3 months for the first 2 years, every 6 months between the 3 and 5 years, and annually (or more often) for subacute and chronic toxicities after the completion of CCRT. Each toxic event was scored according to the Common Terminology Criteria for Adverse Events v3 and reflected the worst grade ascertained.

Although the study design was retrospective, treatment response was assessed prospectively within the aforementioned visit intervals for chronic toxicity evaluations. All patients underwent detailed endoscopic examinations at each follow-up visit for evaluation of the index NPC and other head and neck regions in order to ascertain any local/regional recurrences and the emergence of second head and neck cancers. First imaging evaluations were obtained at the 90-days follow-up visit utilizing restaging PET-CT scans and scored according to the EORTC-1999 guidelines (the PET Response Criteria in Solid Tumors for patients evaluated after 2009). Positron emission computerized tomography scans were replaced by the head and neck CT and/or MRI whenever a complete metabolic response was ascertained. If indicated, restaging neck/abdominal ultrasonography or abdominal CT, chest CT, brain MRI, and bone scintigraphy were additionally utilized. Salvage interventions such as re-irradiation, systemic chemotherapy, neck dissection, or their combinations were offered to patients with confirmed local and/or regional relapses or distant metastases, as indicated.

Statistical Analysis

The primary objective was the association between pre-CCRT PNI values and overall survival (OS) defined as the interval.
between the first day of CCRT and death/last follow-up. Secondary objectives comprised the associations between pre-CCRT PNI values and cancer-specific survival (CSS), locoregional progression-free survival (LR-PFS), DM-free survival (DMFS), and PFS: the interval between the first day of CCRT and exclusive NPC-related deaths (for CSS), or progression/recurrence at the nasopharynx and/or ipsi-/contralateral neck or death/last follow-up (for LR-PFS), or any distant relapses or nonregional lymph nodes or death/last follow-up (for DMFS), or any disease progression or death/last follow-up (for PFS), respectively.

Receiver operating characteristic (ROC) curve analyses were utilized for testing the ability of pre-CCRT PNI levels to discriminate CSS, OS, LR-PFS, PFS, and DMFS. Means, medians, and ranges were used to describe continuous variables, while frequency distributions were used for categorical variables. The frequency distributions and their correlations among different groups were compared by χ² tests, Student t tests, Pearson exact test, or Spearman correlations as appropriate. The interactions between the potential risk factors and CSS, OS, LR-PFS, PFS, and DMFS were assessed with Kaplan–Meier estimates and log-rank tests. Multivariate analyses incorporated only the factors exhibiting significance in univariate analyses and were tested by the Cox proportional hazards model. Although any 2-sided P values <.05 were considered significant for comparisons between any 2 groups, the noteworthiness of within-subgroup treatment influences was adjusted for multiplicity by utilizing Bonferroni corrections for comparisons between 3 or more subgroups in an effort to limit the chance-related false-positive discoveries.

Results

Present retrospective database search revealed 226 patients with NPC, but 72 of them were excluded from the analyses: for receiving upfront induction chemotherapy (N = 68) and lost to follow-up just after completion of CCRT (N = 4), respectively. Therefore, 154 patients were left eligible for this current analysis. Baseline patient and disease characteristics were as demonstrated in Table 1. In general, the CCRT scheme was relatively well tolerated with an overall grade 3 (N = 81; 52.6%) and 4 (N = 28; 18.2%) acute toxicity rate of 70.8% (N = 109). Only 2 (1.3%) treatment-related deaths due to intractable necrotic nodal-cutaneous fistula (n = 1) and

