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RESEARCH ARTICLE

Topkan et al: HCAR score in LANPC treated with CCRT

HCAR score as a prognostic biomarker of survival in locally advanced nasopharyngeal carcinoma treated with concurrent chemoradiotherapy

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is an aggressive malignancy of the head and neck that is often diagnosed at a locally advanced stage (LANPC). In such cases, intensity-modulated radiotherapy combined with concurrent chemoradiotherapy (CCRT) is the standard treatment; however, the occurrence of distant metastasis and treatment failure remains prevalent. This study evaluates the prognostic significance of a novel composite score that combines hemoglobin levels and the C-reactive protein-to-albumin ratio (HCAR) in LANPC patients undergoing CCRT. We conducted a retrospective analysis of 233 LANPC patients treated with intensity-modulated radiotherapy and platinum-based CCRT from 2011 to 2020. Receiver operating characteristic curve analysis determined pretreatment hemoglobin (Hb) and C-reactive protein-to-albumin ratio (CAR) cut-offs of 11.0 g/dL and 3.0, respectively, which were utilized to create a three-tiered HCAR score: HCAR-0 (Hb ≥11.0 g/dL and CAR <3.0), HCAR-1 (Hb ≥11.0 g/dL and CAR ≥3.0 or Hb <11.0 g/dL and CAR <3.0), and HCAR-2 (Hb <11.0 g/dL and CAR ≥3.0). The primary endpoint of the study was overall survival (OS), while progression-free survival (PFS) was the secondary endpoint. With a median follow-up of 85.7 months, the median PFS and OS were 66.0 months and 108.0 months, respectively, with 5-year PFS and OS rates of 52.8% and 75.9%. The HCAR score significantly stratified patient outcomes: median PFS was not reached for HCAR-0, 66.0 months for HCAR-1, and 25.0 months for HCAR-2. Median OS also varied significantly, being not reached for HCAR-0, 108.0 months for HCAR-1, and 55.0 months for HCAR-2 (all $p < 0.001$). Corresponding 10-year PFS rates were 50.2%, 34.4%, and 5.0%, while 10-year OS rates were 68.3%, 41.6%, and 11.1%. Multivariate analysis revealed that the HCAR score remained an independent predictor of both PFS and OS, alongside T and N stage. The HCAR score shows promising prognostic utility for predicting OS and PFS in LANPC; however, performance estimates may be overly optimistic due to the lack of internal validation.

Keywords: Hemoglobins, C-reactive protein, albumins, biomarkers, prognosis, treatment outcome.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an aggressive malignancy of the head and neck, with particularly high prevalence in Southeast Asia and southern China (1). Although the global distribution of NPC is markedly uneven—reaching incidence rates of 20–30 cases per 100,000 individuals in East and Southeast Asia—it ranks only 24th in global cancer incidence and 22nd in mortality (2, 3). Due to the absence of early symptoms, approximately 70% of patients are diagnosed at the locally advanced stage (LANPC) (4). Surgical intervention plays a minimal role in NPC management due to the anatomical constraints of the nasopharyngeal region and is reserved mainly for locoregional recurrences or persistent neck disease (5). For early-stage NPC, radiotherapy (RT) alone remains the preferred treatment approach. In contrast, for LANPC, the high intrinsic radiosensitivity and chemosensitivity of the tumor have established platinum-based concurrent chemoradiotherapy (CCRT) delivered with intensity-modulated RT (IMRT) as the standard of care (6-9). IMRT-based CCRT has significantly improved toxicity profiles, locoregional control, and survival rates. Nonetheless, the overall 5-year survival rate for LANPC remains approximately 80% (10), with distant metastasis (DM) and, to a lesser extent, local and/or regional recurrences continuing to be the predominant causes of treatment failure and mortality (11).

The tumor-node-metastasis (TNM) staging framework is currently the gold standard for prognostic stratification and treatment decision-making for patients with NPC (12). However, it is frequently observed that patients with LANPC exhibit significantly varied outcomes despite receiving equivalent treatments for matching stages of the disease (12-14). The substantial variations in outcomes among patients diagnosed with identical stages of LANPC are primarily due to the limitations inherent in the current TNM staging system. This system fails to account for the biological differences among tumors and their respective hosts, as it relies exclusively on the local and regional progression of the primary tumor and the associated lymph nodes (15, 16). Therefore, such shortages in the TNM staging framework stress the urgent need to identify more relevant and innovative prognostic factors and potentially incorporate them into future staging systems.

Over half of all solid tumors contain hypoxic regions—termed tumor hypoxia—which represent a well-established surrogate marker of resistance to both RT and

chemotherapy across multiple cancer types, including NPC (17, 18). In irradiated cancer cells, molecular oxygen interacts with radiation-induced DNA radicals, thereby "fixing" the damage and preventing subsequent DNA repair, provided that adequate oxygen levels are present. Conversely, under hypoxic conditions, this oxygen fixation process is impaired, which allows for effective repair of DNA lesions and confers radioresistance to the tumor cell population. Beyond impairing radiosensitivity, tumor hypoxia promotes the stabilization of hypoxia-inducible factors (HIFs), which in turn drive neoangiogenesis, genomic instability, and accumulation of genetic mutations. These changes foster the emergence of aggressive tumor phenotypes that display marked resistance to apoptosis induced by reactive oxygen species (17-19). Clinical studies have consistently demonstrated that anemia and hemoglobin (Hb) levels below 11.0 g/dL are significantly associated with reduced median and long-term survival in patients with LANPC undergoing definitive CCRT (20–23).

