Cancer Management and Research

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ORIGINAL RESEARCH

Alcohol Use, Coronary Heart Disease and Hypertension Modify the Predictive Accuracy of Pre-Operative CEA for TNM Staging in Chinese Colorectal Cancer Patients

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Objective: To evaluate the effects of comorbidities and lifestyle factors on the prognostic value of preoperative carcinoembryonic antigen (CEA) for tumor-node-metastasis (TNM) staging in Chinese patients with colorectal cancer (CRC).

Methods: A retrospective cohort study of 307 patients with CRC from Beijing Luhe Hospital (2020–2024) was performed. Clinicopathological data, including TNM and Numerical staging (AJCC 8th edition), serum CEA levels, and covariates (comorbidities and lifestyle factors), were analyzed using univariate and multivariate logistic regression. Multivariable logistic regression with multiplicative interaction terms (CEA × modifier) was used to test for effect modification.

Results: Elevated CEA levels were significantly associated with advanced TNM staging (Stage III–IV vs stage I–II, $p < 0.001$). Multivariate analysis confirmed that CEA was an independent predictor of T stage progression (HR = 1.15, $p = 0.017$), lymph node metastasis (N stage: HR = 1.17, $p = 0.046$), and distant metastasis (M stage: HR = 1.06, $p = 0.018$). Formal interaction analysis revealed that alcohol use significantly amplified the CEA-stage association (HR = 3.11, 95% CI 1.11–8.74, $p = 0.031$), whereas coronary heart disease attenuated the relationship (HR = 0.40, 95% CI 0.18–0.87, $p = 0.022$), yielding a paradoxical inverse association in affected patients. In addition, hypertension nullified the predictive utility of CEA, with a significant stage association observed only in the nonhypertensive subgroup.

Conclusion: Preoperative CEA exhibits robust predictive accuracy for TNM staging in Chinese patients with colorectal cancer; however, this performance is critically modulated by alcohol use, coronary heart disease, and hypertension. Systematic incorporation of these three effect modifiers into preoperative risk-stratification algorithms will refine staging accuracy and enable patient-tailored therapeutic strategies.

Keywords: carcinoembryonic antigen, colorectal cancer, TNM staging, effect modification, precision oncology

Background

Colorectal cancer (CRC) is the third most common malignancy worldwide, with over 1.9 million new cases and 935,000 deaths annually.[1] Accurate staging using the Tumor-Node-Metastasis (TNM) system is critical for prognostic stratification and therapeutic decision-making.[2] However, current staging protocols often rely on invasive procedures, such as lymph node dissection and advanced imaging, underscoring the need for complementary non-invasive biomarkers.[3]

Carcinoembryonic antigen (CEA), a glycoprotein overexpressed in epithelial malignancies, is widely used for postoperative surveillance of CRC.[4] While elevated CEA levels correlate with advanced disease and poor prognosis in Western populations,[5] studies in Asian cohorts have also confirmed their association with tumor stage. Nevertheless, whether comorbidities and lifestyle factors prevalent in specific ethnic groups, such as the Chinese population, modify this relationship remains unclear.

Received: 6 September 2025
Accepted: 17 December 2025
Published: 31 December 2025

Ethnic variations in tumor biology (eg, *KRAS* mutation rates) and lifestyle patterns (eg, smoking and dietary habits) may influence CEA's diagnostic performance.[6] Chinese patients, for instance, exhibit a higher prevalence of left-sided CRC and metabolic comorbidities, such as hypertension and diabetes, than Western cohorts,[7] factors that may modulate CEA expression through inflammatory or metabolic pathways.[8] Hypertension and coronary heart disease are associated with chronic inflammation and endothelial dysfunction, which may alter CEA shedding or clearance. Alcohol intake can induce intestinal permeability and oxidative stress, potentially increasing CEA release, whereas smoking and diabetes may influence its production via systemic metabolic dysregulation.

Despite these plausible mechanisms, the prognostic utility of CEA in Chinese patients with CRC remains inadequately validated, particularly in the context of prevalent comorbidities and lifestyle factors. There is no evidence-based consensus on how to integrate CEA into preoperative risk stratification models for non-Western populations. Although CEA is a well-established prognostic marker for CRC, its predictive accuracy across different ethnic groups, particularly in non-Western populations, remains inadequately validated. Notably, there is a critical lack of evidence on how prevalent host factors, specifically comorbidities such as hypertension and coronary heart disease, and lifestyle factors such as alcohol use, may quantitatively modify the association between preoperative CEA levels and TNM staging in Chinese patients. This gap limits the precise application of CEA in preoperative risk stratification in this population. Therefore, we employed a formal interaction analysis to quantify the effects of hypertension, coronary heart disease, diabetes, smoking, and alcohol consumption on the association between preoperative CEA levels and TNM staging.