| Table 1. Baseline Characteristics of 154 Patients With Locoregionally Advanced Nasopharyngeal Carcinoma. |
|---------------------------------------------------------------|
| Characteristics | All patients (N = 154) | PNI ≥ 51 (N = 95) | PNI < 51 (N = 59) | P Value |
|------------------|------------------------|-----------------|------------------|--------|
| Median age (years) | 53 | 54 | 51 | .76 |
| Range | 32-79 | 32-79 | 34-77 | |
| Age group, n (%) | | | | |
| ≥70 years | 28 (18.2) | 19 (20.0) | 9 (16.7) | .47 |
| <70 years | 126 (81.8) | 76 (80.0) | 50 (83.3) | |
| Gender, n (%) | | | | |
| Female | 29 (18.8) | 21 (22.1) | 8 (13.6) | .51 |
| Male | 125 (81.2) | 94 (78.9) | 31 (86.4) | |
| EOCG performance, n (%) | | | | |
| 0 | 63 (40.9) | 42 (44.2) | 21 (35.6) | .42 |
| 1 | 91 (59.1) | 53 (55.8) | 38 (64.4) | |
| WHO histology, n (%) | | | | |
| 2 | 18 (11.4) | 10 (10.5) | 8 (13.6) | .68 |
| 3 | 136 (88.6) | 85 (89.5) | 51 (86.4) | |
| Weight loss, n (%) | | | | |
| ≤5% | 114 (74.0) | 84 (88.4) | 30 (50.8) | .002 |
| >5% | 40 (26.0) | 11 (11.6) | 29 (49.2) | |
| Median CRP, mg/L | 7.4 | 3.4 | 15.6 | <.001 |
| Median Albumin, g/L | 37.2 | 43.4 | 24.8 | <.001 |
| Median TLC, per mm³ | 2270 | 2780 | 1270 | <.001 |
| T-stage, n (%) | | | | |
| 1-2 | 22 (14.1) | 16 (16.8) | 6 (10.2) | .09 |
| 3-4 | 132 (85.9) | 79 (83.2) | 53 (89.8) | |
| N-stage, n (%) | | | | |
| 0-1 | 42 (27.3) | 31 (32.7) | 11 (18.6) | .06 |
| 2-3 | 112 (72.7) | 64 (67.3) | 48 (81.4) | |
| Clinical stage, n (%) | | | | |
| 2 | 18 (11.7) | 14 (14.7) | 4 (6.8) | .07 |
| 3 | 85 (55.2) | 53 (55.8) | 32 (54.2) | |
| 4A-B | 51 (33.1) | 28 (29.5) | 23 (39.0) | |

Abbreviations: CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; N-stage, node stage; PNI, prognostic nutritional index; TLC, total lymphocyte count; T-stage, tumor stage; WHO, World Health Organization.

aWeight loss over past 6 months.
tracheoesophageal fistula–related aspiration pneumonia (n = 1) were reported at respective 5th and 16th months of follow-up. During the CCRT, 112 (72.7%) patients received 3 courses of concurrent chemotherapy, and additionally, 81 (52.6%) were able to receive 1 (N = 18; 11.7%) or 2 (N = 63; 40.9%) adjuvant chemotherapy courses.

At a median 60.3 months (range: 5.2-137.4) of the follow-up period, 115 (74.7%) patients were still alive with 86 (54.4%) of them being free of disease progression. The median CSS, OS, and LR-PFS times were not reached for the entire cohort, while the median DMFS and PFS times were 102.3 months (95% confidence interval [CI]: 79.1-125.5) and 96.4 months (95% CI: 75.7-120.1), separately. Respective 5- and 10-year survival rates were 81.1% and 74.7% for CSS, 72.6% and 65.3% for OS, 60.9% and 53.9% for LR-PFS, 67.6 and 49.4% for DMFS, and 53.8% and 45.1% for PFS. Actuarial 10-year locoregional control and distant relapse-free rates were 89.0% and 78.6%, respectively.

The median PNI value for the whole study group was 50.6 (95% CI: 45.0-56.2). Receiver operating characteristic curve analyses identified the 50.9 (area under the curve [AUC]: 74.1%, sensitivity: 75.3%, specificity: 70.7%), 50.7 (AUC: 72.4%, sensitivity: 71.3%, specificity: 68.9%), 50.8 (AUC: 78.5%, sensitivity: 77.6%, specificity: 75.1%), and 51.2 (AUC: 72.7%, sensitivity: 73.1%, specificity: 71.3%) values as the cutoffs demonstrating significant association with the CSS, OS, DMFS, and PFS outcomes, respectively (Figure 1), while no particular discriminatory cutoff value was identifiable for LR-PFS. Because all 4 cutoffs were numerically very close, the study cohort was dichotomized into 2 groups at a rounded cutoff value of 51.0 for further analyses: group 1: PNI ≥ 51.0 and group 2: PNI < 51.0. Comparisons of the baseline demographics revealed that, although most factors were almost similarly distributed between the 2 PNI groups, baseline weight loss (WL) > 5% over past 6 months (49.2% vs 11.6%; P = .002) and the C-reactive protein measures were conversely higher (3.4 vs 15.6 mg/L; P < .001) in the PNI < 51.0 group, while the median measures of Alb (43.4 vs 24.8 g/L; P < .001) and total TLC (2780 vs 1270/mm³; P < .001) were significantly higher in the PNI ≥ 51.0 group (Table 1). As depicted in Figure 2 and Table 2, comparative survival analysis exhibited that the PNI ≥ 51.0 group had significantly longer median CSS (P < .001), OS (P < .001), DMFS (P < .001), and PFS (P < .001) durations than their PNI < 51.0 counterparts. Similarly, the respective

