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**SUPPLEMENTAL DATA**

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

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**Full article is available at the following link:** HCAR score as a prognostic biomarker of survival in locally advanced nasopharyngeal carcinoma treated with concurrent chemoradiotherapy

**Supplementary material 1. Cox model diagnostics**

To complement the primary statistical analyses, additional diagnostic procedures were performed to evaluate the adequacy of the multivariable Cox proportional hazards models. The proportional hazards (PH) assumption was examined using Schoenfeld residual–based tests and visual inspection of log–log survival plots. No meaningful violations of the PH assumption were detected, either for individual covariates or for the global model. Residual-based diagnostics were applied to assess the functional form of continuous predictors, including pretreatment hemoglobin, CAR, and age. No significant departures from linearity were observed, supporting the use of these variables in their current forms. Influential case assessment using dfbeta statistics did not identify any observations exerting disproportionate influence on estimated regression coefficients, indicating stability of the multivariable model.

Model discrimination was quantified using Harrell's C-index, reported with corresponding 95% confidence intervals. For the multivariable progression-free survival (PFS) model, Harrell's C-index was 0.71 (95% CI: 0.67–0.75). For the multivariable overall survival (OS) model, Harrell's C-index was 0.73 (95% CI: 0.69–0.77).

Model calibration was summarized using the calibration slope and intercept, demonstrating acceptable agreement between predicted and observed survival probabilities. The calibration slope and intercept were 0.94 and 0.03, respectively, for the PFS model, and 0.97 and 0.02, respectively, for the OS model.

Taken together, these diagnostic evaluations, including proportional hazards testing, functional-form assessment, influential case diagnostics, discrimination, and calibration,support the adequacy and stability of the final multivariable Cox models used in this study.

**Supplementary table S1. Endpoint-specific receiver operating characteristic curve analysis performance of hemoglobin and CAR for OS and PFS**

| Biomarker | Endpoint | AUC (95% CI) | Sensitivity (%) | Specificity (%) | Youden J | Optimal Cut-off |
|---|---|---|---|---|---|---|
| Hemoglobin (g/dL) | OS | 0.816 (0.762–0.869) | 77.9 | 76.8 | 0.547 | 11.1 g/dL |
| Hemoglobin (g/dL) | PFS | 0.789 (0.731–0.846) | 75.3 | 72.4 | 0.477 | 10.9 g/dL |
| CAR | OS | 0.872 (0.829–0.915) | 82.1 | 76.1 | 0.582 | 2.95 |
| CAR | PFS | 0.804 (0.753–0.855) | 78.3 | 75.2 | 0.535 | 3.10 |

Final dichotomization thresholds were established at 11.0 g/dL for hemoglobin and 3.0 for CAR, as these values closely approximated the optimal OS and PFS cut-offs identified in the analyses. Abbreviations: ROC: Receiver operating characteristic; CAR: C-reactive protein-to albümin ratio; OS: Overall survival; PFS: Progression-free survival; AUC: Area under the curve.

**Supplementary table S2. Pairwise comparisons of the four originally defined HCAR categories**

| HCAR Group | Definition | *n* | Median PFS (mo) | Median OS (mo) | Key Pairwise Comparison | HR (95% CI) | Raw P | Bonferroni-adjusted P |
|---|---|---|---|---|---|---|---|---|
| **HCAR-0** | Hb ≥11.0 g/dL and CAR <3.0 | 88 | Not reached | Not reached | vs HCAR-3 (PFS)<br>vs HCAR-3 (OS) | 0.38 (0.24–0.59)<br>0.47 (0.28–0.80) | <0.001<br>0.005 | <0.001<br>0.015 |
| **HCAR-1** | Hb ≥11.0 g/dL and CAR ≥3.0 | 44 | 63.0 | 112.0 | vs HCAR-2 (PFS)<br>vs HCAR-2 (OS) | 1.05 (0.69–1.58)<br>1.06 (0.58–1.92) | 0.612<br>0.641 | 0.207<br>0.234 |
| **HCAR-2** | Hb <11.0 g/dL and CAR <3.0 | 47 | 68.0 | 105.0 | vs HCAR-1 (PFS) | 1.05 (0.69–1.58) | 0.612 | 0.204 |
| **HCAR-3** | Hb <11.0 g/dL and CAR ≥3.0 | 54 | 25.0 | 55.0 | vs HCAR-1 (PFS)<br>vs HCAR-2 (PFS)<br>vs HCAR-1 (OS)<br>vs HCAR-2 (OS) | 0.43 (0.27–0.66)<br>0.41 (0.26–0.63)<br>0.55 (0.33–0.92) | <0.001<br><0.001<br>0.021 | 0.003<br>0.003<br>0.063<br>0.042 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 0.52 (0.31–0.89) | | |

Pairwise comparisons reveal that HCAR-1 and HCAR-2 exhibited no significant differences in PFS or OS (all Bonferroni-adjusted $P > 0.0167$; HR ≈ 1.0). This finding supports their consolidation into the intermediate-risk category within the final three-tier HCAR classification. HCAR-0 consistently demonstrated the most favorable outcomes, while HCAR-3 exhibited the poorest survival rates. Abbreviations: HCAR: Hemoglobin and C-reactive protein-to-albumin ratio composite score; Hb: Hemoglobin; CAR: C-reactive protein-to-albumin ratio; PFS: Progression-free survival; OS: Overall survival: HR: Hazard ratio; CI: Confidence interval; n: Number of patients; Bonferroni P: Bonferroni-adjusted P-value for multiple comparisons.

**Supplementary table S3. Effect-size estimates (with 95% confidence intervals) for baseline demographic, clinical, and treatment-related characteristics across HCAR groups**

| Characteristic | Comparison | Effect size (risk ratio) | 95% CI |
|---|---|---|---|
| Age ≥ 65 years (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 1.03<br>0.74 | 0.69 – 1.53<br>0.43 – 1.25 |
| | | | |
| Male sex (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 0.97<br>0.96 | 0.83 – 1.12<br>0.81 – 1.15 |
| | | | |
| ECOG PS = 1 (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 0.97<br>1.16 | 0.72 – 1.29<br>0.86 – 1.57 |
| | | | |
| WHO Type III (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 1.02<br>1.01 | 0.91 – 1.14<br>0.88 – 1.15 |
| | | | |
| T3–4 stage (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 0.99<br>1.03 | 0.86 – 1.15<br>0.88 – 1.21 |
| | | | |
| N2–3 stage (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 0.98<br>0.95 | 0.84 – 1.14<br>0.79 – |

| | | | |
|---|---|---|---|
| | | | 1.15 |
| | | | |
| Concurrent chemotherapy: 3 cycles (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 1.00<br>0.99 | 0.83 – 1.19<br>0.81 – 1.22 |
| | | | |
| Adjuvant chemotherapy: 1–2 cycles (%) | HCAR-1 vs HCAR-0 HCAR-2 vs HCAR-0 | 1.00<br>1.09 | 0.83 – 1.20<br>0.89 – 1.32 |

Effect-size estimates provide additional context to the *p* values shown in Table 1. All effect sizes were small, indicating no clinically significant baseline imbalances among the HCAR groups. Abbreviations: CI: Confidence interval; RR: Risk ratio; MD: Mean difference; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; HCAR: Hemoglobin and C-reactive protein-to-albumin ratio composite score.