

Prognostic value of the lymphocyte-albumin-neutrophil ratio in *de novo* metastatic colorectal cancer: A continuous-variable analysis

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Abstract. Currently, the continuous prognostic association of the lymphocyte-albumin-neutrophil ratio (LANR) in *de novo* metastatic colorectal cancer remains uncertain. The present retrospective, single-center prognostic study evaluated baseline LANR in 141 patients who received first-line anti-VEGF or anti-EGFR treatment. Serum 25-hydroxyvitamin D was examined as a secondary exploratory biomarker. LANR was modeled per 5-unit increase. Cox regression models assessed associations with overall survival (OS) and progression-free survival (PFS), and sensitivity models evaluated robustness under a clinically selected covariate set. Restricted cubic splines assessed the shape of the associations. Each 5-unit increase in LANR was associated with lower risk of mortality [hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.66-0.96; P=0.015] and progression or mortality (HR, 0.83; 95% CI, 0.72-0.94; P=0.005). The estimates were essentially unchanged in clinically selected models, and spline analyses showed no evidence of departure from linearity. Higher 25-hydroxyvitamin D was associated with longer PFS but not

OS in the primary model; the PFS association was attenuated to non-significant in sensitivity analyses. Incremental discrimination was modest. In this selected treatment population, baseline LANR was associated with OS and PFS when analyzed continuously without a study-derived threshold. These findings support external validation but do not establish current clinical or treatment-selection utility.

Introduction

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related death. Approximately 15-30% of patients present with metastatic disease (1). Diagnosis requires histological confirmation, while contrast-enhanced computed tomography of the chest, abdomen and pelvis is used for staging. Treatment is individualized according to resectability, patient fitness and tumor molecular characteristics. Options include chemotherapy with appropriate targeted agents, immunotherapy for tumors with deficient mismatch repair or high microsatellite instability, and surgery or local ablation in selected patients. Prognosis is heterogeneous: most patients are not candidates for potentially curative resection at diagnosis, although selected patients with resectable metastases may achieve long-term survival or cure (1).

Outcomes vary considerably among patients with *de novo* metastatic colorectal cancer despite contemporary first-line systemic therapy (1). Tumor burden and molecular alterations such as RAS and BRAF account for only part of this variation and primarily characterize the tumor. Host-related factors reflecting systemic inflammation and immune status may provide additional prognostic information.

Neutrophils can support tumor growth and angiogenesis (2), whereas lymphocytes contribute to antitumor immunity (3). Serum albumin decreases during the acute-phase response and therefore reflects systemic inflammation more than nutritional status alone (4). The neutrophil-to-lymphocyte ratio (NLR) has been linked to survival in colorectal cancer (5), while the modified Glasgow prognostic score has shown prognostic value across several tumor types (6). However, these commonly used indices have different component requirements: NLR relies on

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ACCI, age-adjusted Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; IQR, interquartile range; LANR, lymphocyte-albumin-neutrophil ratio; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NLR, neutrophil-to-lymphocyte ratio; NRAS, neuroblastoma RAS viral oncogene homolog; OS, overall survival; PFS, progression-free survival

Key words: metastatic colorectal cancer, lymphocyte-albumin-neutrophil ratio, systemic inflammation, prognostic biomarker, overall survival, progression-free survival, 25-hydroxyvitamin D

immune cell counts alone, whereas the modified Glasgow prognostic score requires measurement of serum C-reactive protein and albumin concentrations (6). The consensus Immunoscore provides validated prognostic information in stage I-III colon cancer but requires tumor tissue, immunohistochemical assessment and digital image analysis (7). Blood-based inflammatory indices can be derived from routinely available laboratory tests and may offer a more accessible approach to host-related prognostic assessment.

The lymphocyte-albumin-neutrophil ratio (LANR) combines lymphocyte count, serum albumin and neutrophil count in a single measure and does not require C-reactive protein levels. LANR was first described in resectable colorectal cancer, in which higher values were associated with longer overall and disease-free survival (8), and a subsequent surgical cohort reported a similar direction of association for a mathematically equivalent index calculated by dividing albumin by NLR (9). Existing LANR evidence has therefore been concentrated mainly in resectable or surgically treated colorectal cancer populations. Prognostic associations for inflammation-based indices have similarly been reported in *de novo* metastatic colon cancer, although that study classified patients using a threshold derived within the analyzed cohort (10). Such cohort-derived thresholds may be sensitive to sample-specific variation and may not generalize to other populations. Categorizing a continuous marker also discards information about differences within the resulting groups. Circulating 25-hydroxyvitamin D concentrations have also been associated with survival outcomes in colorectal cancer (11,12). The prognostic association of LANR in *de novo* metastatic colorectal cancer, and its shape across the continuous range of the index, remain insufficiently characterized.

The primary objective of the present study was to evaluate the prognostic association of baseline LANR, modeled continuously, with overall survival (OS) and progression-free survival (PFS) in patients with *de novo* metastatic colorectal cancer receiving first-line anti-VEGF- or anti-EGFR-based systemic treatment. Serum 25-hydroxyvitamin D was examined as a secondary exploratory biomarker. Secondary analyses characterized the shape of the continuous associations and assessed added discrimination beyond clinical models. The study evaluated whether higher LANR was associated with longer survival and whether the estimates were directionally consistent across different covariate specifications. The analyses addressed prognostic associations, but did not assess whether LANR predicted differential benefit from a particular treatment.