![Figure 1](image-url). Outcomes of receiver operating characteristic curve analyses: (A) cancer-specific survival, (B) overall survival, (C) distant metastasis-free survival, (D) and progression-free survival.
5- and 10-year survival rates were also superior in PNI ≥ 51.0 than the PNI < 51.0 group for each survival end point (Table 2).

Outcomes of univariate analyses demonstrated that the lower T-stage (2-3 vs 4), lower N-stage (0-1 vs 2-3), lower TNM stage (4A/B vs 2-3), lower WL over past 6 months (≤ 5% vs > 5%), and higher pretreatment PNI (≥ 51.0 vs < 51.0) were related with significantly inferior CSS, OS, DMFS, and PFS outcomes (Table 3). Results of multivariate analyses restricted to the covariates exhibiting univariate significance revealed that each variable retained their independent significance for each survival end point (Table 3).

**Discussion**

Present retrospective cohort analysis investigated the prognostic value of pretreatment PNI on survival outcomes of 154 patients with LA-NPC treated with exclusive CCRT, and its results exhibited that PNI < 51 was strongly and independently associated with significantly inferior CSS, OS, DMFS, and PFS outcomes in this patients group. Besides confirming the prognostic utility of PNI in patients with LA-NPC undergoing exclusive CCRT, present results also discovered a significant

![Figure 2. Survival results according to pretreatment PNI groups (red line: PNI ≥ 51 and dark blue line: PNI < 51): (A) cancer-specific survival, (B) overall survival, (C) distant metastasis-free survival, and (D) progression-free survival. PNI indicates prognostic nutritional.](image)

**Table 2. Median and Long-Term Survival Outcomes According to PNI Groups.**

| Survival      | PNI ≥ 51 (N = 95) | PNI < 51 (N = 59) | P Value |
|---------------|-------------------|-------------------|---------|
| CSS           |                   |                   |         |
| Median, months| NR                | 67.8              | <.001   |
| 5 years (%)   | 84.2              | 57.6              |         |
| 10 years (%)  | 77.9              | 42.4              |         |
| OS            |                   |                   |         |
| Median, months| NR                | 49.1              | <.001   |
| 5 years (%)   | 75.8              | 45.7              |         |
| 10 years (%)  | 73.6              | 33.9              |         |
| DMFS          |                   |                   |         |
| Median, months| NR                | 29.6              | <.001   |
| 5 years (%)   | 68.9              | 30.5              |         |
| 10 years (%)  | 57.9              | 27.1              |         |
| PFS           |                   |                   |         |
| Median, months| NR                | 27.3              | <.001   |
| 5 years (%)   | 66.4              | 28.8              |         |
| 10 years (%)  | 52.6              | 23.7              |         |

Abbreviations: CSS, cancer-specific survival; DMFS, distant metastasis-free survival; OS, overall survival; PFS, progression-free survival; PNI, prognostic nutritional index.
correlation between PNI < 51 and WL > 5% over the past 6-month pre-CCRT period.

Besides the well-established genetic basis for cancer development, growing evidence has demonstrated that the systemic inflammation plays crucial roles in survival and proliferation of tumor cells, neoangiogenesis, resistance to apoptosis, escape from the immune system, metastasis to regional and distant sites, and resistance to therapies. Therefore, overall, systemic inflammation supports the carcinogenesis, progression, and metastases steps in many solid and hematologic cancers.28,29 Principally based on this basic evidence, recent studies focused on the prognostic value of several blood markers and their various combinations including the platelet to lymphocyte ratio, neutrophil to lymphocyte ratio, Glasgow prognostic score and its modified form, systemic immune-inflammation index, and PNI.29-35 Before its wide acceptance as an immunonutritional marker in many cancers including the NPC, the PNI was first utilized by Onodera et al in 1984 for prediction of postoperative complication risks in gastrointestinal cancers.36 Although the low PNI values below various cutoffs have been almost consistently demonstrated to be strongly linked with poorer clinical outcomes in patients with NPC, yet most such studies were highly heterogeneous with regards to the disease stages and treatment modalities, and unfortunately focused on just 1 or 2 survival end points. Thus, the present study was designed to investigate the clinical utility of PNI in terms of CSS, OS, LR-PFS, DMFS, and PFS in a relatively more homogenous LA-NPC group treated with exclusive CCRT.