Three other emerging factors closely linked to the prognosis of LANPC are the patient's nutritional, immune, and systemic inflammatory status. Two readily available and cost-effective biochemical parameters that simultaneously reflect these aspects are C-reactive protein (CRP) and serum albumin. The C-reactive protein-to-albumin ratio (CAR), a novel inflammation-based prognostic index, has demonstrated substantial prognostic value in patients with NPC (24, 25). Consistently, elevated CAR values have been associated with unfavorable outcomes across different treatment modalities and disease stages, including LANPCs (24, 25). While both Hb and CAR have been studied independently as prognostic markers in patients with LANPC, the potential of combining these two parameters into a single composite score has yet to be explored. Building on previous evidence supporting the individual prognostic significance of Hb and CAR, we hypothesized that integrating them into a unified score—referred to as the HCAR (Hb–CAR) score—could enhance prognostic discrimination compared to either parameter on its own. To evaluate this hypothesis, we conducted a retrospective analysis to determine the predictive value of the HCAR score in LANPC patients who underwent definitive CCRT followed by adjuvant chemotherapy.

MATERIALS AND METHODS

Study population, ethics, and consent

The research protocol received approval from the Institutional Review Board (IRB) of Baskent University Medical Faculty (Project No: D-KA-2058) prior to the commencement of patient data collection. This study was conducted in full compliance with the ethical standards set forth by the Declaration of Helsinki and its subsequent revisions. All participants who met the eligibility criteria were thoroughly informed about the study's objectives and voluntarily provided signed informed consent. This consent included permission for the collection and analysis of patient and disease characteristics, blood samples, and pathology specimens, as well as the anonymous dissemination of research findings in academic venues

Study design and participants

This study followed the reporting recommendations established by the REMARK guidelines (26). We executed a single-center, retrospective cohort study at the Department of Radiation Oncology at Baskent University Medical Faculty. Our investigation involved a thorough review of the medical records for patients diagnosed with LANPC who underwent CCRT at our institution from June 2011 to December 2020.

Eligible patients were required to meet all of the following criteria: age between 18 and 80 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and a body mass index (BMI) ≥18.5 kg/m². Pretreatment evaluations had to include a complete clinical ear–nose–throat (ENT) examination, head and neck magnetic resonance imaging (MRI), and fluorodeoxyglucose-positron emission computed tomography (FDG-PET/CT). Disease staging was based on the 8th edition of the American Joint Committee on Cancer (AJCC) staging system, and included clinical or radiological stages T3-4N0-3M0 or T1-4N1-3M0. Histopathological confirmation of non-keratinizing or undifferentiated squamous cell carcinoma was mandatory. World Health Organization (WHO) type I keratinizing nasopharyngeal carcinoma was not included because of its extreme rarity in our population and its well-recognized biological and prognostic distinctions from WHO type II/III tumors.

Patients were excluded if they had a history of other malignancies, prior chemotherapy or RT, active infectious diseases, or immunosuppressive drug use

within 30 days before starting CCRT. All included patients must have received at least one cycle of platinum-based concurrent chemotherapy. Additionally, the availability of complete RT and chemotherapy records, baseline complete blood count results, and follow-up ENT examinations, MRI, and PET-CT scans was required for inclusion.

Chemoradiotherapy protocol

All research participants received definitive CCRT with previously established dosages of RT and chemotherapy (22). All patients were treated with simultaneous integrated boost–intensity-modulated radiotherapy (SIB-IMRT) following a uniform institutional protocol. Target volumes were defined according to contemporary international guidelines for nasopharyngeal carcinoma. The gross tumor volume (GTV) included the primary nasopharyngeal tumor and any involved lymph nodes identified on MRI and/or PET-CT. The high-risk clinical target volume (CTV1) encompassed the GTV with a 5–10 mm margin adjusted to anatomical boundaries, including regions at highest risk for microscopic extension. The low-risk clinical target volume (CTV2) included bilateral cervical nodal regions at risk but without radiologic involvement. Planning target volumes (PTVs) were generated by expanding each CTV by 3–5 mm to account for setup uncertainties. A three-level SIB-IMRT prescription was used for all patients: 70 Gy to PTV-GTV, 60 Gy to PTV-CTV1, and 54 Gy to PTV-CTV2, delivered in 33 fractions over 6.5 weeks. Treatment planning was performed exclusively using the Varian Eclipse treatment planning system with 6-MV photon beams. Dose constraints adhered to departmental standards, including maximum allowable doses of <45 Gy to the spinal cord, <54 Gy to the brainstem and optic chiasm, and a mean parotid dose of ≤26 Gy whenever feasible. Constraints for the temporal lobes, cochleae, mandible, and other organs at risk were set according to international NPC IMRT guidelines. Daily image guidance was performed using kilovoltage (kV) orthogonal imaging and/or cone-beam CT to ensure accurate patient positioning and reproducibility throughout the treatment course. All patients received concurrent cisplatin 75–80 mg/m² every 3 weeks; adjuvant chemotherapy was administered for two cycles when tolerated. Appropriate supportive care interventions, including oral or intravenous hydration, antiemetic agents, and oral or enteral nutritional supplements, were administered as clinically warranted.