Materials and methods

Study design and patients. This was a single-center retrospective cohort study conducted at Ankara Etlik City Hospital (Ankara, Türkiye). Patients with *de novo* metastatic colorectal cancer treated between November 2022 and June 2025 were identified from institutional records. Follow-up was updated until June 2026.

The present study was approved by the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital (approval no. AEŞH-BADEK2-2025-160; 10 June 2025) and was conducted in accordance with the Declaration

of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective study design.

Patients were eligible if distant metastases were present at the initial diagnosis of colorectal cancer and they received first-line anti-VEGF- or anti-EGFR-based systemic treatment. Patients were excluded for metachronous or recurrent metastatic disease, systemic treatment before referral, absence of anti-VEGF- or anti-EGFR-based treatment, missing laboratory data within the required 7-day baseline window, incomplete clinical or molecular data or inadequate outcome data. Restriction to *de novo* metastatic disease was intended to reduce heterogeneity related to prior disease course and treatment history. Because eligibility also required receipt of a biologic agent, the cohort represents a selected treatment population and does not include patients managed without anti-VEGF or anti-EGFR therapy because of frailty, comorbidity, access or an alternative treatment strategy. Of 372 patients screened, 141 were included in the final cohort (Fig. 1). The study was reported in accordance with the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) (13).

Data collection and definitions. Baseline laboratory values, including serum 25-hydroxyvitamin D, were the closest measurements obtained within 7 days before initiation of first-line systemic treatment. LANR was calculated as lymphocyte count multiplied by serum albumin and divided by neutrophil count, using albumin in g/l and lymphocyte and neutrophil counts in / μ l. Because the numerical value of LANR is unit-dependent, the same measurement units are required to reproduce or interpret the estimates reported in the present study. Baseline vitamin D was defined as the serum 25-hydroxyvitamin D concentration measured within the same pretreatment window. All measurements were generated as part of routine clinical care; no research specimens or control samples were collected or stored for the present study.

Clinical and molecular data were extracted from electronic medical records. Comorbidity burden was summarized using the age-adjusted Charlson Comorbidity Index (ACCI), in which age contributes to the total score (14). Primary tumor location was classified as right-sided colon, left-sided colon or rectum. Molecular variables included KRAS, neuroblastoma RAS viral oncogene homolog and BRAF alterations, HER2 status, and microsatellite instability status. HER2 was classified as negative, positive or not assessed. First-line treatment was classified by targeted therapy as anti-VEGF or anti-EGFR and by chemotherapy backbone as folinic acid, fluorouracil and oxaliplatin (FOLFOX), folinic acid, fluorouracil and irinotecan (FOLFIRI), or capecitabine-based treatment.

Treatment selection was determined by the treating oncologist as part of routine care, with consideration of tumor sidedness, molecular profile, performance status, comorbidity and other clinical factors. The patient-specific rationale for choosing anti-VEGF or anti-EGFR therapy and the chemotherapy backbone was not systematically recorded in the retrospective dataset.

Outcomes. OS was defined as the time from initiation of first-line systemic therapy to mortality from any cause. Patients who were alive at data cut-off were censored at the date of last