The first vital finding of our study was the exhibition of a strong relationship between the low PNI values and WL > 5% over the past 6 months. Acute phase reactants Alb and CRP are well-recognized factors to be associated with a hypercatabolic state and resultant WL in patients with cancer either in the pre-cachectic or cachectic periods. In consequence, both low Alb and high CRP levels were incorporated to the cachexia definition of Washington Consensus reported by Evans et al in 2008.36,37 In our study, we observed significantly lower Alb and conversely higher CRP levels in the PNI < 51 group compared to its PNI ≥ 51 counterpart. Probably as a consequence of this observation, meeting the major diagnostic criteria of Delphi Consensus’ cancer cachexia definition (WL > 5% over the past 6 months in the absence of simple starvation), the rate of WL > 5% over the past 6 months was significantly higher in the PNI < 51 group (49.2% vs 11.6% for PNI ≥ 51; P = .002).37 Previously, McMillan et al noted that the CRP and Alb concentrations were inversely correlated in many tumor types, that any increase in CRP was almost always accompanied with decreased Alb concentrations, as observed in our study.38 Hence, the demonstration of a significant connection between the WL > 5% over the past 6 months pre-CCRT period and low PNI values appears to be mainly associated with low Alb levels, which is the common factor shared by increased WL and decreased PNI status on the basis of a same chronic systemic inflammatory condition.

In this research, besides the other well-recognized traditional prognostic factors including the higher T- and N- and TNM-stage, and WL > 5% over past pre-CCRT 6 months, the results of multivariate analysis revealed that pre-CCRT PNI < 51 was strongly and independently associated with significantly inferior CSS, OS, DMFS, and PFS, but not LR-PFS. This finding accords well with the previous NPC studies proposing the low PNI levels (range: 49-55) as a predictor of poor prognosis with regard to the systemic disease control and survival end points.19-23 Although our results appear to confirm these studies, yet we additionally demonstrated a notable prognostic worth for PNI in the prediction of the CSS outcomes alike with the recent study by Miao

---

**Table 3. Outcomes of Uni- and Multivariate Analysis.**

| Factor                        | Univariate CSS | Multivariate CSS | HR (Univariate) | Univariate OS | Multivariate OS | HR (Univariate) | Univariate DMFS | Multivariate DMFS | HR (Univariate) | Univariate PFS | Multivariate PFS | HR (Univariate) |
|-------------------------------|----------------|------------------|-----------------|----------------|-----------------|-----------------|-----------------|------------------|-----------------|----------------|------------------|-----------------|
| Age group (<70 vs ≥70 years)  | .77            | .71              | .82             | .55            | .82             | .55             | .82             | .55              | .82             | .55            | .82               | .55             |
| Gender (F vs M)               | .69            | .63              | .75             | .67            | .75             | .67             | .75             | .67              | .75             | .67            | .75               | .67             |
| ECOG (0 vs 1)                 | .83            | .72              | .93             | .71            | .93             | .71             | .93             | .71              | .93             | .71            | .93               | .71             |
| Histology (2 vs 3)            | .72            | .66              | .80             | .87            | .80             | .87             | .80             | .87              | .80             | .87            | .80               | .87             |
| T-stage (1-2 vs 3-4)          | .026           | .09              | 1.14            | .018           | .09             | 1.14            | .015            | .07              | 1.21           | .018          | .09               | 1.14            |
| N-stage (0-1 vs. 2-3)         | .005           | .009             | 1.41            | .004           | .003            | 1.36            | .004            | .003             | 1.36           | .006          | .005             | 1.46            |
| TNM stage (2-3 vs 4A-B)       | .008           | .014             | 1.29            | .007           | .013            | 1.27            | .005           | .017             | 1.39           | .007          | .005             | 1.34            |
| Weight loss (≤ vs >5%)        | <.001          | <.001            | 2.32            | <.001          | <.001           | 1.83            | <.001          | <.001            | 3.17           | <.001        | <.001             | 2.86            |
| PNI (≥ vs <51)                | <.001          | <.001            | 1.84            | <.001          | <.001           | 2.17            | <.001          | <.001            | 2.14           | <.001        | <.001             | 2.23            |

Abbreviations: CSS, cancer-specific survival; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology; N-stage, node stage; OS, overall survival; PFS, progression-free survival; PNI, prognostic nutritional index; T-stage, tumor stage; TNM, tumor-node-metastasis.

