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Combined Prognostic Value of CEA and Prognostic Nutritional Index in Metastatic Colon Cancer

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ABSTRACT

Aim: To evaluate the combined prognostic value of carcinoembryonic antigen (CEA) and the prognostic nutritional index (PNI) for overall survival (OS) and progression-free survival (PFS) in *de novo* stage IV colon cancer, and to compare their performance at baseline and at the first response assessment during treatment.

Methods: This single-center retrospective study included 102 patients with *de novo* stage IV colon cancer who were diagnosed between 2018 and 2025. CEA and PNI were measured at baseline (T0) and at the first response assessment (T1). CEA cut-offs were derived by receiver operating characteristic analysis, and a literature-based PNI cut-off of 48.0 was applied. Patients were classified into four CEA/PNI groups. Survival was analyzed by Kaplan-Meier and Cox regression methods, with $p<0.05$ considered significant.

Results: Median OS was 33.0 months, and median PFS was 12.4 months. At baseline, the highest-risk group (high CEA, low PNI) had shorter OS than the reference group (21.6 vs. 37.6 months, p=0.01) and was an independent predictor of death [hazard ratio (HR): 2.76, 95% confidence interval: 1.18-6.44, p=0.02]. The score was more discriminative at T1, where OS ranged from 19.8 to 60.6 months across groups (p=0.001). Bone metastasis (HR: 3.19) and absence of primary tumor surgery were the other independent predictors of poor OS. For PFS, left-sided location and surgery were independent favorable factors.

Conclusion: The combined CEA/PNI score identifies a high-risk subgroup in *de novo* stage IV colon cancer using routine laboratory data. Its prognostic value was greatest when measured early in treatment, supporting serial assessments over a single baseline measurement.

Keywords: Colonic neoplasms, carcinoembryonic antigen, nutritional status, prognosis, neoplasm metastasis

Introduction

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death, accounting for close to 10% of new cancer cases. The 2022 global estimates report about 1.9 million diagnoses and 904,000 deaths [1]. In Türkiye, it ranked third in terms of incidence in 2022, with 21,718 new cases and second among cancer-related deaths, with 11,698 deaths [2]. Between 15% and 30% of patients already have distant metastases at first diagnosis, and even with current treatment the five-year survival in stage IV disease stays below 15% [3]. This poor prognosis points to the need for reliable and readily available prognostic biomarkers to complement the tumor, node, metastasis staging system.

Serum carcinoembryonic antigen (CEA) is the marker most often used for diagnosis and follow-up in CRC [3]. It tracks tumor burden, and its prognostic weight holds across stages: in a pooled analysis of 10,114 patients, raised postoperative CEA predicted worse overall survival (OS) regardless of disease extent [hazard ratio (HR): 2.92] [4]. In stage IV disease, over 75% of patients present with elevated CEA, and high values predict poorer response and survival [5]. However, CEA reflects only tumor burden and does not capture the patient's nutritional or immune status, both of which influence cancer outcomes.

Onodera et al. [6] described the prognostic nutritional index (PNI) in 1984 as serum albumin (g/L) plus five times the peripheral lymphocyte count ($\times 10^9$/L) [6]. It captures host status as a single value by merging a nutritional measure

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(albumin) with an immune measure (lymphocytes). Across 43 studies covering 19,214 CRC patients, a low PNI carried an 89% higher mortality risk independent of stage [HR: 1.89; 95% confidence interval (CI): 1.70-2.10] [7]. A Turkish study of 253 advanced CRC patients reported shorter median OS in the low-PNI group (38.80 vs. 53.06 months; p=0.039) [8]. However, since PNI alone is insufficient for predicting progression-free survival (PFS), it is recommended to combine it with a tumor burden marker such as CEA [7,8].

Combining CEA and PNI is clinically rational: CEA quantifies tumor burden, while PNI reflects host disease tolerance. In stage II-III colon cancer, Xu et al. [9] reported that this combination predicted OS superiorly to either marker alone, increasing the area under the curve (AUC) to 0.797 (vs. 0.568 for CEA and 0.427 for PNI). In 512 stage IV CRC patients, Fernández Figueroa et al. [5] confirmed this, with the high-risk profile (CEA-high/PNI-low) carrying the poorest OS (HR: 2.41; 95% CI: 1.19-4.86) and PFS (HR: 2.16; 95% CI: 1.24-3.75). However, that study evaluated a mixed Mexican colorectal population with stage II-III disease, leaving this combined score untested in patients with exclusively advanced (stage IV) colon cancer. Therefore, we investigated the combined prognostic values of CEA and PNI for OS and PFS, comparing the performance at baseline versus the first response assessment during systemic treatment.

Methods

Study Design and Setting

We carried out a single-center retrospective cohort analysis in the Department of Medical Oncology, Aydın Adnan Menderes University Faculty of Medicine Hospital. Records of patients diagnosed with *de novo* stage IV colon cancer between January 2018 and December 2025 were retrieved from the hospital information system and the pathology archives.