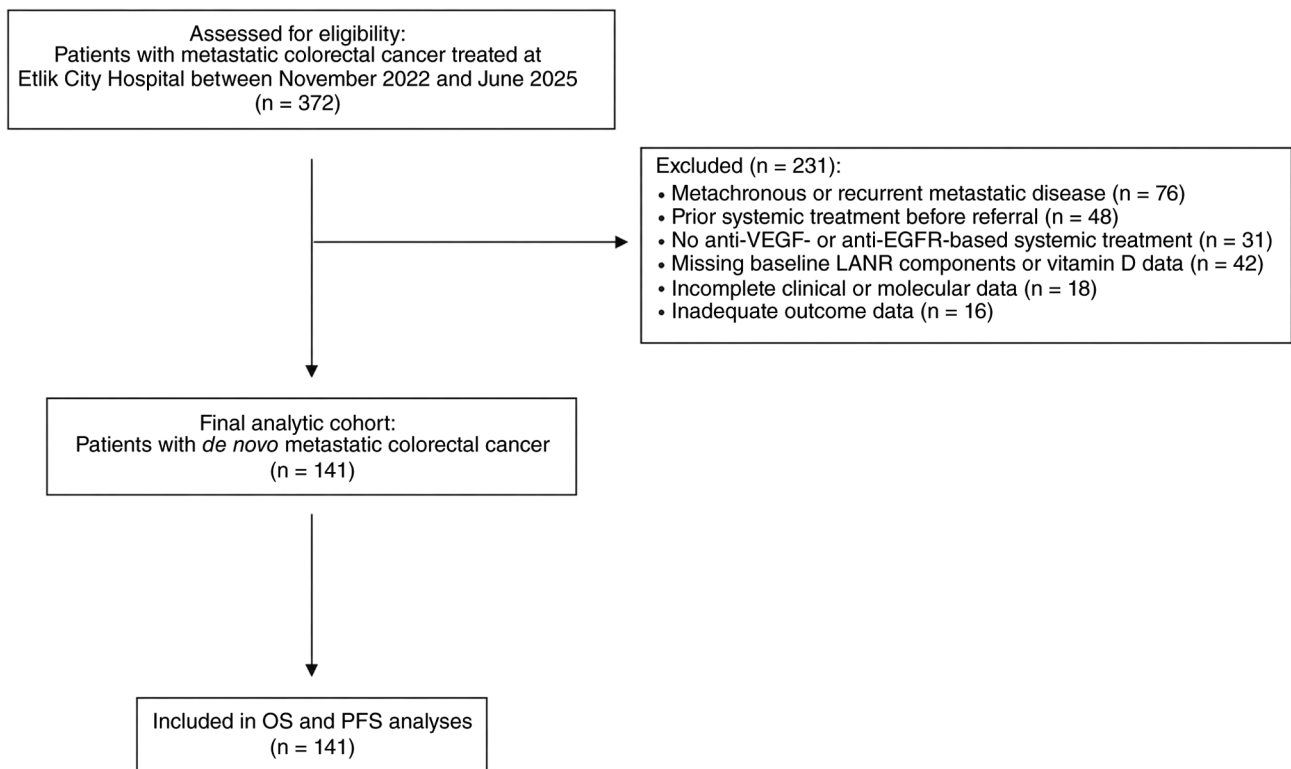


Figure 1. Flow diagram of patient selection. OS, overall survival; PFS, progression-free survival.

known follow-up. PFS was defined as the time from initiation of first-line systemic therapy to radiologic or clinical disease progression or mortality from any cause, whichever occurred first. Patients without progression or mortality were censored at the date of their last disease assessment. Progression was determined by the treating physician based on routine imaging and clinical findings.

Statistical analysis. All analyses were performed in Python 3.12 (Python Software Foundation; <https://www.python.org/>) using pandas, numpy, scipy, statsmodels, lifelines, patsy, scikit-learn and matplotlib. Continuous variables are presented as median and interquartile range (IQR) and categorical variables as frequencies and percentages. Carcinoembryonic antigen and carbohydrate antigen 19-9 were log-transformed. Patients with missing data required for eligibility or analysis were excluded during cohort assembly; among the 141 patients in the final cohort, no analysis variable was missing and no imputation was performed. Two-sided P-values <0.05 were considered statistically significant.

No formal sample-size calculation was performed for the present prognostic analysis; all eligible patients who met the study criteria during the study period were included.

Survival was estimated using the Kaplan-Meier method, and median follow-up was calculated using the reverse Kaplan-Meier method. Univariable Cox proportional hazards models were fitted for baseline variables. Given the number of outcome events relative to the number of candidate variables, variables with $P < 0.10$ were entered into the corresponding primary multivariable model to limit the number of fitted coefficients. This pragmatic screening strategy was not intended to define a definitive covariate set and may yield

unstable estimates. Clinically selected multivariable models were therefore fitted as sensitivity analyses and given greater interpretive weight when assessing robustness. LANR was modeled per 5-unit increase and vitamin D per 10 ng/ml increase. Albumin, neutrophil count and lymphocyte count were not entered separately because they are components of LANR.

HER2 status was represented by two dummy variables, with negative status as the reference. Only the not-assessed contrast met the entry criterion and was retained in the multivariable OS model. Because the capecitabine group included only 3 patients, its treatment contrast could not be estimated, and the primary multivariable PFS model was restricted to 138 patients treated with FOLFOX- or FOLFIRI-based regimens, including 121 PFS events. The final OS and PFS models contained 11 and 6 regression coefficients, respectively. Proportional hazards were assessed using Schoenfeld residuals and log-minus-log plots, with no relevant violations identified. Variance inflation factors were assessed against a threshold of 5; no value exceeded 1.76.

Continuous associations of LANR and vitamin D with survival were examined separately using restricted cubic splines in univariable Cox models. Each spline used three degrees of freedom and four knots, with the observed minimum and maximum as boundary knots and two internal knots placed at equally spaced quantiles. Cohort medians were used as reference values. Overall association was assessed with a joint Wald test, and departure from linearity with a likelihood ratio test. Tied event times in these spline models were handled using the Breslow method. Additional implementation and verification details are provided in Data S1 and Table S1.

Discrimination was assessed using Harrell's C-index (15). For each endpoint, a separate clinical reference model was used rather than the full multivariable Cox model. The OS model included metformin use, Eastern Cooperative Oncology Group (ECOG) performance status (16), liver metastasis and BRAF alteration. The PFS model included age group, ACCI group, liver metastasis and chemotherapy backbone. In the PFS model, chemotherapy backbone was coded as FOLFIRI-based vs. non-FOLFIRI-based treatment, so all 141 patients could be included. LANR and vitamin D were then added separately and together. C-index values are apparent estimates and were not corrected for optimism. From 1,000 percentile bootstrap resamples, 95% confidence intervals (95% CIs) were obtained. C-index differences were assessed by paired bootstrap resampling, refitting both models in each resample.

Fixed-horizon discrimination at 12 and 24 months was assessed using receiver operating characteristic analyses with cumulative cases and dynamic controls. Patients who experienced the event by each time point were considered cases, and those who remained event-free beyond that time were controls. Patients censored before the time point had an indeterminate outcome status at that horizon and were therefore excluded; inverse probability of censoring weighting was not used. For single-marker analyses, the negative biomarker value was used so that higher scores indicated higher risk. For the combined analysis, the linear predictor from a Cox model containing both continuous biomarkers was used. CIs for the areas under the curve were obtained from 1,000 percentile bootstrap resamples.

Two sensitivity analyses were performed. First, vitamin D was analyzed as a binary variable, defined as <20 vs. ≥20 ng/ml. Second, Cox models were fitted using clinically selected covariates rather than variables selected by univariable P-value. These models included age group, ECOG performance status, primary tumor location, metastatic burden, BRAF status, targeted therapy class, LANR and vitamin D. Metastatic burden was defined as two or more vs. fewer than two involved sites. The same covariates were used for OS and PFS, and all 141 patients were included. These models assessed whether the biomarker associations persisted under a clinically based adjustment structure that did not depend on univariable P-values and were emphasized when interpreting robustness.