Measurement of hemoglobin and C-reactive protein-to-albumin ratio (CAR): construction of the HCAR score

Pretreatment Hb, CRP, and albumin levels were measured on the first day of CCRT using a standardized automated chemistry analyzer (Beckman Coulter AU-series). CRP values were reported in mg/L and albumin in g/L, with internal quality-control (QC) procedures performed daily in accordance with manufacturer standards (typical institutional QC ranges: CRP 0–5 mg/L; albumin 35–50 g/L). The C-reactive-protein-to-albumin ratio (CAR) was calculated as: CRP (mg/L) ÷ albumin (g/L).

Response assessment

This study employed a retrospective design, but the evaluation of treatment response was conducted prospectively according to institutional protocols. During the first two years of follow-up, patients received clinical and radiological assessments every three months. This frequency then changed to every six months during years three through five, and later shifted to annual evaluations or more frequently if clinically necessary. Endoscopic examinations were routinely performed at each follow-up to detect local or regional tumor recurrences and any second primary tumors of the head and neck region. To assess treatment response and identify possible distant metastases, PET-CT scans were used following the PET Response Criteria for Solid Tumors (PERCIST). Subsequent imaging surveillance primarily consisted of MRI and/or CT scans of the head and neck instead of PET-CT scans, once we established a complete metabolic response. Additional imaging methods were utilized for further investigation of suspicious lesions or to reassess cases where tumor recurrence was suspected.

Clinical endpoints and statistics

The primary objective of this study was to evaluate the prognostic significance of the HCAR score for overall survival (OS) in patients with LANPC treated with CCRT. OS was calculated from the onset of CCRT to death from any cause, with patients who were alive at last contact censored at their most recent follow-up visit. The secondary objective was to assess the association between the HCAR score and progression-free survival (PFS), defined as the interval from the onset of CCRT to the first documented relapse or death. Patients without an event were right-censored at the date of last clinical contact.

Continuous variables were summarized as medians and ranges, while categorical variables were described as frequency distributions. Baseline characteristics were compared using distribution-appropriate tests: chi-square or Fisher's exact tests for categorical variables (according to expected cell frequencies) and Student's t-tests or non-parametric aligned rank tests for continuous variables, depending on distributional assumptions. Effect sizes (mean differences or risk ratios) with corresponding 95% confidence intervals were calculated to supplement P-values and enhance clinical interpretability.

Receiver operating characteristic (ROC) curve analysis was performed to determine optimal pre-CCRT hemoglobin and CAR cut-off values that yielded maximal separation of OS and PFS outcomes. All ROC analyses were performed using conventional status-based (binary outcome) ROC with OS or PFS status at last follow-up as the classifier, rather than time-dependent ROC. Kaplan–Meier curves and log-rank tests were used to examine associations between clinical or biomarker variables and survival outcomes. Variables demonstrating significance in univariate analysis were subsequently entered into multivariable Cox proportional hazards models to evaluate their independent prognostic contribution. For all comparisons, a two-tailed P value < 0.05 was considered statistically significant. Bonferroni-adjusted P-values were used for comparisons involving three or more groups, including analyses across HCAR score categories, to reduce the risk of false-positive findings.

Cox proportional hazards model diagnostics were conducted to assess model adequacy. The proportional hazards (PH) assumption was evaluated using Schoenfeld residual–based tests and visual inspection of log–log survival plots. The functional form of continuous variables (hemoglobin, CAR, and age) was examined using residual-based diagnostics to detect non-linearity. Influential observations were assessed using dfbeta statistics to identify cases exerting disproportionate influence on model coefficients. Model discrimination was quantified using Harrell's C-index with 95% confidence intervals, and calibration was assessed using the calibration slope and intercept. Additional details are provided in Supplementary Material 1.

A total of 105 progression-free survival (PFS) events and 83 overall survival (OS) events contributed to the multivariable Cox models. To further ensure the adequacy of the multivariable models, we documented the number of events contributing to each

Cox model and evaluated the corresponding events-per-variable (EPV). All models satisfied commonly accepted EPV thresholds for exploratory prognostic Cox regression, supporting stability of coefficient estimation and minimizing the risk of overfitting. Because only essential covariates were included and EPV criteria were met, penalized Cox regression was not required within the scope of this study.

Assessment of incremental prognostic value using nested Cox models (e.g., Hb-only, CAR-only, HCAR-only, or HCAR + TNM) was not performed because the number of available events did not support the additional model complexity. Although the primary multivariable model met acceptable events-per-variable (EPV) criteria, constructing multiple nested alternatives would have substantially reduced EPV, leading to unstable coefficient estimates and increasing the risk of overfitting. Under these constraints, likelihood-ratio testing, ΔC-index estimation, and AIC-based comparisons would not yield reliable or interpretable incremental-value estimates. For these reasons, nested-model evaluation was deferred to future studies with larger event counts.

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

Ethics approval and consent to participate

Before acquiring any information from the patient, the study design has been approved by the Institutional Review Board of the Baskent University School of Medicine and has complied with the Declaration of Helsinki.