Methods

This retrospective cohort study enrolled all consecutive patients with colorectal cancer (CRC) admitted to the Digestive Center at Beijing Luhe Hospital, Capital Medical University, between January 2020 and December 2024. From an initial screening pool of 319 patients, exclusion criteria were rigorously applied to ensure data completeness and cohort homogeneity. Patients with concurrent malignancies (eg, malignant melanoma, n = 1) or incomplete tumor marker profiles (n = 6) and TNM staging data (n = 5) were excluded, resulting in a final cohort of 307 participants (Figure 1).

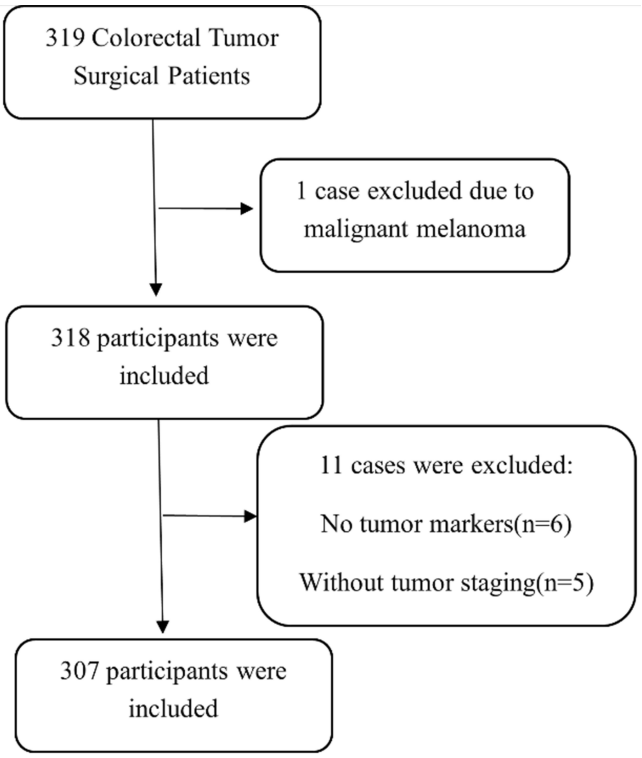

Figure 1 Flowchart of the study population with inclusion and exclusion criteria.

This constituted a complete real-world cohort from our institution for the specified timeframe. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was formally approved by the Ethics Committee of Beijing Luhe Hospital (Approval No. 2023LH-KY-062). Clinical trial number: Not applicable. In accordance with internationally recognized standards (CIOMS International Ethical Guidelines for Health-Related Research Involving Humans, Guideline 7), the committee granted a waiver for individual informed consent for this study. This determination considered the exclusive use of fully anonymized retrospective data presenting minimal risk to participants, coupled with the impracticality of obtaining consent due to cohort size, temporal scope, and lack of current contact information, while ensuring that the waiver would not adversely affect the rights and welfare of the participants.

Standardized protocols were used to systematically extract de-identified demographic, clinical, and pathological data from electronic medical records. Data extraction was performed by two trained researchers using a standardized pre-piloted electronic form. To ensure accuracy, a random sample (10%) of records underwent independent re-abstraction, and discrepancies were resolved by consensus involving a senior clinician. All personally identifiable information, including patient names, identification numbers, contact details, and exact admission dates, was removed or obscured during the data extraction phase to ensure anonymity, comply with institutional data protection policies and ethical guidelines. Baseline variables included age, sex, alcohol use (regular consumption of ≥1 standard drink per week for a duration of over six months), and smoking status, which was classified as never (<100 lifetime cigarettes), former (quit ≥12 months prior to diagnosis), or current (smoked within 12 months of diagnosis). Comorbidities were categorized as hypertension (systolic blood pressure ≥140 mmHg, diastolic ≥90 mmHg, or use of antihypertensive medications), diabetes mellitus (fasting plasma glucose ≥7.0 mmol/L, HbA1c ≥6.5%, or use of hypoglycemic therapy), and hyperlipidemia (LDL cholesterol ≥3.4 mmol/L, triglycerides ≥1.7 mmol/L, or use of lipid-lowering treatment). Tumor characteristics included anatomical location (left colon: splenic flexure to rectum; right colon: cecum to transverse colon) and TNM staging, which was independently verified by two blinded pathologists in accordance with the American Joint Committee on Cancer (AJCC) 8th edition.