Participants

Inclusion criteria: (1) biopsy-proven colon adenocarcinoma with distant metastasis present at first diagnosis, staged by the American Joint Committee on Cancer 8th edition; (2) age ≥18 years; (3) baseline serum CEA, albumin, and complete blood count with lymphocyte count, obtained within seven days before systemic treatment; and (4) at least three months of follow-up. Exclusion criteria: rectal cancer; metachronous metastasis; second primary malignancy; conditions affecting baseline albumin or lymphocyte levels (active infection, liver cirrhosis, systemic corticosteroids); and insufficient follow-up data. Of the 235 patients screened, 133 were excluded for the following reasons: rectal cancer (n=48), metachronous metastasis (n=33), missing laboratory data (n=22), second primary malignancy (n=15), and insufficient follow-up (n=15), leaving 102 for analysis. Baseline (T0) analysis included all 102 patients; at the 2-month assessment (T1), CEA and PNI were available for 88 patients and missing for 14 patients.

Data Collection

All records were captured using a standardized form. The fields covered age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor side (right or left), and the number and sites of metastases (liver, lung, peritoneum, bone, distant lymph nodes, and other sites). Pathological data included histological subtype, mismatch repair/microsatellite instability (MSI) status, and KRAS/NRAS/BRAF mutations. Treatment data included first-line chemotherapy, biological agents (anti-vascular endothelial growth factor or anti-epidermal growth factor receptor), and surgical history. Survival data included dates of diagnosis, progression, and either death or last follow-up. Laboratory values were collected at baseline (T0, <7 days pre-treatment) and at first response assessment (T1, ~2 months post-treatment). T1 analyses included the 88 patients with complete data.

Calculation of PNI and CEA/PNI Grouping

The PNI was calculated as: PNI=albumin (g/L)+5×lymphocyte count ($\times 10^9$/L), as originally described by Onodera et al. [6]. For T0 CEA, the optimal cut-off value was determined by receiver operating characteristic (ROC) curve analysis using the Youden index with OS as the endpoint, yielding 14.28 ng/mL (AUC: 0.621). For T0 PNI, ROC analysis showed limited discrimination (AUC: 0.565); therefore, a literature-based cut-off of 48.0 was adopted from the largest published stage IV CRC cohort validating this threshold and applied to both time points [10]. For T1 CEA, ROC analysis identified an optimal cut-off of 5.42 ng/mL (AUC: 0.682), which approximated the standard clinical threshold of 5 ng/mL; therefore, the standard threshold was applied. The PNI cut-off of 48.0 was used at both time points. Due to these differing CEA cut-off values, no direct statistical comparisons were made between the T0 and T1 groups. Patients were classified into four groups: Group 1 (CEA-high/PNI-low, highest risk); Group 2 (CEA-high/PNI-high); Group 3 (CEA-low/PNI-low); and Group 4 (CEA-low/PNI-high, reference group).

Endpoints Definitions

The two co-primary endpoints, OS and PFS, were measured from diagnosis to death and from diagnosis to progression (response evaluation criteria in solid tumors 1.1), respectively. Event-free patients were censored at their last follow-up. The secondary endpoint was to determine optimal prognostic CEA and PNI cut-offs in *de novo* stage IV colon cancer.

Ethics Committee Approval

This study received ethical approval from the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Aydın Adnan Menderes University (approval no: 16, date: 14.05.2026). All procedures followed the Declaration of Helsinki. Given the retrospective design and the use of anonymized records, the requirement for informed consent was waived.

Statistical Analysis

Categorical data are shown as counts and percentages. Continuous data departed from normality as assessed by the Kolmogorov-Smirnov test and are presented as medians with interquartile range (IQR). Categorical groups were compared using the chi-square test or Fisher's exact test, and continuous groups were compared using the Kruskal-Wallis test followed by Bonferroni post-hoc testing. To check whether the missing T1 data caused bias, we compared the baseline characteristics of patients with and without T1 measurements using the Mann-Whitney U test and the chi-square or Fisher's exact test. Survival was estimated using the Kaplan-Meier method and compared by the log-rank test, with the comparison between Group 1 and Group 4 pre-specified. Univariable and multivariable Cox proportional hazards models identified independent factors; variables with $p<0.20$ in univariable testing entered the multivariable model alongside established confounders. Multicollinearity was ruled out by ensuring variance inflation factors <5. For each endpoint, Model 1 analyzed the T0 grouping (n=102), and Model 2 analyzed the T1 grouping (n=88). The number of events per variable was checked for each model to avoid overfitting. The OS models included 82 deaths (T0) and 68 deaths (T1) for 6 parameters; the PFS models included 96 and 82 events for 8 parameters, yielding between 10 and 14 events per variable across models. The proportional hazards assumption was assessed using Schoenfeld residuals and log-log plots. Tests were two-sided (α=0.05) and were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Characteristics

Among the 102 patients, 74.5% were male, 88.2% had ECOG 0-1, and the median age was 65.5 years (IQR: 11.0). Most tumors were left-sided (64.7%), and 54.9% of patients had two or more metastatic sites. The liver was the most frequent metastatic site (72.5%), followed by distant lymph nodes (41.2%), lung (31.4%), peritoneum (21.6%), and bone (11.8%). Mutations in KRAS, NRAS, and BRAF were present in 53.5%, 5.0%, and 7.1% of cases, respectively; 3.0% of cases were MSI-H, and 35.6% of cases had unknown MSI status. FOLFOX was the most common first-line regimen (52.0%). Biological agents were administered to 88.2% of patients, and 45.1% underwent surgery. Median OS was 33.0 months (95% CI: 25.1-40.8) and median PFS was 12.4 months (95% CI: 9.9-14.9). Baseline characteristics are shown in Table 1.