RESULTS

A total of 233 patients with LANPC who underwent definitive CCRT were eligible for inclusion (Table 1). The median age was 57 years (range, 19–79 years) at presentation, and 33.5% of patients were aged 65 years or older. Males comprised the majority of the cohort (80.0%). All patients had an ECOG performance status of 0 (47.6%) or 1 (52.4%). Histologically, most patients (87.1%) had a WHO type III undifferentiated carcinoma, while the remainder had a WHO type II. The majority presented with advanced primary and nodal disease, with 81.1% staged T3–4 and 78.1% staged N2–3. Treatment compliance was relatively high (Table 1). A total of 72.5% of patients completed all three prescribed cycles of concurrent cisplatin, while

27.5% received one or two cycles of treatment. Following CCRT, 73.0% of patients proceeded to adjuvant chemotherapy, with the majority receiving two cycles (58.4%). The median interval between pathological diagnosis and initiation of CCRT was 18 days (range: 9–28).

At a median follow-up of 85.7 months (95% CI, 67.9–103.5), 150 patients (64.4%) were alive, and 128 (54.9%) remained free of disease progression. Local control was achieved in 212 patients (91.4%). The median PFS was 66.0 months (95% CI, 53.6–78.4), with 5- and 10-year PFS rates of 52.8% and 31.6%, respectively. The median OS was 108.0 months (95% CI, 92.3–123.7), and the corresponding 5- and 10-year OS rates were 75.9% and 43.1% (Table 2).

ROC curve analyses were performed separately for each biomarker–endpoint pair, and the results are summarized in Supplementary Table S1. For Hb, the optimal cut-off for OS was 11.1 g/dL (AUC: 0.816, sensitivity: 77.9%, specificity: 76.8%, Youden J: 0.547), while the optimal cut-off for PFS was 10.9 g/dL (AUC: 0.789, sensitivity: 75.3%, specificity: 72.4%, Youden J: 0.477). For CAR, the OS-specific cut-off was 2.95 (AUC: 0.872, sensitivity: 82.1%, specificity: 76.1%, Youden J: 0.582), and the PFS-specific cut-off was 3.10 (AUC: 0.804, sensitivity: 78.3%, specificity: 75.2%, Youden J: 0.535) (Figure 1). Because these OS- and PFS-specific Hb and CAR values were close to each other across endpoints, we selected rounded thresholds of 11.0 g/dL for Hb and 3.0 for CAR for all subsequent analyses. Using these cut-offs, four possible HCAR score groups were created: HCAR-0: Hb $\geq$ 11.0 and CAR < 3.0; HCAR-1: Hb $\geq$ 11.0 and CAR $\geq$ 3.0; HCAR-2: Hb < 11.0 and CAR < 3.0; and HCAR-3: Hb < 11.0 and CAR $\geq$ 3.0. However, because comparisons between four groups revealed no statistically meaningful differences in terms of either PFS or OS between the original HCAR-1 and HCAR-2 groups (Supplementary Table S2), these two groups were merged, creating the final three-tiered HCAR score groups: HCAR-0 (Hb $\geq$ 11.0 and CAR < 3.0), HCAR-1 (Hb $\geq$ 11.0 and CAR $\geq$ 3.0 or Hb < 11.0 and CAR < 3.0), and HCAR-2 (Hb < 11.0 and CAR $\geq$ 3.0). Comparative survival analyses between the three HCAR groups indicated that the median PFS (not reached vs.66.0 vs. 25.0 months; P < 0.001) and median OS (not reached vs.108.0 vs. 55.0; P < 0.001) durations were significantly longer in the HCAR-0 group, with the HCAR-2 group having the shortest durations and the HCAR-1 group lying in between them (Table 2 and Figure 2). Corresponding 5-year and 10-year PFS and OS rates were also

more favorable in the HCAR-0 than the HCAR-1 and HCAR-2 groups. Similarly, the HCAR-1 group had superior 5-year and 10-year PFS and OS rates than its HCAR-2 counterpart (Table 2). Importantly, these findings were observed without any statistically significant imbalances in baseline demographic, clinical, or treatment-related variables across the three HCAR groups (all Bonferroni corrected $P > 0.0167$; Table 1). Additionally, effect sizes with 95% confidence intervals were uniformly small and demonstrated no clinically meaningful baseline imbalances across HCAR groups, further supporting the comparability of the cohorts (Supplementary Table 3). Notably, there were no statistically significant differences in treatment adherence among the HCAR categories regarding the concurrent ($P = 0.87$) and adjuvant chemotherapy cycles ($P= 0.42$), which suggests that the observed outcome differences cannot be attributed to variations in treatment compliance.

In the univariate analysis, T stage (PFS: $P = 0.008$; OS: $P = 0.003$), N stage (PFS: $P < 0.001$; OS: $P < 0.001$), and HCAR score (PFS: $P < 0.001$; OS: $P < 0.001$) were identified as significant prognostic indicators. Conversely, factors such as age, gender, ECOG performance status, histology, and the number of cycles of concurrent or adjuvant chemotherapy showed no correlation with outcomes (Table 3). Furthermore, multivariate Cox regression analysis confirmed that HCAR score, T stage, and N stage serve as independent prognostic factors for both PFS and OS (Table 3).