Preoperative serum biomarkers, including carcinoembryonic antigen (CEA), carbohydrate antigens 125 (CA125), 153 (CA153), and 19–9 (CA199), alpha-fetoprotein (AFP), and ferritin, were quantified using a chemiluminescent microparticle assay (Abbott i2000SR, Abbott Laboratories Diagnostics Division, Abbott Park, IL 60064, USA). All assays were performed in duplicate under strict quality control protocols, with inter- and intra-assay coefficients of variation maintained below 5% to ensure analytical precision.

The primary outcome was the association between preoperative serum CEA levels and advanced colorectal cancer staging (Stage III–IV vs stage I–II). The secondary outcomes included the independent associations of CEA with tumor invasion depth (T stage), lymph node metastasis (N stage), and distant metastasis (M stage).

Statistical analyses were conducted using the Free Statistics platform (version 2.1). Continuous variables were assessed for normality using histograms, Q-Q plots, and the Kolmogorov–Smirnov test, with normally distributed data expressed as mean ± standard deviation (SD) and non-normally distributed data expressed as median (interquartile range, IQR). Categorical variables are expressed as frequencies and percentages. Group comparisons were performed using the Student's *t*-test or Mann–Whitney *U*-test for continuous variables and Pearson's χ^2 or Fisher's exact test for categorical variables. Missing covariate data were addressed using multiple imputation by chained equations (MICE), generating five complete data sets. The final estimates were obtained by pooling the results across these datasets, following Rubin's rules. Elevated CEA levels were defined as serum levels ≥5 ng/mL based on the NCCN clinical cutoff. The primary analysis tested the interaction effects between CEA (continuous) and modifiers (comorbidities/lifestyle) using multiplicative interaction terms in the logistic regression. Multivariate logistic regression models were constructed using a conceptual approach. Core demographic variables (age and sex) were included a priori. Tumor location was also retained for its clinical relevance. Other covariates (comorbidities and additional biomarkers) were selected for inclusion if they demonstrated a univariate association with the outcome ($p < 0.01$) or were established prognostic factors in the literature. This strategy ensured a parsimonious yet clinically comprehensive adjustment. The key model assumptions were verified. The linearity of the logit for the continuous predictor (CEA) was tested using the Box-Tidwell procedure, and the absence of multicollinearity among all covariates was confirmed by variance inflation factors (all VIF < 2.0). The

goodness of fit of the final multivariate models was assessed using the Hosmer-Lemeshow test. Sensitivity and subgroup analyses were performed to validate robustness, with a two-sided p-value <0.05 deemed statistically significant.

Results

The study cohort included 307 patients with colorectal cancer (CRC) with a mean age of 61.4 ± 10.2 years and predominantly male (57.7%). Hypertension (45.0%), diabetes (22.1%), and hyperlipidemia (28.0%) were the most common comorbidities, and left-sided tumors accounted for 79.8% of cases. For analytical clarity, TNM stages were categorized into Stage I–II (45.3%, n = 139) and Stage III–IV (54.7%, n = 168). Preoperative serum carcinoembryonic antigen (CEA) levels were significantly elevated in Stage III–IV patients (8.6 ± 6.9 ng/mL) compared to Stage I–II patients (5.2 ± 3.5 ng/mL; $p < 0.001$), underscoring its potential utility in distinguishing advanced disease (Table 1).

Table 1 Basic Characteristics of the Study Population and the Results of Observations