Results

Patient characteristics and survival outcomes. Baseline characteristics of the 141 patients are shown in Table I. The median age was 68.4 years (IQR, 57.8-73.4 years), 79 patients (56.0%) were male and 114 (80.9%) had an ECOG performance status of 0 or 1. The primary tumor was right-sided in 54 patients (38.3%), left-sided in 51 (36.2%) and rectal in 36 (25.5%). Liver metastases were present in 103 patients (73.0%). KRAS alterations were found in 100 patients (70.9%) and BRAF alterations in 10 (7.1%). Anti-VEGF-based treatment was given to 122 patients (86.5%). Median baseline LANR was 10.49 (IQR, 6.75-16.38), and median baseline vitamin D was 11.0 ng/ml (IQR 7.0-21.0), with 103 patients (73.0%) <20 ng/ml.

After a median follow-up of 30.7 months (95% CI, 27.8-36.9 months), 88 mortalities (62.4%) and 124 PFS events

Table I. Baseline characteristics of patients with *de novo* metastatic colorectal cancer.

A, Demographic and anthropometric	
Characteristic	No. of patients
Median age, years	68.4 (57.8-73.4)
Age, years	
<65 years	53 (37.6%)
≥65 years	88 (62.4%)
Sex	
Female	62 (44.0%)
Male	79 (56.0%)
Height, cm	161 (156-170)
Weight, kg	67 (60-75)
BMI, kg/m ²	25.4 (21.9-27.9)
B, Clinical	
Characteristic	No. of patients
ECOG PS	
0-1	114 (80.9%)
2-3	27 (19.1%)
ACCI	
<8	26 (18.4%)
≥8	115 (81.6%)
Smoking history	
Absent	28 (19.9%)
Present	113 (80.1%)
Primary tumor location	
Right-sided colon	54 (38.3%)
Left-sided colon	51 (36.2%)
Rectum	36 (25.5%)
Metastatic sites, present	
Peritoneal metastasis	37 (26.2%)
Liver metastasis	103 (73.0%)
Lung metastasis	33 (23.4%)
Bone metastasis	9 (6.4%)
Ovarian metastasis	5 (3.5%)
Distant lymph node metastasis	35 (24.8%)
C, Treatment	
Characteristic	No. of patients
Anti-EGFR-based treatment	19 (13.5%)
Anti-VEGF-based treatment	122 (86.5%)
FOLFOX-based chemotherapy	101 (71.6%)
FOLFIRI-based chemotherapy	37 (26.2%)
Capecitabine-based chemotherapy	3 (2.1%)
Metformin use	
Absent	82 (58.2%)
Present	59 (41.8%)

Table I. Continued.

D, Molecular	
Characteristic	No. of patients
KRAS alteration	
Absent	41 (29.1%)
Present	100 (70.9%)
NRAS alteration	
Absent	133 (94.3%)
Present	8 (5.7%)
BRAF alteration	
Absent	131 (92.9%)
Present	10 (7.1%)
HER2 status	
Negative	48 (34.0%)
Positive	6 (4.3%)
Not assessed	87 (61.7%)
Microsatellite stable	137 (97.2%)
MSI-H	4 (2.8%)
E, Baseline laboratory markers	
Characteristic	No. of patients
LANR	10.49 (6.75-16.38)
Baseline 25-hydroxyvitamin D, ng/ml	11.0 (7.0-21.0)
Baseline 25-hydroxyvitamin D	
<20 ng/ml	103 (73.0%)
≥20 ng/ml	38 (27.0%)
Albumin, g/l	38.0 (33.0-41.0)
Neutrophil count, /μl	6,210 (4,230-7,460)
Lymphocyte count, /μl	1,650 (1,210-2,050)
Platelet count, /μl	352,000 (296,000-410,000)
Hemoglobin, g/dl	11.8 (10.9-13.2)
CEA, ng/ml	18.0 (5.0-188.0)
CA19-9, U/ml	56.0 (19.0-223.0)

Continuous variables are presented as median (interquartile range) and categorical variables as n (%). LANR was calculated as lymphocyte count multiplied by serum albumin and divided by neutrophil count, using albumin in g/l and lymphocyte and neutrophil counts in /μl. Baseline 25-hydroxyvitamin D is presented both as a continuous variable and dichotomized at 20 ng/ml, the threshold used in the sensitivity analysis. Institutional laboratory reference ranges were as follows: Albumin, 31-46 g/l; neutrophil count, 1,800-7,500/μl; lymphocyte count, 800-3,200/μl; platelet count, 150,000-450,000/μl; hemoglobin, 12-16 g/dl in women and 13-17 g/dl in men; CEA, <5 ng/ml (<6.5 ng/ml in smokers); CA19-9, <34 U/ml; and 25-hydroxyvitamin D, 30-180 ng/ml. LANR is a derived index without an established reference range. 25(OH) D, 25-hydroxyvitamin D; ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index; BRAF, B-Raf proto-oncogene; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; LANR, lymphocyte-albumin-neutrophil ratio; MSI-H, microsatellite instability-high; NRAS, neuroblastoma RAS viral oncogene homolog.

(87.9%) had occurred. Median OS was 23.5 months (95% CI, 19.3-31.5 months), and median PFS was 12.4 months (95% CI, 11.0-13.6 months). These outcomes are summarized in Table SII.