Because the prognostic strengths of the anatomic components were markedly different in our cohort—N stage showing a highly significant association with PFS ($p < 0.001$), whereas T stage demonstrated a much weaker effect ($p = 0.011$)—the combined AJCC/UICC stage group was not included in the multivariate model. As all patients had M0 disease, the stage group represents a deterministic composite of T and N; incorporating this variable would introduce structural collinearity and obscure the independent contribution of each component. This well-known masking phenomenon, in which the more decisive factor (N) accounts for most of the shared variance, can lead to unstable or biased hazard estimates. For this reason, stage distributions are presented descriptively in Table 1, while only variables demonstrating independent prognostic value without collinearity concerns were retained in the final multivariable analysis. Importantly, in univariate analyses (Kaplan–Meier and univariate Cox), AJCC/UICC stage group exhibited patterns fully consistent with the separate T- and N-stage effects, with N stage functioning as the principal prognostic determinant;

therefore, no prognostic information was lost by excluding stage group from the multivariable model. Model performance assessment demonstrated acceptable discrimination (PFS C-index: 0.71, OS C-index: 0.73) and good calibration for both multivariable models; full metrics are provided in Supplementary Material 1.

DISCUSSION

In this retrospective cohort analysis, our results have shown that the novel three-tiered HCAR score introduced here, derived from baseline Hb levels and the calculated CAR values, is an independent prognostic biomarker for both PFS and OS in patients with LANPC treated with definitive CCRT. To our knowledge, this is the first study to integrate a host-related hypoxia surrogate (Hb) with an immune-inflammation–nutrition index (CAR) into a composite score and systematically evaluate its prognostic value in this patient population.

Our findings reaffirm the established prognostic significance of T and N stages, which together constitute the foundation of the TNM staging system in non-metastatic NPC (27). However, notable heterogeneity is frequently observed in survival outcomes among patients with LANPC at the same stage of disease, despite receiving similar CCRT regimens (22, 28). Illustrating the extent of wide variations in the survival outcomes of LANPC patients presenting with identical TN stages, the 95% CIs ranged from 53.6 to 78.4 months for PFS and from 92.3 to 123.7 months for OS in our study, corresponding to 24.8 and 31.4 months between the lower and upper ends of the 95% CI of the two survival endpoints, respectively. The observed variations clearly indicate that anatomical staging is inadequate for fully comprehending the complex biological and host-related factors that affect treatment responses and outcomes (15, 16, 29). Therefore, there is a pressing need to incorporate additional prognostic markers that accurately reflect tumor biology as well as the specific systemic conditions of patients. In this context, while both Hb and CAR have been independently validated as prognostic factors in LANPC, to our knowledge, no prior study has combined these parameters into a cohesive scoring system (20-25). Consequently, we developed the HCAR score, an innovative composite biomarker that combines Hb, a surrogate for tumor oxygenation and radiosensitivity, with the CAR, which serves as a recognized indicator of systemic inflammation, immune

competence, and nutritional status to complement the TNM staging system, aiming to improve the accuracy of outcome predictions in these patients.

The principal contribution of this study is the introduction of the HCAR Score, the first prognostic model to integrate Hb and CAR into a single, clinically accessible composite index for LANPC patients. The HCAR scoring system effectively stratified patients into three distinct prognostic groups with markedly different PFS and OS outcomes: HCAR-0 patients demonstrated excellent long-term survival (10-year OS 68.3%), HCAR-2 patients had poor outcomes (10-year OS 11.1%), and HCAR-1 patients exhibited intermediate survival (10-year OS 41.6%). These findings underscore the additive prognostic value of jointly capturing systemic oxygenation, inflammatory, immune, and nutritional status in LANPC patients. Importantly, the prognostic significance of the HCAR Score was independent of T and N stages, and the observed survival differences were not attributable to baseline clinicopathologic imbalances or variations in the intensity of concurrent or adjuvant chemotherapy. Collectively, these results suggest that the HCAR Score may serve as a practical complement to conventional TNM staging, enabling more refined risk stratification and informing personalized therapeutic strategies for patients with LANPC.

Interpreting these novel findings in relation to the existing literature on LANPC is unattainable due to the absence of prior research examining the prognostic implication of the HCAR Score in this patient population. Nevertheless, these findings are compatible with prior reports on the prognostic relevance of Hb and CAR, which together constitute the HCAR Score, in similar LANPC cohorts (20-25). For instance, Topkan and colleagues demonstrated that pre-CCRT Hb levels below 11.0 g/dL were independently associated with significantly inferior median OS ($P < 0.001$), PFS ($P < 0.001$), and locoregional PFS ($P = 0.004$) (22). Notably, this association was more superior than that observed after categorizing patients according to the customary anemia cut-offs for men and women established by the World Health Organization (30). These findings were later affirmed by a recent study reported by Cobanoglu et al. (31). Likewise, Guo and colleagues. showed that Hb levels, measured both before and during CCRT and categorized as anemic or non-anemic, are significant prognostic markers for survival outcomes in NPC patients treated with IMRT (21). Considering the implications of the CAR, prior studies on NPC patients treated with definitive RT have consistently demonstrated a strong association between elevated pretreatment

CAR values and unfavorable clinical outcomes. For example, Tao and colleagues reported that NPC patients undergoing IMRT with high CAR values had significantly lower 5-year OS compared to those with low CAR values (78.1% vs. 91.9%; $P < 0.001$) (32). Similarly, a meta-analysis by Yang and colleagues confirmed that elevated pretreatment CAR is an adverse prognostic indicator, showing significant correlations with both inferior OS (HR = 1.58, 95% CI = 1.36–1.83, $P < 0.001$) and reduced distant metastasis-free survival (HR = 1.25, 95% CI = 1.09–1.44, P = 0.002) (25). Taken together, the available research results underscore the prognostic utility of Hb and CAR providing a compelling rationale for their integration into a single composite index, namely HCAR Score, to improve risk stratification and guide treatment personalization in NPC. Nonetheless, confirmatory evidence from rigorously designed studies is needed before the HCAR Score can be adopted as an adjunct to the TNM staging system for patients with LANPC.