Variables	Total (n = 307)	Stage I–II (n = 136)	Stage III–IV (n = 171)	*p* values
Gender, n (%)				0.428
Female	130 (42.3)	61 (44.9)	69 (40.4)	
Male	177 (57.7)	75 (55.1)	102 (59.6)	
Age, n (%)				0.618
<50	30 (9.8)	12 (8.8)	18 (10.5)	
≥50	277 (90.2)	124 (91.2)	153 (89.5)	
HBp, n (%)				0.666
No	169 (55.0)	73 (53.7)	96 (56.1)	
Yes	138 (45.0)	63 (46.3)	75 (43.9)	
DM, n (%)				0.973
No	239 (77.9)	106 (77.9)	133 (77.8)	
Yes	68 (22.1)	30 (22.1)	38 (22.2)	
HLP, n (%)				0.458
No	221 (72.0)	95 (69.9)	126 (73.7)	
Yes	86 (28.0)	41 (30.1)	45 (26.3)	
CHD, n (%)				0.07
No	261 (85.0)	110 (80.9)	151 (88.3)	
Yes	46 (15.0)	26 (19.1)	20 (11.7)	
Smoking, n (%)				0.306
No	240 (78.2)	110 (80.9)	130 (76)	
Yes	67 (21.8)	26 (19.1)	41 (24)	
Drinking, n (%)				0.02
No	251 (81.8)	119 (87.5)	132 (77.2)	
Yes	56 (18.2)	17 (12.5)	39 (22.8)	
Family History, n (%)				0.697
No	301 (98.0)	134 (98.5)	167 (97.7)	
Yes	6 (2.0)	2 (1.5)	4 (2.3)	
Location, n (%)				0.661
Left-sided	245 (79.8)	107 (78.7)	138 (80.7)	
Right-sided	62 (20.2)	29 (21.3)	33 (19.3)	
CA125, Mean ± SD	14.5 ± 10.9	13.9 ± 9.9	15.0 ± 11.7	0.415
AFP, Mean ± SD	3.0 ± 1.8	3.0 ± 1.8	3.0 ± 1.8	0.972
CEA, Mean ± SD	6.8 ± 7.5	5.2 ± 6.5	8.1 ± 8.0	< 0.001
CA199, Mean ± SD	13.7 ± 19.6	11.0 ± 16.1	16.2 ± 22.0	0.026
CA153, Mean ± SD	7.9 ± 3.9	7.9 ± 4.0	8.0 ± 3.8	0.789
Ferritin, Mean ± SD	101.2 ± 92.1	98.8 ± 81.9	103.2 ± 99.8	0.688

Univariate analysis demonstrated a strong association between elevated CEA levels and advanced-stage CRC (Stage III–IV vs stage I–II: hazard ratio [HR] = 1.06 per 1 ng/mL increase, 95% confidence interval [CI]: 1.02–1.11, $p < 0.022$). This association remained robust in multivariate models adjusted for age, sex, comorbidities (hypertension, diabetes, hyperlipidemia), lifestyle factors (smoking, alcohol use), tumor location, and additional biomarkers (CA125, CA199, AFP, CA153, Ferritin), with CEA retaining independent prognostic value (HR = 1.05, 95% CI: 1.01–1.9, $p = 0.019$) (Table 2).

Elevated preoperative serum carcinoembryonic antigen (CEA) levels were significantly correlated with advanced tumor invasion (T stage: univariate HR = 1.16, 95% CI: 1.04–1.28, $p = 0.007$; multivariate HR = 1.15, 95% CI: 1.02–1.28, $p = 0.017$), lymph node metastasis (N stage: univariate HR = 1.04, 95% CI: 1.01–1.08, $p = 0.022$; multivariate HR = 1.17, 95% CI: 1.15–2.95, $p = 0.046$), and distant metastasis (M stage: univariate HR = 1.07, 95% CI: 1.03–1.11, $p = 0.001$; multivariate HR = 1.06, 95% CI: 1.01–1.11, $p = 0.018$), indicating consistent associations across the TNM components (Table 3).

Table 2 Association Between CEA Levels and Numerical Staging in Colorectal Cancer: Univariate and Multivariate Analysis

Covariables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Male	1.2 (0.76~1.9)	0.428	0.89 (0.47~1.67)	0.709
≥50	0.82 (0.38~1.77)	0.618	1.17 (0.46~2.95)	0.746
HBp	0.91 (0.58~1.42)	0.666	0.84 (0.47~1.51)	0.568
DM	1.01 (0.59~1.74)	0.973	1.29 (0.64~2.61)	0.47
HLP	0.83 (0.5~1.36)	0.458	1.08 (0.58~2)	0.818
CHD	0.56 (0.3~1.05)	0.073	0.40 (0.18~0.87)	0.022
Smoking	1.33 (0.77~2.32)	0.307	0.89 (0.35~2.26)	0.801
Drinking	2.07 (1.11~3.85)	0.022	3.11 (1.11~8.74)	0.031
Family History	1.60 (0.29~8.9)	0.588	1.11 (0.12~9.83)	0.927
Right-sided	0.88 (0.5~1.54)	0.661	0.98 (0.46~2.08)	0.958
CEA	1.06 (1.02~1.11)	0.002	1.05 (1.01~1.09)	0.019
AFP	1.00 (0.88~1.13)	0.972	0.92 (0.78~1.08)	0.292
CA125	1.01 (0.99~1.03)	0.415	1.01 (0.98~1.04)	0.500
CA153	1.01 (0.95~1.07)	0.788	0.99 (0.92~1.06)	0.765
CA199	1.02 (1~1.03)	0.031	1.01 (0.99~1.03)	0.193
Ferritin	1.00 (1~1)	0.687	1.00 (1~1)	0.530