Cox regression analyses. Univariable and multivariable Cox regression results for both endpoints are shown in Table II. Univariable results for variables that did not enter either multivariable model are shown in Table SIII.

Higher LANR was associated with a lower risk of mortality in univariable analysis (HR, 0.76 per 5-unit increase; 95% CI, 0.65-0.89; $P<0.001$) and remained after multivariable analysis (HR, 0.80; 95% CI, 0.66-0.96; $P=0.015$). Metformin use (HR, 0.31; 95% CI, 0.19-0.52; $P<0.001$), higher body mass index (HR, 0.94 per 1 kg/m²; 95% CI, 0.90-0.99; $P=0.020$), ECOG performance status of 2 or 3 (HR, 1.71; 95% CI, 1.00-2.93; $P=0.048$), distant lymph node metastasis (HR, 2.38; 95% CI, 1.27-4.35; $P=0.007$) and BRAF alteration (HR, 3.63; 95% CI, 1.62-8.13; $P=0.002$) were also independently associated with OS. Higher baseline vitamin D was associated with a lower risk of mortality in the univariable analysis (HR, 0.65 per 10 ng/ml increase; 95% CI, 0.50-0.85; $P=0.002$), but the association was not statistically significant after multivariable analysis (HR, 0.80; 95% CI, 0.60-1.08; $P=0.147$).

For PFS, both markers remained associated with outcome after adjustment: LANR (HR, 0.83; 95% CI, 0.72-0.94; $P=0.005$) and vitamin D (HR, 0.80; 95% CI, 0.67-0.93; $P=0.038$). FOLFIRI-based chemotherapy was associated with a higher risk of progression or mortality than FOLFOX-based chemotherapy (HR, 1.67; 95% CI, 1.08-2.57; $P=0.020$).

Spline analyses. Restricted cubic spline curves are shown in Fig. 2 for LANR and Fig. 3 for vitamin D. Higher LANR was associated with lower hazards for both endpoints (overall association: OS, $P<0.001$; PFS, $P=0.010$), with no evidence of non-linearity ($P=0.137$ and $P=0.737$, respectively). Higher vitamin D was also associated with lower hazards (overall association: OS, $P=0.008$; PFS, $P=0.017$), with no evidence of non-linearity ($P=0.519$ and $P=0.815$, respectively).

Discrimination and sensitivity analyses. Discrimination results are shown in Table III. For OS, the C-index of the clinical model was 0.689. Adding LANR (0.721), vitamin D (0.706) or both markers (0.722) increased the C-index, but none of these changes reached statistical significance ($P=0.083$, 0.233 and 0.071, respectively). For PFS, the clinical model C-index was 0.585. Adding LANR (0.618), vitamin D (0.622) or both markers (0.636) increased the C-index, but only the combined addition reached statistical significance ($P=0.135$, 0.061 and 0.039, respectively; Δ C-index 0.051 for the combined model).

In the sensitivity analysis using clinically selected covariates (Table SIV), LANR remained associated with both endpoints (OS: HR, 0.80; 95% CI, 0.68-0.96; $P=0.013$; PFS: HR, 0.83; 95% CI, 0.73-0.94; $P=0.004$). The associations for vitamin D were attenuated and did not reach statistical significance (OS: HR, 0.79; 95% CI, 0.60-1.05; $P=0.108$; PFS: HR, 0.82; 95% CI, 0.66-1.02; $P=0.077$). Results with vitamin D as a binary variable are shown in Tables SV and SVI. Fixed-horizon areas under the curve at 12 and 24 months are shown in Table SVII.

Table II. Univariable and multivariable Cox proportional hazards regression analyses for OS and PFS.

Variable	OS univariable	OS multivariable	PFS univariable	PFS multivariable
LANR, per 5-unit increase	0.76 (0.65-0.89); P<0.001	0.80 (0.66-0.96); P=0.015	0.81 (0.73-0.91); P<0.001	0.83 (0.72-0.94); P=0.005
Baseline 25-hydroxyvitamin D, per 10 ng/ml increase	0.65 (0.50-0.85); P=0.002	0.80 (0.60-1.08); P=0.147	0.73 (0.60-0.89); P=0.002	0.80 (0.67-0.93); P=0.038
Metformin use, present vs. absent	0.43 (0.26-0.69); P<0.001	0.31 (0.19-0.52); P<0.001	0.94 (0.66-1.35); P=0.747	Not entered
Age, ≥65 vs. <65 years	0.90 (0.58-1.41); P=0.648	Not entered	0.72 (0.49-1.04); P=0.078	0.75 (0.45-1.26); P=0.272
BMI, per 1 kg/m ² increase	0.94 (0.90-0.99); P=0.018	0.94 (0.90-0.99); P=0.020	0.97 (0.93-1.01); P=0.110	Not entered
ECOG PS, 2-3 vs. 0-1	2.82 (1.77-4.49); P<0.001	1.71 (1.00-2.93); P=0.048	1.43 (0.92-2.20); P=0.110	Not entered
ACCI, <8 vs. ≥8	0.76 (0.45-1.29); P=0.317	Not entered	0.62 (0.40-0.96); P=0.033	0.93 (0.50-1.72); P=0.816
Liver metastasis, present vs. absent	1.59 (0.94-2.67); P=0.084	1.40 (0.80-2.45); P=0.243	1.63 (1.07-2.47); P=0.022	1.50 (0.95-2.37); P=0.081
Distant lymph node metastasis, present vs. absent	2.04 (1.18-3.57); P=0.012	2.38 (1.27-4.35); P=0.007	2.03 (0.90-4.24); P=0.176	Not entered
FOLFIRI vs. FOLFOX-based chemotherapy	1.13 (0.71-1.80); P=0.611	Not entered	1.47 (0.99-2.19); P=0.059	1.67 (1.08-2.57); P=0.020
BRAF alteration, present vs. absent	2.08 (1.00-4.37); P=0.052	3.63 (1.62-8.13); P=0.002	1.35 (0.65-2.78); P=0.421	Not entered
HER2 status, not assessed vs. absent	1.63 (1.03-2.60); P=0.038	1.42 (0.88-2.30); P=0.156	1.19 (0.81-1.74); P=0.380	Not entered
CA19-9, log-transformed	1.12 (1.01-1.26); P=0.038	1.12 (0.98-1.27); P=0.100	1.06 (0.96-1.16); P=0.248	Not entered
Hemoglobin, per 1 g/dl increase	0.87 (0.77-0.98); P=0.025	0.93 (0.81-1.06); P=0.270	0.93 (0.84-1.03); P=0.169	Not entered