ROC Analysis and Cut-off Determination

Baseline medians were 19.5 ng/mL for CEA (IQR: 141.9) and 49.0 for PNI (IQR: 6.4). Against OS, CEA yielded an AUC of 0.621, and the Youden-optimal cut-off was 14.28 ng/mL. Although higher than the conventional 5.0 ng/mL, this threshold provided superior discrimination in our cohort and was selected for stratification. For PNI, the AUC was 0.565, and no robust data-driven threshold was identified. Therefore, a literature-supported cut-off of 48.0 was applied, consistent with large-scale stage IV series. ROC curves are shown in Figure 1.

CEA/PNI Score Distribution and Grouping

Based on these cut-offs, the baseline distribution was as follows: 20.6% highest-risk (CEA-high/PNI-low), 34.3% CEA-high/PNI-high, 12.7% CEA-low/PNI-low, and 32.4% reference (CEA-low/PNI-high). Groups were comparable except for sex distribution (p=0.043) and a borderline difference in surgery rates (p=0.070), with men predominating in the highest-risk group (Table 1). At T1 (~2 months), data were available for 88 patients (86.3%). Median CEA decreased to 5.5 ng/mL (IQR: 31.0), and median PNI decreased to 48.1 (IQR: 6.8). The T1 risk distribution shifted to 26.1% highest risk, 27.3% CEA-high/PNI-high, 22.7% CEA-low/PNI-low, and 23.9% reference (Table 2). Patients with T1 data and those without were similar in most baseline features, including age, baseline CEA, PNI, CEA/PNI score distribution, ECOG status, and tumor location (all p>0.05). The two groups differed only with respect to bone metastasis (p=0.036) and primary tumor surgery (p=0.013).

Overall Survival

Median follow-up was 33.0 months (95% CI: 25.1-40.8). Overall, 82 patients (80.4%) died, and 20 (19.6%) were alive at the last follow-up (Table 3).

By baseline CEA/PNI score, median OS was 21.6, 30.6, 42.5, and 37.6 months for groups 1-4, respectively (log-rank p=0.057, Figure 2A, Table 3). The highest-risk group had shorter OS than the reference group (21.6 vs. 37.6 months; p=0.010; Figure 2B).

At T1, median OS was 19.8, 24.8, 31.1, and 60.6 months for groups 1-4, respectively (log-rank p=0.001, Figure 2C), representing a 41-month difference between the highest-risk and reference groups (p<0.001) (Table 3).

Progression-free Survival

A total of 96 patients (94.1%) progressed during follow-up, while 6 (5.9%) were censored. The median PFS for the cohort was 12.4 months (95% CI: 9.9-14.9) (Table 3).

Baseline CEA/PNI grouping showed no significant difference in PFS across groups (p=0.254) or between highest-risk and reference groups (p=0.290); baseline CEA alone was borderline significant (p=0.050) (Table 3).

At T1, median PFS across groups 1-4 was 9.4, 8.9, 14.6, and 21.4 months (log-rank p=0.006; Figure 2D), representing about a 12-month gap between the highest-risk and reference groups (p<0.001) (Table 3).

Independent Prognostic Factors

Univariable and multivariable Cox analyses were performed for T0 and T1 OS/PFS models (Table 4). In the T0 OS model, univariable analysis identified the highest-risk group (CEA-high/PNI-low; HR: 2.33, 95% CI: 1.04-5.24; p=0.039), metastatic site count, bone metastasis, and surgery as significant. In multivariable analysis, only the highest-risk group (HR: 2.75,

Table 1. Baseline clinical and demographic characteristics of patients with *de novo* stage IV colon cancer stratified by CEA/PNI score group (n=102)