Table 3 Association Between CEA Levels and TNM Staging in Colorectal Cancer: Univariate and Multivariate Analysis

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
T	1.16 (1.04~1.28)	0.007	1.15 (1.02~1.28)	0.017
N	1.04 (1.01~1.08)	0.022	1.02 (1.01~2.35)	0.046
M	1.07 (1.03~1.11)	0.001	1.06 (1.01~1.11)	0.018

Notes: Adjusted Variables in Multivariate Model: sex, age, Hypertension, Diabetes, Hyperlipidemia, Coronary Heart disease, smoking, Family history, Tumor location.

https://doi.org/10.2147/CMAR.S565785

Table 4 Effect Modification of CEA-Staging Association by Comorbidities and Lifestyle Factors

Modifier	Interaction OR (95% CI)	*P*-Interaction
Alcohol use	3.11 (1.11–8.74)	0.031
CHD	0.40 (0.18–0.87)	0.022
Hypertension	0.84 (0.47~1.51)	0.568

The forest plot displays hazard ratios (HR) and 95% confidence intervals derived from the logistic regression analysis. The model was adjusted for age, sex, comorbidities (hypertension; DM: diabetes mellitus, hyperlipidemia; CHD: coronary heart disease), lifestyle factors (smoking and drinking), family history, tumor location (left vs right colon), and serum biomarkers (CEA, CA125, AFP, CA153, ferritin, CA199). Asterisks (*) indicate statistically significant predictors ($p < 0.05$), The vertical line at HR = 1 represents the null effect. Notably, Interaction testing revealed that alcohol use significantly amplified the CEA stage association (interaction HR 3.11, 95% CI 1.11–8.74, $p = 0.031$). Conversely, CHD attenuated this association (interaction HR 0.40, 95% CI 0.18–0.87, $P = 0.022$) (Table 4), yielding a paradoxical inverse relationship. Hypertension abolished predictive utility (Adj.OR 1.11, significant solely in non-hypertensive patients). No significant interactions were observed for diabetes (HR = 1.29, 95% CI, 0.64–2.61; $p = 0.470$), hyperlipidemia (HR = 1.08, 95% CI, 0.58–2.00; $p = 0.818$), or tumor location (HR = 0.98, 95% CI, 0.46–2.08; $p = 0.958$) (Figure 2).