Variables entering at least one endpoint-specific multivariable model are displayed; complete univariable analyses for all assessed variables are provided in Table SIII. Univariable Cox regression was performed for all baseline variables. Variables with P<0.10 in univariable analysis were entered into the corresponding multivariable model. LANR was modeled per 5-unit increase and baseline 25-hydroxyvitamin D per 10 ng/ml increase. Albumin, neutrophil count and lymphocyte count were not entered separately because they are components of LANR. The final OS model included 141 patients with 88 mortalities. The primary multivariable PFS model included 138 patients treated with FOLFOX- or FOLFIRI-based regimens and 121 PFS events, because the capecitabine contrast could not be estimated. ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; LANR, lymphocyte-albumin-neutrophil ratio; OS, overall survival; PFS, progression-free survival.

Discussion

In the present cohort of 141 patients with *de novo* metastatic colorectal cancer who received first-line biologic treatment, higher baseline LANR was associated with lower risks of mortality and of progression or mortality. The estimates were essentially unchanged in models using clinically selected covariates, and spline analyses showed no evidence of departure from linearity. However, the added discrimination beyond the clinical models was modest. Vitamin D, which was evaluated as a secondary exploratory biomarker, showed less consistent associations across endpoints and model specifications.

LANR was initially described in resectable colorectal cancer, in which higher values were associated with longer

overall and disease-free survival (8). A subsequent surgical cohort reported a similar direction of association for a mathematically equivalent albumin to NLR (9), and prognostic associations have been reported in other solid tumors (17-21). These studies largely involved surgically resected or definitively treated populations and commonly categorized the index using study-derived thresholds. The present study examined LANR on its continuous scale in a *de novo* metastatic cohort, thereby evaluating a different disease and treatment setting without deriving an optimal cut-off value from the same data.

The components of LANR provide biological plausibility for a prognostic association, as neutrophils, lymphocytes and albumin relate to systemic inflammation and host

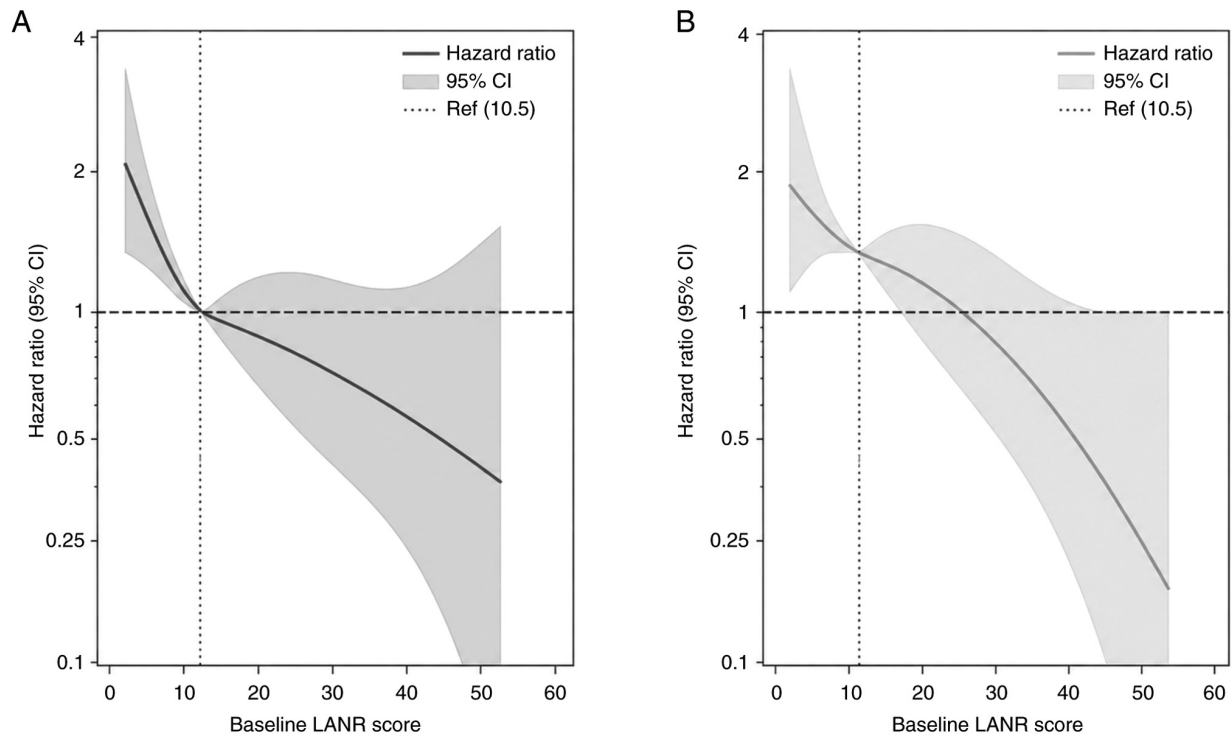


Figure 2. Association between baseline lymphocyte-albumin-neutrophil ratio and survival. (A) Overall survival. (B) Progression-free survival. The solid line denotes the estimated hazard ratio, the shaded area the 95% confidence interval, the horizontal dashed line a hazard ratio of 1.0 and the vertical dotted line the median reference value of 10.5. CI, confidence interval; LANR, lymphocyte-albumin-neutrophil ratio.