CEA/PNI score group (n) (%)	Total (102) (%100.0)	CEA-HIGH PNI-LOW Group 1 (21) (%20.6)	CEA-HIGH PNI-HIGH Group 2 (n=35) (%34.3)	CEA-LOW PNI-LOW Group 3 (n=13) (12.7%)	CEA-LOW PNI-HIGH(Ref) Group 4 (n=33) (32.4%)	p value
Demographics						
Age, years, median (IQR)	65.5 (11.0)	67.0 (10.5)	61.0 (15.0)	68.0 (14.0)	66.0 (11.5)	**0.019**
Sex, n (%)						
Male	76 (74.5)	20 (95.2)	24 (68.6)	11 (84.6)	21 (63.6)	**0.043**
Female	26 (25.5)	1 (4.8)	11 (31.4)	2 (15.4)	12 (36.4)	
Clinical characteristics						
ECOG-PS, n (%)						
0-1	90 (88.2)	19 (90.5)	31 (88.6)	11 (84.6)	29 (87.9)	0.965
2+	12 (11.8)	2 (9.5)	4 (11.4)	2 (15.4)	4 (12.1)	
Primary tumor location, n (%)						
Right-sided	36 (35.3)	6 (28.6)	11 (31.4)	7 (53.8)	12 (36.4)	0.454
Left-sided	66 (64.7)	15 (71.4)	24 (68.6)	6 (46.2)	21 (63.6)	
Metastatic sites, n (%)						
Single	46 (45.1)	9 (42.9)	13 (37.1)	6 (46.2)	18 (54.5)	0.545
Multiple (2^{+})	56 (54.9)	12 (57.1)	22 (62.9)	7 (53.8)	15 (45.5)	
Metastatic sites						
Liver, n (%)	74 (72.5)	16 (76.2)	28 (80.0)	9 (69.2)	21 (63.6)	0.475
Lung, n (%)	32 (31.4)	7 (33.3)	13 (37.1)	3 (23.1)	9 (27.3)	0.741
Bone, n (%)	12 (11.8)	3 (14.3)	3 (8.6)	2 (15.4)	4 (12.1)	0.887
Peritoneum, n (%)	22 (21.6)	3 (14.3)	5 (14.3)	4 (30.8)	10 (30.3)	0.273
Distant lymph nodes, n (%)	42 (41.2)	9 (42.9)	17 (48.6)	5 (38.5)	11 (33.3)	0.639
Molecular profile						
KRAS, n (%)						
Wild-type	47 (46.5)	8 (40.0)	15 (42.9)	7 (53.8)	17 (51.5)	0.767
Mutant	54 (53.5)	12 (60.0)	20 (57.1)	6 (46.2)	16 (48.5)	
NRAS, n (%)						
Wild-type	96 (95.0)	19 (95.0)	32 (91.4)	13 (100.0)	32 (97.0)	0.591
Mutant	5 (5.0)	1 (5.0)	3 (8.6)	0 (0.0)	1 (3.0)	
BRAF, n (%)						
Wild-type	92 (92.9)	18 (94.7)	33 (97.1)	12 (92.3)	29 (87.9)	0.519
Mutant	7 (7.1)	1 (5.3)	1 (2.9)	1 (7.7)	4 (12.1)	
MSI-H, n (%)	3 (3.0)	0 (0.0)	1 (2.9)	1 (7.7)	1 (3.0)	0.570
Treatment						
First-line chemotherapy, n (%)						
FOLFOX	53 (52.0)	10 (47.6)	26 (57.1)	6 (46.2)	17 (51.5)	0.282
CAPOX	31 (30.4)	3 (14.3)	11 (31.4)	5 (38.5)	12 (36.4)	
FOLFIRI	14 (13.7)	7 (33.3)	3 (8.6)	1 (7.7)	3 (9.1)	
Other	4 (3.9)	1 (4.8)	1 (2.9)	1 (7.7)	1 (3.0)	
Biological agent, n (%)	90 (88.2)	19 (90.5)	29 (82.9)	11 (84.6)	31 (93.9)	0.517
Surgical intervention, n (%)	46 (45.1)	7 (33.3)	12 (34.3)	9 (69.2)	18 (54.5)	0.070

Group 1: CEA-HIGH/PNI-LOW; **Group 2:** CEA-HIGH/PNI-HIGH; **Group 3:** CEA-LOW/PNI-LOW; **Group 4:** CEA-LOW/PNI-HIGH (reference). Continuous variables were compared by the Kruskal-Wallis test; categorical variables were compared by the chi-square test or Fisher's exact test. Bold p values indicate statistical significance ($p<0.05$)
BMI: Body mass index, ECOG-PS, Eastern Cooperative Oncology Group performance status, MSI-H: High microsatellite instability, IQR: Interquartile range, CEA: carcinoembryonic antigen, PNI: prognostic nutritional index

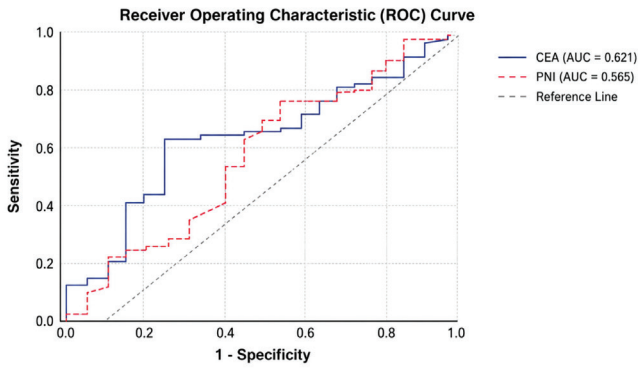

Figure 1. ROC curves for baseline CEA and PNI
CEA: Carcinoembryonic antigen, PNI: Prognostic nutritional index, ROC: Receiver operating characteristic, AUC: Area under the curve

95% CI: 1.18-6.43; p=0.019) and bone metastasis (HR: 3.18, 95% CI: 1.05-9.65; p=0.041) remained independent predictors (Table 4).

For T1 OS, all three risk groups were significant in univariable analysis. In multivariable analysis, CEA-low/PNI-low (HR: 4.84, 95% CI: 1.43-16.38; p=0.011), bone metastasis (HR: 5.45, 95% CI: 1.38-21.55; p=0.016), and surgery (HR: 0.45, 95% CI: 0.21-0.95; p=0.038) were independent predictors, whereas CEA-high/PNI-low and CEA-high/PNI-high showed borderline significance (Table 4).