*Weight loss over past 6 months.
Conclusions
The outcomes of current retrospective research confirmed the usefulness pretreatment PNI in the stratification of patients with LA-NPC into 2 groups with distinctive CSS, OS, DMFS, and PFS following definitive CCRT. Therefore, the immunonutritional biomarker PNI with its easy to calculate, reproducible, and inexpensive test characteristics may supplement the standard TNM classification in further prognostic stratification of radically treated patients with LA-NPC.

Authors’ Note
Erkan Topkan and Ugur Selek contributed to conception and design. Nur Y. Ekici, Yurday Ozdemir, Ali Ayberk Besen, Huseyin Mertsoylu, and Ahmet Sezer contributed to collection and assembly of data. Erkan Topkan, Ugur Selek, Yurday Ozdemir, Ali Ayberk Besen, Ahmet Sezer, and Huseyin Mertsoylu contributed to data analysis and interpretation. Erkan Topkan and Ugur Selek contributed to manuscript writing. All authors contributed in Final approval of manuscript.

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.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Erkan Topkan  https://orcid.org/0000-0001-8120-7123

References
1. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. Int J Radiat Oncol Biol Phys. 2006;64(1):47-56.
2. Lin JC, Jan JS, Hsu CY, et al. Phase III study of concurrent chemoradiodotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. J Clin Oncol. 2003;21(4):631-637.
3. Gordin A, Golz A, Daitzchman M, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography imaging in patients with carcinoma of the nasopharynx: diagnostic accuracy and impact on clinical management. Int J Radiat Oncol Biol Phys. 2007;68(2):370-376.
4. Lee AW, Lin JC, Ng WT. Current management of nasopharyngeal cancer. Semin Radiat Oncol. 2012;22(3):233-244.
5. Lee AW, Ng WT, Chan LL, et al. Evolution of treatment for nasopharyngeal cancer-success and setback in the intensity-modulated radiotherapy era. Radiother Oncol. 2014;110(3):377-384.
6. Wan XB, Zhao Y, Fan XJ, et al. Molecular prognostic prediction for locally advanced nasopharyngeal carcinoma by support vector machine integrated approach. PLoS One. 2012;7(3):e31989.
7. Lu K, Feng X, Deng Q, et al. Prognostic role of serum cytokines in patients with nasopharyngeal carcinoma. Onkologie. 2012;35(9):494-498.
8. Elinav E, Nowarski R, Thaiss CA, et al. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer. 2013;13(11):759-771.
9. Liebowitz D. Nasopharyngeal carcinoma: the Epstein-Barr virus association. Semin Oncol. 1994;21(3):376-381.
10. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-867.
11. Shigdar S, Li Y, Bhattacharya S, et al. Inflammation and cancer stem cells. Cancer Lett. 2014;345(2):271-278.
12. Lee SH, Chung MJ, Kim B, et al. The significance of the prognostic nutritional index for all stages of pancreatic cancer. Nutr Cancer. 2017;69(3):512-519.
13. Tokunaga R, Sakamoto Y, Nakagawa S, et al. Prognostic nutritional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. *Dis Colon Rectum*. 2015;58(11):1048-1057.

14. Yang Y, Gao P, Song Y, et al. The prognostic nutritional index is a predictive indicator of prognosis and postoperative complications in gastric cancer: a meta-analysis. *Eur J Surg Oncol*. 2016;42(8):1176-1182.

15. Okamura Y, Sugiura T, Ito T, et al. The optimal cut-off value of the preoperative prognostic nutritional index for the survival differs according to the TNM stage in hepatocellular carcinoma. *Surg Today*. 2017;47(8):986-993.

16. Mori S, Usami N, Fukumoto K, et al. The significance of the prognostic nutritional index in patients with completely resected non-small cell lung cancer. *PLoS One*. 2015;10(9):e0136897.