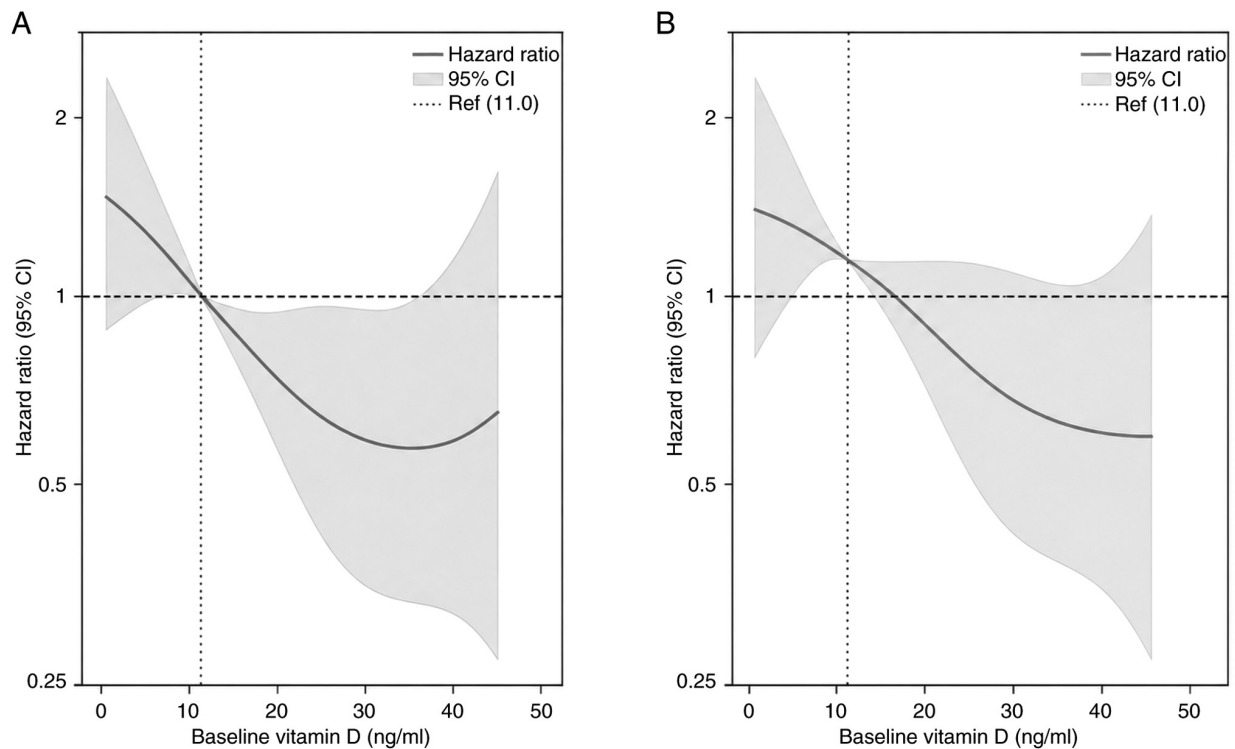


Figure 3. Association between baseline 25-hydroxyvitamin D and survival. (A) Overall survival. (B) Progression-free survival. The solid line denotes the estimated hazard ratio, the shaded area the 95% confidence interval, the horizontal dashed line a hazard ratio of 1.0 and the vertical dotted line the median reference value of 11.0 ng/ml. CI, confidence interval.

condition (2-4). However, LANR does not directly measure antitumor immunity or demonstrate a specific biological mechanism. Its components can be altered by intercurrent infection,

hepatic dysfunction, hydration status, corticosteroids or other medications, recent clinical events, and comorbidity. LANR should therefore be interpreted as a composite prognostic

Table III. Discrimination of clinical and biomarker-augmented models for OS and PFS.

Model	OS C-index (95% CI)	OS ΔC-index	OS P-value	PFS C-index (95% CI)	PFS ΔC-index	PFS P-value
Clinical model	0.689 (0.624-0.751)	Reference		0.585 (0.531-0.641)	Reference	
Clinical model + LANR	0.721 (0.661-0.781)	+0.032	0.083	0.618 (0.560-0.675)	+0.033	0.135
Clinical model + 25(OH)D	0.706 (0.641-0.771)	+0.017	0.233	0.622 (0.568-0.674)	+0.037	0.061
Clinical model + LANR + 25(OH)D	0.722 (0.660-0.782)	+0.033	0.071	0.636 (0.582-0.690)	+0.051	0.039

Clinical reference models were endpoint-specific. The OS model included metformin use, ECOG performance status, liver metastasis and BRAF alteration. The PFS model included age group, ACCI group, liver metastasis and chemotherapy backbone, coded as FOLFIRI-based versus non-FOLFIRI-based treatment. All C-index analyses were performed in the full cohort of 141 patients. Harrell's C-index values are apparent estimates and were not corrected for optimism. Confidence intervals were estimated using 1,000 percentile bootstrap resamples, and differences from the clinical model were tested using paired bootstrap comparisons. The clinical and biomarker-augmented models were refitted and assessed within the same bootstrap samples. 25(OH)D, 25-hydroxyvitamin D; ACCI, age-adjusted Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LANR, lymphocyte-albumin-neutrophil ratio; OS, overall survival; PFS, progression-free survival.

signal rather than a direct measure of a single immune or inflammatory pathway.