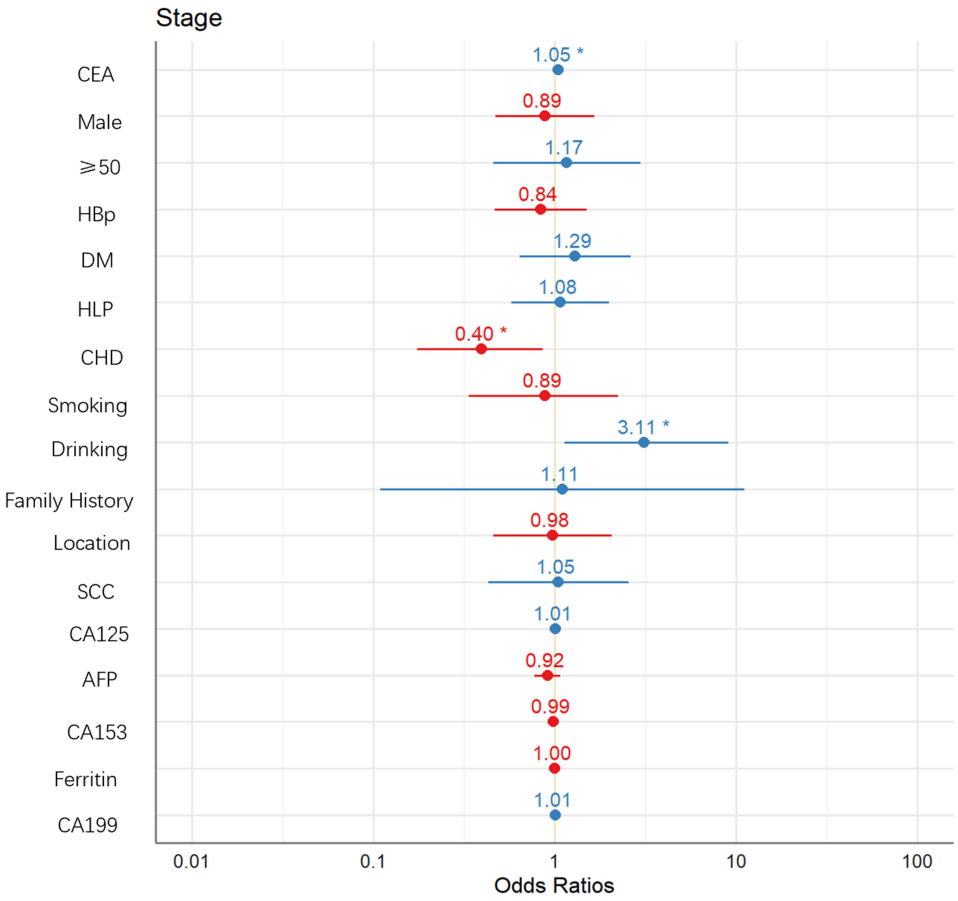

Figure 2 Multivariable-adjusted associations between clinical factors and advanced colorectal cancer staging (Stage III–IV vs I–II). Forest plot displays adjusted odds ratios (adj.OR) and 95% confidence intervals (horizontal lines) derived from logistic regression analysis. The model was adjusted for all variables listed. The vertical dashed line at an odds ratio of 1 represents the null effect (no association). An odds ratio >1 indicates increased odds of advanced-stage disease, while an odds ratio <1 indicates decreased odds. Symbols: Red-colored data points and asterisks (*) denote statistically significant associations (p* < 0.05). Blue-colored data points represent non-significant associations.

Abbreviations: CEA, carcinoembryonic antigen; HBP, hypertension; DM, diabetes mellitus; HLP, hyperlipidemia; CHD, coronary heart disease; SCC, squamous cell carcinoma antigen; CA125, cancer antigen 125; CA15-3, carbohydrate antigen 15–3; CA19-9, carbohydrate antigen 19–9; AFP, alpha-fetoprotein.

Table 5 CEA Levels and Clinical Outcomes in Colorectal Cancer: Multivariable Subgroup and Interaction Analysis

Subgroup	Variable	n.total	n.event_%	crude.OR_95CI	crude. P_value	adj.OR_95CI	adj.P_value	P.for. interaction_1	P.for. interaction_2
Gender=1	CEA	130	69 (53.1)	1.04 (0.99~1.09)	0.094	1.03 (0.98~1.09)	0.292	0.315	0.324
Gender=2	CEA	177	102 (57.6)	1.09 (1.03~1.17)	0.005	1.07 (1~1.15)	0.058		
HBp=0	CEA	169	96 (56.8)	1.14 (1.05~1.23)	0.001	1.11 (1.03~1.2)	0.006	0.061	0.077
HBp=1	CEA	138	75 (54.3)	1.03 (0.98~1.08)	0.199	1.03 (0.98~1.09)	0.264		
DM=0	CEA	239	133 (55.6)	1.08 (1.03~1.13)	0.001	1.05 (1.01~1.1)	0.025	0.295	0.291
DM=1	CEA	68	38 (55.9)	1.02 (0.94~1.09)	0.679	1.04 (0.92~1.17)	0.536		
HLP=0	CEA	221	126 (57)	1.08 (1.03~1.13)	0.002	1.07 (1.01~1.12)	0.011	0.319	0.315
HLP=1	CEA	86	45 (52.3)	1.03 (0.96~1.1)	0.371	0.98 (0.9~1.07)	0.66		
Drinking=0	CEA	251	132 (52.6)	1.09 (1.04~1.14)	0.001	1.12 (1.06~1.19)	0.002	0.003	0.004
Drinking=1	CEA	56	39 (69.6)	1.25 (1.12~1.40)	0.001	1.35 (1.16~1.57)	0.001		
Smoking=0	CEA	240	130 (54.2)	1.06 (1.01~1.1)	0.013	1.04 (1~1.09)	0.08	0.376	0.4
Smoking=1	CEA	67	41 (61.2)	1.09 (1~1.19)	0.06	1.12 (0.98~1.27)	0.085		
CHD=0	CEA	261	151 (57.9)	1.07 (1.02~1.12)	0.006	1.05 (1.00~1.10)	0.051	0.022	0.028
CHD=1	CEA	46	20 (43.5)	0.88 (0.99~0.98)	0.021	0.85 (0.75~0.96)	0.012		
Location=1	CEA	245	138 (56.3)	1.06 (1.02~1.1)	0.006	1.04 (1~1.09)	0.064	0.471	0.515
Location=2	CEA	62	33 (53.2)	1.10 (0.96~1.26)	0.16	1.42 (0.84~2.41)	0.186		

Notes: Subgroups of patients aged <50 years (n=30) and those with a family history of colorectal cancer (n=6) were excluded from this analysis due to an insufficient number of events to ensure statistical stability.