Left-sided tumor location and surgery were independent predictors of PFS in both T0 and T1 models, whereas the CEA/PNI score was not significant. In the T1 PFS model, the highest-risk group showed only a nonsignificant trend (HR: 1.72; p=0.216, Table 4).

Table 2. CEA, PNI and combined CEA/PNI score distribution at baseline (T0) and first response assessment (T1)

Variable	Baseline (T0) (n=102)	First response assessment (T1) (n=88)
CEA, ng/mL, median (IQR)	19.5 (141.9)	5.5 (31.0)
PNI, median (IQR)	49.0 (6.4)	48.1 (6.8)
CEA category, n (%)		
CEA-high	56 (54.9)	48 (54.5)
CEA-low	46 (45.1)	40 (45.5)
PNI category, n (%)		
PNI-low (<48.0)	34 (33.3)	48 (54.5)
PNI-high (≥48.0)	68 (66.7)	40 (45.5)
CEA/PNI combined group, n (%)		
Group 1: CEA-high/PNI-low	21 (20.6)	23 (26.1)
Group 2: CEA-high/PNI-high	35 (34.3)	24 (27.3)
Group 3: CEA-low/PNI-low	13 (12.7)	20 (22.7)
Group 4: CEA-low/PNI-high (ref)	33 (32.4)	21 (23.9)

CEA categorization thresholds differed between time points: at baseline (T0), an ROC-derived cut-off of 14.28 ng/mL (AUC=0.621) was applied, while at the first response assessment (T1), the standard clinical threshold of 5 ng/mL was adopted, as the ROC-derived optimal value at T1 (5.42 ng/mL, AUC=0.682) closely approximated this conventional cut-off. PNI cut-off: 48.0 (adopted from Takamizawa et al. [10]).
A direct comparison between the T0 and T1 groups was not performed because different CEA cut-off values were applied at each time point (T0: 14.28 ng/mL; T1: 5 ng/mL)
CEA: Carcinoembryonic antigen, PNI: Prognostic Nutritional Index, (~2 months after initiation of systemic treatment), AUC: Area under the curve, ROC: Receiver operating characteristic

Table 3. Kaplan-Meier survival outcomes according to CEA/PNI score group at baseline (T0) and first response assessment (T1)

Group	Median OS (months)	95% CI	Log-rank p (OS)	Median PFS (months)	95% CI	Log-rank p (PFS)
Baseline CEA/PNI score (T0, n=102)						
Overall cohort	33.0	25.1-40.8	-	12.4	9.9-14.9	-
Group 1: CEA-high/PNI-low	21.6	14.9-28.4	0.057	12.2	10.4-19.4	0.254
Group 2: CEA-high/PNI-high	30.6	14.6-46.6		9.9	6.3-14.4	
Group 3: CEA-low/PNI-low	42.5	15.4-69.6		17.4	4.9-13.5	
Group 4: CEA-low/PNI-high (ref)	37.6	30.5-44.6		13.8	3.1-28.2	

Table 3. Continued

Group	Median OS (months)	95% CI	Log-rank p (OS)	Median PFS (months)	95% CI	Log-rank p (PFS)
Group 1 vs. Group 4	21.6 vs. 37.6	14.9-28.4 vs. 30.5-44.6	0.010	12.2 vs. 13.8	7.0-17.4 vs. 7.7-20.0	0.290
First response assessment CEA/PNI score (T1, n=88)						
Group 1: CEA-high/PNI-low	19.8	14.9-24.7	0.001	9.4	7.2-11.6	0.006
Group 2: CEA-high/PNI-high	24.8	14.6-35.1		8.9	7.0-10.9	
Group 3: CEA-low/PNI-low	31.1	15.4-46.8		14.6	11.6-17.5	
Group 4: CEA-low/PNI-high (ref)	60.6	33.0-88.2		21.4	8.2-34.7	
Group 1 vs. Group 4	19.8 vs. 60.6	12.0-27.7 vs. 46.6-74.6	<0.001	9.4 vs. 21.4	7.2-11.6 vs. 8.2-34.7	<0.001

OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval, ref: Reference group, CEA: Carcinoembryonic antigen, PNI: Prognostic nutritional index