The precise biological mechanisms linking an elevated HCAR Score to poorer PFS and overall survival OS remain to be fully comprehended. However, prior research has highlighted the critical roles of its components—Hb, albumin, and CRP—in tissue oxygenation, nutritional status, systemic inflammation, and immune regulation functions (17–25). These factors have been associated with facilitated tumor growth, metastatic spread, resistance to treatment, and ultimately, a poorer prognosis, which may explain the unfavorable outcomes observed in patients with higher HCAR scores (25, 33–35). Nevertheless, the clinical implications of our findings may be substantial, as Hb and CAR are inexpensive, routinely available laboratory parameters, allowing the HCAR score to be easily incorporated into clinical practice without additional testing. Importantly, the incremental prognostic value of the HCAR score beyond hemoglobin or CAR individually was not quantified in this exploratory dataset; whether HCAR offers additional discrimination or reclassification benefit over single-marker models remains to be determined in larger studies with sufficient statistical power. By stratifying patients into three prognostic categories, the score can help tailor treatment—escalating therapy, increasing surveillance, or adding novel agents for high-risk patients (HCAR-2), while identifying low-risk patients (HCAR-0) who may achieve excellent outcomes with standard CCRT and avoid unnecessary intensification. Its prognostic independence from T and N stages further supports its role as an additional stratification factor in future clinical trials, enabling risk-adapted

designs and more precise evaluation of novel therapies in LANPC. If prospectively validated in large, multi-institutional cohorts, the HCAR score could provide a practical step toward more personalized and biologically informed patient management.

This study has several limitations. First, its retrospective, single-institution design introduces potential selection bias, despite generally balanced baseline characteristics across the HCAR groups. Second, although the cohort size and follow-up duration were adequate, external validation in independent, multi-institutional datasets is required to confirm generalizability. Third, hemoglobin and CAR are dynamic biomarkers that may fluctuate during treatment; our analysis relied solely on baseline measurements, and future prospective studies should evaluate the prognostic relevance of on-treatment or post-treatment changes in the HCAR score. Fourth, despite the biological rationale for integrating hemoglobin and CAR, mechanistic studies are needed to clarify how different HCAR strata influence NPC progression and CCRT resistance. Fifth, hemoglobin and CAR were dichotomized using ROC-derived cut-offs rather than modeled as continuous predictors through flexible methods such as restricted cubic splines. While this approach enabled the construction of a simple, clinically practical score, it may not fully capture the continuous nature of these biomarkers. Additionally, EBV DNA levels, LDH, smoking status, and comorbidity indices were not uniformly available and could not be incorporated into the sensitivity analyses, which represents another limitation. Larger multicenter cohorts should explore spline-based modeling, coefficient-derived scoring, and formal internal validation (e.g., bootstrap optimism-correction, calibration assessment, and cross-validated C-indices) to determine whether refined HCAR frameworks offer superior prognostic performance. Because our dataset contained a limited number of events and was not originally designed for complete model construction, rigorous internal validation and nested-model comparisons could not be performed without risking model instability. Consequently, some degree of optimism is expected regarding ROC-derived cut-offs and performance estimates, and the present findings should be interpreted as preliminary until confirmed in larger, independently validated cohorts.

CONCLUSION

In conclusion, this study introduced the HCAR score as a novel composite biomarker that can effectively stratify LANPC patients into three distinct prognostic groups before the initiation of definitive CCRT. By simultaneously reflecting host hypoxia status, systemic immune response, inflammation levels, and nutritional reserve, the HCAR score has the potential to enhance risk stratification when used in conjunction with the traditional TNM staging system, if validated by future research.

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Data availability: Data cannot be shared publicly because it is owned and saved by the Baskent University Medical Faculty. However, for researchers who meet the criteria for access to confidential data, data are available from the Baskent University Institutional Data Access / Ethics Committee (contact via Baskent University Ethics Committee): contact address, adanabaskent@baskent.edu.tr.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Baseline demographic, clinical, and treatment-related characteristics of the entire study cohort and according to HCAR groups