Formal interaction tests revealed significant effect modification: alcohol use amplified CEA's association with advanced staging (p-interaction=0.031), whereas CHD attenuated it (p-interaction=0.022). Elevated CEA levels were significantly associated with adverse outcomes in non-hypertensive (adj.OR = 1.11, 95% CI: 1.03–1.20, p=0.006) and non-diabetic patients (adj.OR=1.05, 95% CI: 1.01–1.10, p= 0.025), but not in hypertensive or diabetic subgroups (p> 0.05). Significant associations were also observed in non-drinkers (adj.OR = 1.12, 95% CI: 1.06–1.19, p = 0.002) and non-hyperlipidemic patients (HLP=0: adj.OR = 1.07, 95% CI: 1.01–1.12, p= 0.011). A borderline association existed for non-smokers (adj. OR = 1.04, 95% CI: 1.00–1.09, p= 0.080). Notably, drinkers exhibited a stronger effect size than non-drinkers (adj.OR = 1.35 vs 1.12; interaction p = 0.004). Patients with coronary heart disease (CHD) showed a paradoxical protective association (adj.OR = 0.85, 95% CI: 0.75–0.96, p= 0.012), contrasting with non-CHD patients (adj.OR = 1.05, p = 0.051; interaction p = 0.028). It is important to note that the subgroup of patients with CHD was relatively small (n=46). Consequently, the point estimate for the paradoxical inverse association (adj.OR = 0.85), while statistically significant, should be interpreted with caution because of its limited precision and potential instability. Tumor location did not significantly modify CEA's prognostic value of CEA (p > 0.05).

Interaction analyses revealed no statistically significant effect modification by demographic factors, comorbidities, or lifestyle factors (p>0.05 for all variables). Subgroups with insufficient event numbers (eg, age <50 years, n = 30; family history of CRC, n = 6) were excluded to ensure robust estimates of the hazard ratios. These results indicate that while CEA's association between CEA and advanced TNM staging varies across subgroups, its association with advanced TNM staging is consistent in magnitude without multiplicative interaction effects (Table 5).

Discussion

This study demonstrates that the prognostic utility of preoperative CEA is critically modified by alcohol use, CHD, and hypertension. Notably, elevated CEA levels were significantly correlated with Stage III–IV disease (adjusted HR = 1.05, 95% CI: 1.01–1.09, p = 0.019). After multivariable adjustment, similar associations were observed for T-stage progression (adj.HR = 1.15, p = 0.017), N-stage metastasis (adj.HR = 1.2, p = 0.046), and M-stage metastasis (adj.HR = 1.06, p = 0.018). These results are consistent with those of prior studies conducted in Western and Asian cohorts.[9,10] This study confirmed that elevated preoperative CEA levels correlated with advanced T stage, supporting its role in modulating cell adhesion and immune evasion during local invasion.[11] Its association with lymph node and distant metastases further

establishes CEA as a systemic biomarker of tumor aggressiveness,[12] which is particularly valuable in resource-limited settings, where minimally invasive tools are needed for staging.[13]

Subgroup analyses revealed critical effect modifications: alcohol consumption amplified CEA's prognostic value of CEA (interaction HR = 3.11, 95% CI: 1.11–8.74, $p = 0.031$), with drinkers demonstrating stronger associations (adj.OR = 1.35 compared to 1.12 in non-drinkers). Conversely, coronary heart disease (CHD) was linked to an attenuation of the association (interaction HR = 0.40, 95% CI: 0.18–0.87, $p = 0.022$), resulting in a paradoxical inverse association in patients with CHD (adj.OR = 0.85, 95% CI: 0.75–0.96, $p = 0.012$), suggesting that systemic inflammation or cardiovascular medications might influence CEA dynamics, warranting mechanistic investigations.[14] Clinically, CEA may underestimate the tumor stage in patients with CHD; therefore, corroboration with imaging is mandatory. It was also observed that hypertension negated CEA's predictive utility, with significant associations being confined to non-hypertensive patients (adj.OR = 1.11, 95% CI: 1.03–1.20, $p = 0.006$). These findings emphasize the importance of integrating ethnicity-specific modifiers into CEA-based staging models.[15] Subgroup analyses revealed heterogeneity in CEA's prognostic utility of CEA. The significant interaction between CEA and alcohol consumption suggests that ethanol-induced mucosal damage or metabolic alterations may amplify CEA's association between CEA and advanced disease.[16] Clinically, a CEA $\geq$ 5 ng/mL in alcohol users should trigger intensified staging work-up. Conversely, the lack of association in hypertensive subgroups could reflect competing pathways involving angiotensin-converting enzyme inhibitors or beta-blockers, which may independently influence tumor biology.[17] Clinically, CEA should not be used as a solitary staging tool in patients with hypertension. These findings emphasize the need for personalized biomarker interpretation that integrates both tumor and host factors.