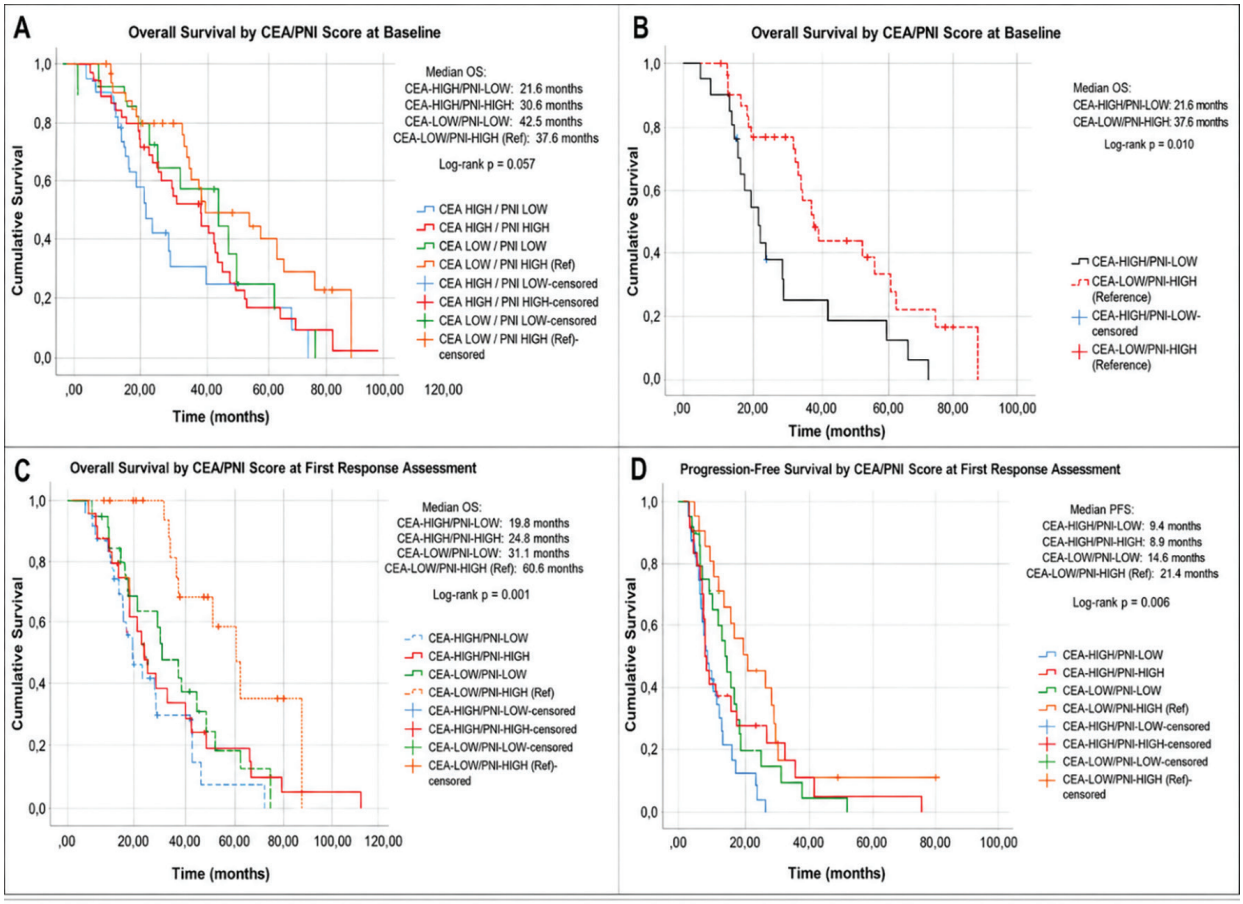

Figure 2. Kaplan-Meier curves for overall and PFS according to CEA/PNI score: (A) OS by baseline CEA/PNI score (T0), (B) OS in the highest-risk group (Group 1) versus the reference group (Group 4) at baseline (T0), (C) OS by CEA/PNI score at first response assessment (T1), (D) PFS by CEA/PNI score at first response assessment (T1)
CEA: Carcinoembryonic antigen, PNI: Prognostic nutritional index, ROC: Receiver operating characteristic, PFS: progression-free survival, OS: Overall survival

Table 4. Univariable and multivariable Cox proportional hazards regression analysis for OS and PFS