LANR can be calculated from routine pretreatment blood counts and serum albumin, but this practicality does not establish clinical utility. Adding LANR to the clinical models increased the C-index by 0.032 for OS and 0.033 for PFS, however neither increment was statistically significant. The analyses were prognostic and did not test treatment-by-biomarker interactions; therefore, they do not show that LANR predicts differential benefit from anti-VEGF therapy, anti-EGFR therapy or chemotherapy backbone. Treatment was not randomly assigned. Although targeted therapy class was included in the clinically selected models and chemotherapy backbone was evaluated, residual confounding by indication and by uncaptured treatment-selection factors remains possible.

Vitamin D was evaluated as a secondary exploratory biomarker and showed a less consistent pattern than LANR. Vitamin D receptor signaling has been proposed to influence colorectal cancer biology (22). Higher baseline 25-hydroxyvitamin D was associated with longer PFS in the primary model but not with OS, and the PFS association was attenuated to non-significant in clinically selected models. Observational studies have linked higher circulating concentrations with improved colorectal cancer outcomes (11,12), but randomized evidence has not established a survival benefit from supplementation of vitamin D. SUNSHINE suggested a possible PFS benefit, although its primary log-rank comparison was not statistically significant (23); AMATERASU did not improve relapse-free survival (24), and SOLARIS did not improve PFS or OS (25). The present findings are hypothesis-generating and do not support a therapeutic benefit from vitamin D supplementation.

Metformin use was associated with OS but not PFS. A previous meta-analysis found that metformin use was associated with better overall survival among patients with colorectal cancer and diabetes, but the association with cancer-specific survival was not statistically significant (26). Because diabetes was not coded as a separate variable and metformin users

were compared with all other patients, this secondary finding is vulnerable to residual confounding and confounding by indication and should be regarded as hypothesis-generating.

The present study has important limitations. Its retrospective, single-center design and relatively small sample of 141 patients limit generalizability. Eligibility required first-line anti-VEGF- or anti-EGFR-based treatment, so the findings do not represent all patients with *de novo* metastatic colorectal cancer, particularly those who did not receive a biologic agent because of frailty, comorbidity, access, or treatment strategy. Exclusion of patients with unavailable laboratory, clinical, molecular or outcome data and the resulting complete-case cohort may also have introduced selection bias.

The primary models used univariable P-value screening, which is data-driven and may produce unstable or overly optimistic estimates. This concern is greater for OS, for which 88 mortalities supported 11 coefficients. Greater emphasis was therefore placed on the similar LANR estimates from the clinically selected sensitivity models. C-index estimates were not corrected for optimism, and no external validation was performed. Treatment-selection criteria and potential transient influences on baseline blood measurements were not systematically captured. Progression was assessed in routine practice without central radiologic review or a standardized study-specific schedule. Fixed-horizon analyses excluded patients censored before each time point without inverse probability weighting, and spline models were unadjusted. The cohort also had low vitamin D concentrations, and LANR was not directly compared with established inflammatory indices. Studies are needed to validate the continuous association and determine whether LANR provides clinically meaningful information beyond established prognostic factors.

To address these limitations, future studies should use larger, prospective, multicenter cohorts with consecutive enrollment, including patients treated without biologic agents. Sample size should be planned according to anticipated outcome events and model complexity, with clinically relevant covariates specified before analysis. Pretreatment sampling, laboratory units and outcome assessment should be standardized, and factors

influencing LANR and treatment selection should be recorded prospectively. LANR should remain a continuous variable, with internal validation to assess optimism and independent external validation to evaluate discrimination and calibration. Direct comparisons with established inflammatory indices and assessment of added value beyond clinical prognostic factors are needed before considering clinical use.

In the present selected cohort of patients with *de novo* metastatic colorectal cancer receiving first-line anti-VEGF- or anti-EGFR-based treatment, higher baseline LANR was associated with longer OS and PFS when analyzed continuously. Its incremental discrimination beyond clinical models was modest, and the study did not assess predictive value for treatment benefit. External validation is required before LANR is considered for clinical application. The vitamin D findings remain secondary and exploratory.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EY conceptualized the study, contributed to the methodology and investigation, curated the data, prepared the visualizations and drafted the manuscript. GCU contributed to the methodology, performed the formal analysis and validation, and critically revised the manuscript. KB, KBY and HS contributed to the investigation, data curation, interpretation of the clinical data and critical revision of the manuscript. MA and OBCO supervised the study, contributed to the clinical interpretation of the survival findings and the associations of LANR and vitamin D with outcomes, and critically revised the manuscript. OS contributed to the conception and design of the study and critically revised the manuscript. All authors contributed to interpretation of the results. EY and GCU confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Scientific Research Evaluation and Ethics Committee of Ankara Etlik City Hospital (approval no. AEŞH-BADEK2-2025-160; 10 June 2025) and was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the ethics committee because of the retrospective study design.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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