This study provides a crucial refinement to the conventional use of preoperative CEA by demonstrating that its prognostic value is not uniform but is significantly modified by specific comorbidities and lifestyle factors. While the correlation between elevated CEA levels and advanced TNM stage is well established, our findings introduce a more nuanced, patient-specific interpretive framework. The significant interaction effects observed suggest that a single CEA threshold may be insufficient for accurate risk stratification in all patient subgroups. Instead, clinical interpretation should be contextualized by the patient's profile of hypertension, coronary heart disease, and alcohol use. This conceptual shift aligns with the principles of precision oncology and, upon further validation, could inform more tailored preoperative evaluation protocols.

Despite its strengths, including the rigorous adjustment for confounders, this study had several limitations. The retrospective, single-center design may have introduced selection bias and limited the generalizability of the findings. Although rigorous exclusion criteria for incomplete records and standardized blinded pathological review of TNM staging were implemented to enhance data quality, the inherent risks of selection bias and unmeasured confounding in retrospective studies persist in this study. Notably, residual confounding from unrecorded factors, such as detailed medication use and dietary habits, cannot be excluded. Furthermore, the lack of data on common genetic alterations (eg, in KRAS, BRAF, or TP53) represents a limitation, as such mutations may influence both tumor aggressiveness and CEA expression, contributing to unmeasured confounding factors. Additionally, while the overall cohort size was sufficient for the primary analysis, the statistical power was limited in specific subgroup analyses, particularly for smaller groups, such as patients with coronary heart disease (n = 46). The finding of an attenuated and even inverse association between CEA and advanced stage in patients with CHD is intriguing but requires validation in larger, prospective cohorts. The limited sample size of this subgroup precludes definitive conclusions and highlights the need for future studies with dedicated recruitment for such comorbidities to confirm these findings. Future research should explore the molecular mechanisms linking CEA to CRC progression, particularly its interaction with immune checkpoints (eg, PD-L1) or epigenetic regulators,[18] and evaluate CEA's utility in the longitudinal monitoring of treatment response.[19]

Although circulating tumor DNA (ctDNA) has emerged as a promising tool for molecular profiling and minimal residual disease detection in colorectal cancer,[20,21] its clinical utility remains constrained by high costs, technical complexity, and limited accessibility in resource-constrained settings. In contrast, CEA has critical advantages as a cost-effective and widely available biomarker for preoperative risk stratification. CEA remains a cost-effective staging adjunct to precision oncology, guiding ctDNA triage in resource-limited settings.

In conclusion, this study establishes that preoperative CEA retains independent prognostic power for TNM staging in Chinese colorectal cancer patients, but its predictive performance is critically reshaped by alcohol use, coronary heart disease, and hypertension. These findings support a more personalized interpretation of this common biomarker. However, the strength of the observed interactions, particularly within smaller subgroups, should be interpreted cautiously. Future prospective multicenter studies with larger sample sizes are essential to validate these effect modifications and explore the underlying biological mechanisms. If confirmed, these results could provide an evidence base for integrating these specific modifiers into preoperative risk-stratification algorithms, thereby advancing precision oncology for this population.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to patient privacy restrictions but are available from the corresponding author (Baohong Xu; email: bhxu_22@126.com) upon reasonable request. All shared data will be de-identified to comply with the institutional data protection policies.

Acknowledgment

Dayu Kuai and Juan Cheng are co-first authors. We gratefully acknowledge all participating patients for their essential contributions to this study. We also thank the medical and technical staff at Beijing Luhe Hospital for their dedicated clinical and laboratory support of this study. Special recognition is extended to Dr. Jie Liu (Department of Vascular Surgery, Chinese PLA General Hospital) for his expert consultation on the study design and statistical analyses.

Disclosure

The authors report no conflicts of interest in this study.

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