Variable	Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
OS						
Model 1: baseline CEA/PNI score (T0, n=102)						
CEA/PNI group (ref: Group 4)						
Group 1 (CEA-high/PNI-low)	2.33	1.04-5.24	0.039	2.75	1.18-6.43	0.019
Group 2 (CEA-high/PNI-high)	1.11	0.53-2.31	0.768	1.21	0.56-2.62	0.622
Group 3 (CEA-low/PNI-low)	1.16	0.46-2.90	0.746	1.50	0.56-4.00	0.415
Bone metastasis (ref: absent)	4.12	1.54-10.98	0.005	3.18	1.05-9.65	0.041
Multiple metastatic sites (ref: single)	1.98	1.04-3.79	0.037	1.43	0.72-2.86	0.301
Surgical interven (ref: no surgery)	0.52	0.29-0.95	0.033	0.56	0.28-1.10	0.093
Model 2: first response assessment CEA/PNI score (T1, n=88)						
CEA/PNI group (ref: Group 4)						
Group 1 (CEA-high/PNI-low)	4.28	1.36-13.46	0.013	3.48	0.97-12.4	0.055
Group 2 (CEA-high/PNI-high)	3.20	1.01-10.16	0.048	3.16	0.96-10.37	0.057
Group 3 (CEA-low/PNI-low)	4.30	1.35-13.69	0.013	4.84	1.43-16.38	0.011
Bone metastasis (ref: absent)	4.12	1.54-10.98	0.005	5.45	1.38-21.55	0.016
Multiple metastatic sites (ref: single)	1.98	1.04-3.79	0.037	1.33	0.57-3.11	0.506
Surgical interven (ref: no surgery)	0.52	0.29-0.95	0.033	0.45	0.219-0.9	0.038
PFS						
Model 1: baseline CEA/PNI score (T0, n=102)						
CEA/PNI group (ref: Group 4)						
Group 1 (CEA-high/PNI-low)	1.35	0.67-2.70	0.394	1.40	0.68-2.86	0.350
Group 2 (CEA-high/PNI-high)	1.13	0.59-2.16	0.707	1.09	0.54-2.20	0.808
Group 3 (CEA-low/PNI-low)	0.54	0.22-1.30	0.173	0.63	0.24-1.61	0.337
Primary tumor location (ref: right)	0.83	0.71-0.97	0.021	0.42	0.23-0.74	0.003
Multiple metastatic sites (ref: single)	1.92	1.12-3.29	0.016	1.45	0.78-2.69	0.228
Lung metastasis (ref: absent)	2.00	1.16-3.45	0.013	1.69	0.93-3.09	0.084
Bone metastasis (ref: absent)	2.07	0.82-5.24	0.122	1.14	0.39-3.25	0.811
Surgical interven (ref: no surgery)	0.45	0.25-0.78	0.005	0.49	0.25-0.93	0.031
Model 2: first response assessment CEA/PNI Score (T1, n=88)						
CEA/PNI group (ref: Group 4)						
Group 1 (CEA-high/PNI-low)	2.64	1.19-5.82	0.016	1.72	0.72-4.10	0.216
Group 2 (CEA-high/PNI-high)	1.23	0.53-2.85	0.625	1.14	0.46-2.85	0.770
Group 3 (CEA-low/PNI-low)	1.69	0.74-3.85	0.211	1.61	0.68-3.81	0.277
Primary tumor location (ref: right)	0.56	0.33-0.96	0.035	0.47	0.25-0.89	0.021
Multiple metastatic sites (ref: single)	1.92	1.12-3.29	0.016	1.49	0.75-2.98	0.250
Lung metastasis (ref: absent)	2.00	1.16-3.45	0.013	1.54	0.77-3.06	0.213
Bone metastasis (ref: absent)	2.07	0.82-5.24	0.122	1.14	0.30-4.31	0.837
Surgical interven (ref: no surgery)	0.45	0.25-0.78	0.005	0.43	0.21-0.87	0.019

Bold values indicate statistical significance (p<0.05). T0 model: n=102; T1 model: n=88 (patients with available T1 laboratory data)
HR: Hazard ratio, CI: Confidence interval, PFS: Progression-free survival, OS: Overall survival, CEA: Carcinoembryonic antigen, PNI: Prognostic nutritional index

Discussion

Among our patients with *de novo* stage IV colon cancer, the combination of CEA and PNI had greater prognostic value than either marker alone. At baseline, membership in the highest-risk group (high CEA/low PNI) was associated with a median survival of 21.6 months compared with 37.6 months in the reference group, and remained an independent predictor of mortality after multivariable adjustment (HR: 2.75). The prognostic value of the score increased at the first

response assessment (T1), when the median OS ranged from 19.8 months in the highest-risk group to 60.6 months in the reference group. Among clinical variables, bone metastasis was the strongest independent predictor of poor survival, whereas primary tumor resection was associated with longer survival.

Combining a marker of tumor burden with a marker of host status outperformed either marker alone, echoing earlier work predominantly in earlier-stage disease. In stage II-III colon cancer, Xu et al. [9] reported an AUC of 0.797 for the combined score, well above CEA (0.568) or PNI (0.427) singly, and a larger metastatic series found the high-CEA/low-PNI profile again carried the shortest survival [5]. Composite indices pairing CEA with inflammatory or immune markers, such as the C-systemic inflammation response index score validated by Cai et al. [11] and the inflammation-nutrition score proposed by Li et al. [12], consistently retain independent prognostic value in multivariable models where individual markers frequently lose statistical significance. Our colon-specific, *de novo*, stage IV Turkish cohort adds to this evidence.

The primary finding of our study is the gain in prognostic power from baseline (T0) to the first response assessment (T1). While the four-group survival stratification was only borderline significant at baseline (p=0.057), it became clearly significant at T1 (p=0.001). A similar pattern was observed for CEA and PNI when evaluated separately, suggesting that a single baseline measurement may underestimate the value of serial assessment. The early treatment measurement likely reflects not only initial tumor burden and host reserve, but also treatment response. The individual group results at T1 should be interpreted with caution. Because each group was small, the confidence intervals were wide; the highest-risk group reached only borderline significance (p=0.055), and the CEA-low/PNI-low group had a particularly wide interval (95% CI: 1.43-16.39). The clear result of the overall four-group comparison (p=0.001) is, therefore, the stronger finding.

This interpretation is supported by previous studies on biomarker dynamics. Konishi et al. [13] found that postoperative CEA normalization brought outcomes in line with patients who started with normal CEA, while CEA that stayed high tracked with worse prognosis. Similarly, Muñoz-Montaño et al. [14] reported that failure to normalize CEA identified the group with the worst outcomes. Regarding nutritional status, Lee and Kang [15] found that combining pre- and postoperative PNI provided better prognostic performance than either value alone, and PNI has been shown to change during chemotherapy [16]. Our findings emphasize the added prognostic value of serial CEA and PNI measurements when this dynamic assessment is extended from the surgical setting to systemic treatment for metastatic colon cancer.