Characteristics	**Whole cohort (*n* = 233)**	**HCAR-0 (*n*=88)**	**HCAR-1 (*n*=91)**	**HCAR-2 (*n*=54)**	***p* value**
Median age, years (range)	57 (19 - 79)	58 (27 - 79)	57 (28 - 79)	56 (19 - 77)	0.86
Age group (N; %)					
≥ 65 years	78 (33.5)	31 (35.2)	33 (36.3)	14 (25.9)	0.19
< 65 years	155 (66.5)	57 (64.8)	58 (63.7)	40 (74.1)	
Gender (N; %)					
Male	184 (80.0)	71 (80.7)	71 (78.0)	42 (77.8)	0.86
Female	49 (20.0)	17 (19.3)	20 (22.0)	12 (22.2)	
ECOG performance (N; %)					
0	111 (47.6)	43 (48.9)	46 (50.5)	22 (40.7)	0.28
1	122 (52.4)	45 (51.1)	45 (49.5)	32 (59.3)	
WHO histology (N; %)					
2	30 (12.9)	12 (13.6)	11 (12.1)	7 (13.0)	0.84
3	203 (87.1)	76 (86.4)	80 (87.9)	47 (87.0)	
T-stage (N; %)					
1-2	44 (18.9)	17 (19.3)	18 (19.8)	9 (16.7)	0.63
3-4	189 (81.1)	71 (80.7)	73 (80.2)	45 (83.3)	
N-stage (N; %)					
0-1	51 (21.9)	18 (20.5)	20 (22.0)	13 (24.1)	0.57
2-3	182 (78.1)	70 (79.5)	71 (78.0)	41 (75.9)	
Concurrent chemotherapy cycles (N; %)	64 (27.5)	24 (27.3)	25 (27.5)	15 (27.8)	0.87
1-2	169 (72.5)	64 (72.7)	66 (72.5)	39 (72.2)	
3					
Adjuvant chemotherapy cycles (N; %)	63 (27.0)	25 (28.4)	26 (28.6)	12 (22.2)	0.42

0 1-2	170 (73.0)	63 (71.6)	65 (71.4)	42 (77.8)	

The Bonferroni corrected *p* value is significant at < 0.0167. Corresponding effect size estimates, along with their 95% confidence intervals, are detailed in Supplementary Table S3. Abbreviations: HCAR: Combination of Hb and the CAR; Hb: Hemoglobin; CAR: C-reactive-protein-to-albumin ratio; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; T-stage: Tumor stage; N-stage: Nodal stage.

Table 2. Survival outcomes for the overall study population and groups categorized by HCAR score

Outcome	Whole cohort (*n* = 233)	HCAR-0 (*n* = 88)	HCAR- 1 (*n* = 91)	HCAR- 2 (*n* = 54)	*p* value
Progression-free survival					
Median; mo. (95% CI)	66.0 (53.6 – 78.4)	NR	66.0 (50.6 – 81.4)	25.0 (17.8 – 32.2)	< 0.001
5-year (%)	52.8	66.0	52.2	33.3	
10-year (%)	31.6	50.2	34.4	5.0	
Overall survival					
Median; mo. (95% CI)	108.0 (92.3 – 123.7)	NR	108.0 (89.3 – 126.7)	55.0 (43.8 – 66.2)	< 0.001
5-year (%)	75.9	83.7	78.5	48.3	
10-year (%)	43.1	68.3	41.6	11.1	

Significant Bonferroni corrected *p* value: < 0.0167. Abbreviations: HCAR: Combination of hemoglobin (Hb) and the C-reactive-protein-to-albumin ratio (CAR); CI: Confidence interval; mo: Months; NR: Not reached.

Table 3. Univariate and multivariate Cox regression analyses of prognostic factors for progression-free survival and overall survival.

	PFS			OS		
Factor	**Univariate *p* value**	**Multivariate *p* value**	**HR (95% CI)**	**Univariate *p* value**	**Multivariate *p* value**	**HR (95% CI)**
Age group (<65vs. ≥65 y)	0.63	–	–	0.57	–	–
Gender (Male vs. Female)	0.69	–	–	0.61	–	–
ECOG (0 vs. 1)	0.88	–	–	0.82	–	–
WHO histology (2 vs. 3)	0.76	–	–	0.63	–	–
T-stage (1-2 vs. 3-4)	0.008	0.011	0.65 (0.42 – 0.83)	0.003	0.009	0.52 (0.33 – 0.81)
N-stage (0-1 vs. 2-3)	< 0.001	0.001	0.47 (0.37 - 0.78)	< 0.001	0.001	0.44 (0.22 – 0.69)
Concurrent chemotherapy cycles (1-2 vs. 3)	0.27	–	–	0.22	–	–
Adjuvant chemotherapy cycles (0 vs. 1-2)	0.43	–	–	0.49	–	–
HCAR group (reference = HCAR-0)[a]	0.012	0.014	1.76 (1.34 – 2.93)	0.007	0.011	3.06 (1.89 – 5.12)
1 vs. 0	< 0.001	< 0.001		< 0.001	< 0.001	9.17 (6.12 – 15.62)
2 vs. 0	< 0.001	< 0.001	7.69 (5.17 –	< 0.001	< 0.001	5.84 (4.18 – 7.26)

2 vs. 1			11.84) 3.76 (2.28 – 4.98)			

Events included in the Cox models: 105 PFS events; 83 OS events. [a] Significant Bonferroni corrected P-value: < 0.0167. Abbreviations: PFS: Progression-free survival; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; T-stage: Tumor stage; N-stage: Nodal stage; HCAR score = combination of hemoglobin (Hb) and the C-reactive-protein-to-albumin ratio (CAR).