17. Yao ZH, Tian GY, Wan YY, et al. Prognostic nutritional index predicts outcomes of malignant pleural mesothelioma. *J Cancer Res Clin Oncol*. 2013;139(12):2117-2123.

18. Zhou XW, Dong H, Yang Y, et al. Significance of the prognostic nutritional index in patients with glioblastoma: a retrospective study. *Clin Neurol Neurosurg*. 2016;151:86-91.

19. Oei RW, Ye L, Kong F, et al. Prognostic value of inflammation-based prognostic index in patients with nasopharyngeal carcinoma: a propensity score matching study. *Cancer Manag Res*. 2018;10:2785-2797.

20. Miao J, Xiao W, Wang L, et al. The value of the Prognostic Nutritional Index (PNI) in predicting outcomes and guiding the treatment strategy of nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy (IMRT) with or without chemotherapy. *J Cancer Res Clin Oncol*. 2017;143(7):1263-1273.

21. Yang L, Xia L, Wang Y, et al. Low Prognostic Nutritional Index (PNI) predicts unfavorable distant metastasis-free survival in nasopharyngeal carcinoma: a propensity score-matched analysis. *PLoS One*. 2016;11(7):e0158853.

22. Wei GB, Lu YY, Liao RW, et al. Prognostic nutritional index predicts prognosis in patients with metastatic nasopharyngeal carcinoma. *Onco Targets Ther*. 2016;9:5955-5961.

23. Du XJ, Tang LL, Mao YP, et al. Value of the prognostic nutritional index and weight loss in predicting metastasis and long-term mortality in nasopharyngeal carcinoma. *J Transl Med*. 2015;13:364.

24. Topkan E, Ekici NY, Ozdemir Y, et al. Baseline hemoglobin <11.0 g/dl has stronger prognostic value than anemia status in nasopharynx cancers treated with chemoradiotherapy. *Int J Biol Markers*. 2019;13. doi:10.1177/1724600818821688.

25. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*. 1984;85:1001-1005.

26. Colotta F, Allavena P, Sica A, et al. Cancer related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009;30(7):1073-1081.

27. Tenesa A, Theodoratou E, Din FY, et al. Ten common genetic variants associated with colorectal cancer risk are not associated with survival after diagnosis. *Clin Cancer Res*. 2010;16(14):3754-3759.

28. Diakos CI, Charles KA, McMillan DC, et al. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol*. 2014;15(11):e493-503.

29. Su L, Zhang M, Zhang W, et al. Pretreatment hematologic markers as prognostic factors in patients with nasopharyngeal carcinoma: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96(11):e6364.

30. Zheng J, Cai J, Li H, et al. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as prognostic predictors for hepatocellular carcinoma patients with various treatments: a meta-analysis and systematic review. *Cell Physiol Biochem*. 2017;44(3):967-981.

31. He L, Li H, Cai J, et al. Prognostic value of the Glasgow prognostic score or modified Glasgow prognostic score for patients with colorectal cancer receiving various treatments: a systematic review and meta-analysis. *Cell Physiol Biochem*. 2018;51(3):1237-1249.

32. Zhu L, Chen S, Ma S, et al. Glasgow prognostic score predicts prognosis of non-small cell lung cancer: a meta-analysis. *Springerplus*. 2016;5:439.

33. Jin J, Hu K, Zhou Y, et al. Clinical utility of the modified Glasgow prognostic score in lung cancer: a meta-analysis. *PLoS One*. 2017;12(9):e0184412.

34. Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2014;140(9):1537-1549.

35. Martin L. Diagnostic criteria for cancer cachexia: data versus dogma. *Curr Opin Clin Nutr Metab Care*. 2016;19(3):188-198.

36. Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. *Clin Nutr*. 2008;27(6):793-799.

37. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011;12(5):489-495.

38. McMillan DC, Elahi MM, Sattar N, et al. Measurement of the systemic inflammatory response predicts cancer-specific and non-cancer survival in patients with cancer. *Nutr Cancer*. 2001;41(1):64-69.

39. An X, Ding PR, Wang FH, et al. Elevated neutrophil to lymphocyte ratio predicts poor prognosis in nasopharyngeal carcinoma. *Tumour Biol*. 2011;32(2):317-324.

40. Cho O, Oh YT, Chun M, et al. Minimum absolute lymphocyte count during radiotherapy as a new prognostic factor for nasopharyngeal cancer. *Head Neck*. 2016;38(Suppl 1):E1061-E1067.