Our baseline CEA cut-off of 14.28 ng/mL sits well above the usual 5 ng/mL; this is consistent with work showing that a single fixed threshold performs poorly across different stages. Jeon et al. [17] found mean CEA rising from 3.0 ng/mL at stage I to 9.2 at stage III and argued for stage-specific thresholds; Jia et al. [18] used cut-offs of 4.9 and 27.2 ng/mL tied to nodal status; and Cai et al. [11] adopted 13.0 ng/mL, close to ours. When every patient is at stage IV and has a high tumor burden, a higher cut-off is expected, and the conventional 5 ng/mL loses its value when most exceed it. At T1, however, we applied the standard 5 ng/mL because the ROC-derived 5.42 ng/mL closely matched it and preserved the clinical practicality of the measurement. Because the two time points used different CEA thresholds, the T0 and T1 groups are not directly comparable, so we did not treat them as a single variable over time. Each time point was analyzed on its own. The two measurements also convey different information: the baseline value reflects the tumor burden before treatment, while the T1 value reflects an early response. The stronger separation at T1 should therefore be interpreted as indicating that an early on-treatment check adds prognostic information, rather than as a direct comparison of the same score over time. Because this cut-off came from a single center, it should be considered exploratory and should be tested in other independent groups before wider use.

PNI behaved differently. Weak at baseline (p=0.121), it became significant at the first response assessment (p=0.009), in line with Xu et al. [7] meta-analysis showing PNI a robust predictor of OS but weaker for PFS. Reported PNI cut-offs vary: 46.6 in the Turkish series of Keskinkilic et al. [8], 48.0 in the Japanese cohort of Takamizawa et al. [10], and 47.05 by Li et al. [12]. Our analysis did not yield a stable threshold; therefore, we adopted 48.0 from the largest stage IV series. The 46-48 clustering suggests that this value is reasonable for advanced disease. Only the CEA cut-off came from our own data; the PNI cut-off was taken from the literature. The combined score is therefore better regarded as a practical, ready-to-use tool rather than as a score specific to our population.

Bone metastasis was our strongest single clinical predictor, raising the risk of death about threefold at baseline and more than fivefold at T1. This fits the literature: survival after skeletal involvement is short, around 5 to 18 months, and high CEA adds to the risk [19,20]. In the surveillance, epidemiology, and end results nomogram by Guan et al. [21], CEA positivity, absence of primary resection, and bone involvement were all associated with worse survival, consistent with our results.

Primary tumor resection was associated with longer survival, and left-sided tumor location predicted better PFS. This matches large series that tie resection to lower mortality and several months of added survival, with the benefit mainly in left-sided tumors [22-24]. However, this association should be interpreted with caution, as patients selected for surgery often have lower disease burden and better clinical status; therefore, part of the observed survival advantage may reflect selection bias rather than the direct effect of surgery. In this context, the poorer outcomes observed in the high-CEA/low-PNI group may reflect the combined effect of higher tumor burden and impaired host nutritional-inflammatory status.

Study Limitations

A few limitations apply. The study was retrospective, single-center, and included 102 patients; the small size of the low-

CEA/low-PNI group (n=13) limited the precision of subgroup estimates. T1 data were missing for 14 patients, and the PNI cut-off was based on previous literature rather than being derived from the present cohort. The T1 models were based on 88 patients across four groups, so some subgroups were small and their individual estimates were less stable. The overall four-group comparison, rather than any single group's HR, should therefore be considered the primary evidence of the score's value. Patients missing T1 data did not differ from the remaining patients with respect to baseline CEA, PNI, or the CEA/PNI score, which argues against systematic bias in the on-treatment analyses. The associations observed for primary tumor resection and tumor sidedness should also be interpreted cautiously, as patients selected for surgery are often fitter and have lower disease burden, which may introduce selection bias [22,24]. Although the first-line treatment regimen was not associated with survival and was therefore not included in the models, treatment heterogeneity remains a potential confounder. Finally, MSI status was unavailable in more than one-third of patients, thereby limiting molecular interpretation.

Conclusion

In patients with *de novo* stage IV colon cancer, the combined CEA/PNI score identifies a high-risk group with markedly shorter survival using laboratory values already collected in routine care. The score was more informative when measured early in treatment than at diagnosis alone, suggesting that a second assessment after initiation of systemic therapy provides additional prognostic information. Bone metastasis and the absence of primary tumor surgery were the other main determinants of poor outcome. These results require confirmation in prospective multicenter studies before the score can be recommended for routine clinical use, but they support its potential as a low-cost tool for risk stratification in advanced colon cancer.

Ethics

Ethics Committee Approval: This study received ethical approval from the Non-Interventional Clinical Research Ethics Committee of the Faculty of Medicine, Aydın Adnan Menderes University (approval no: 16, date: 14.05.2026).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.T., M.N.B., Design: M.T., M.N.B., Data Collection or Processing: M.T., M.N.B., Analysis or Interpretation: M.T., M.N.B., Literature Search: M.T., M.N.B., Writing: M.T., M.N.B.

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