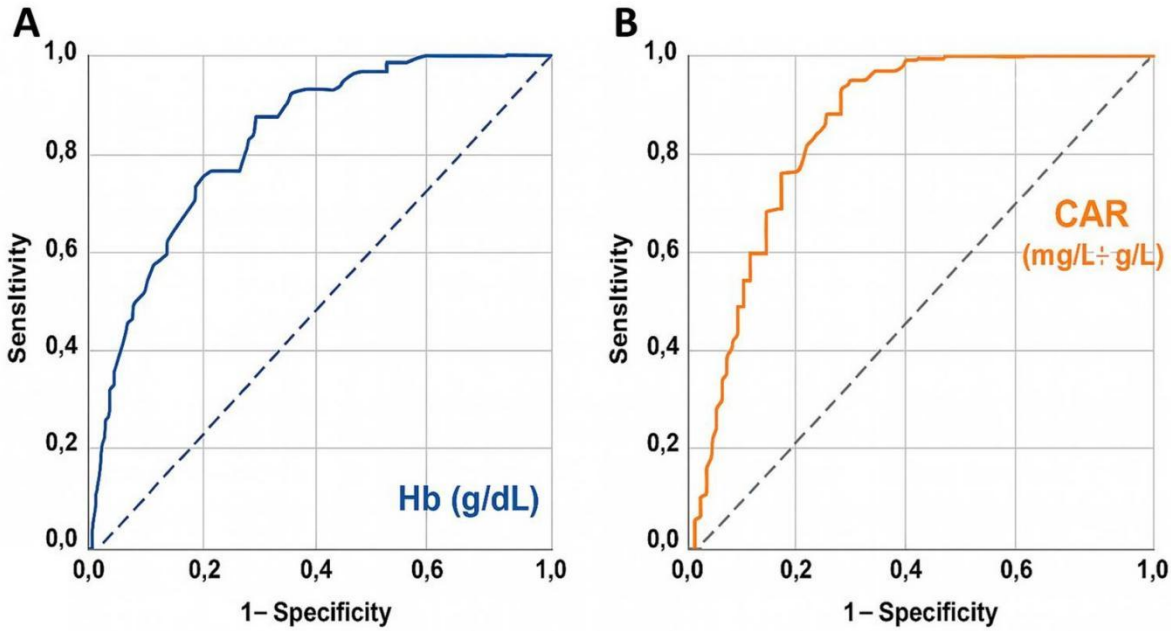

Figure 1. ROC curve analysis assessing the relationship between OS and pretreatment biomarkers. (A) the association between pretreatment Hb levels and OS status, and (B) the relationship between the pretreatment CAR and OS status. PFS-specific ROC performance is detailed in Supplementary Table S1. Abbreviations: ROC: Receiver Operating Characteristic; OS: Overall survival; Hb: Hemoglobin; CAR: C-reactive protein-to-albumin ratio; PFS: Progression-free survival.

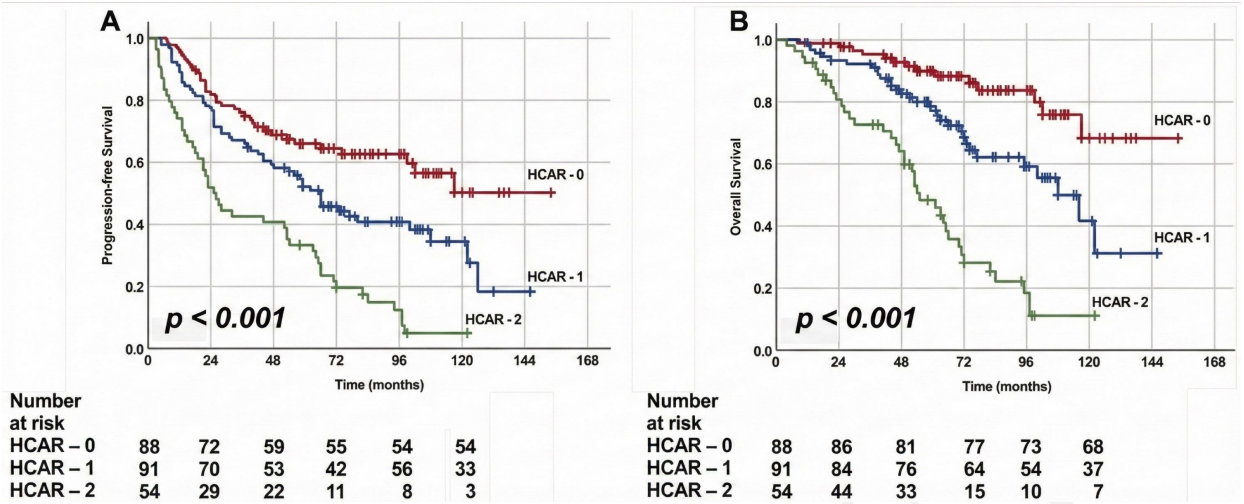

Figure 2. Kaplan–Meier curves for (A) progression-free survival and (B) overall survival according to the three-tiered HCAR score. The HCAR score was derived from pretreatment Hb and CAR using cut-offs of 11.0 g/dL and 3.0, respectively, and categorized as HCAR-0 (Hb ≥11.0 and CAR <3.0), HCAR-1 (Hb ≥11.0 and CAR ≥3.0 or Hb <11.0 and CAR <3.0), and HCAR-2 (Hb <11.0 and CAR ≥3.0). Both progression-free and overall survival differed significantly across HCAR groups (log-rank $p < 0.001$). Numbers at risk at selected time points are shown below each plot. Abbreviations: HCAR: Combination of hemoglobin (Hb) and the C-reactive-protein-to-albumin ratio (CAR); Hb: Hemoglobin; CAR: C-reactive-protein-to-albumin ratio; PFS: Progression-free survival; OS: Overall survival.

SUPPLEMENTAL DATA

Supplemental data are available at the following link:

https://www.bjbms.org/ojs/index.php/bjbms/article/view/13398/4069