

Dynamic CEA trajectories predict survival for non-metastatic colon cancer: development and validation of a combined prognostic model

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Abstract

Background

Accurate postoperative risk stratification is critical for stage I–III colon cancer. While carcinoembryonic antigen (CEA) is the standard biomarker, static thresholds overlook temporal dynamics. This study developed a novel CEA trajectory-based classification and evaluated its prognostic value for overall survival (OS) and disease-free survival (DFS) after curative resection.

Methods

This single-center retrospective cohort study included 1,126 patients with stage I–III colon cancer who underwent R0 resection at Zhejiang Cancer Hospital between January 2010 and December 2025. A four-category CEA trajectory grouping method (low-stable, early-rising, late-rising, and sustained-high) was developed based on temporal slope parameters. Prognostic models (clinicopathological, CEA trajectory, combined) were compared using C-index, AUC, calibration, and DCA with 500 bootstrap resamples.

Results

The four CEA trajectory groups showed significantly different survival outcomes (log-rank $P < 0.001$ for both OS and DFS). The sustained-high group exhibited the worst prognosis, with 5-year OS and DFS rates of 34.9% and 36.6%, respectively. The CEA trajectory model alone demonstrated non-inferior performance compared with the clinicopathological model for both OS (C-index: 0.773 vs. 0.736, $P = 0.314$) and DFS (C-index: 0.738 vs. 0.735, $P = 0.802$). The combined model significantly outperformed both individual models, achieving C-indexes of 0.841 for OS and 0.819 for DFS (both $P < 0.001$ vs. individual models), with time-dependent AUC values ranging from 0.811 to 0.865. Calibration curves showed good agreement for all models (integrated absolute error < 0.03). DCA showed trajectory model offered higher net benefit for OS across most thresholds and for high-risk DFS (> 0.2). Inflammatory markers (NLR, PLR, LMR, SII) showed no significant prognostic value in multivariable analyses.

Conclusion

Dynamic CEA trajectory provides complementary prognostic value. Combined model achieves excellent performance, but optimal model choice depends on clinical threshold. Integrating longitudinal CEA monitoring into postoperative risk assessment is recommended.

1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies worldwide. According to GLOBOCAN 2020 data, there are approximately 1.9 million new cases and 0.93 million deaths annually [1]. The disease burden is projected to increase further to 3.2 million new cases and 1.6 million deaths per year by 2040 [2]. Despite continuous advances in surgical techniques and adjuvant therapy, approximately 30%-50% of patients with stage I–III CRC experience disease recurrence after curative resection [3, 4]. Therefore, accurate postoperative risk stratification is essential to guide adjuvant treatment decisions and optimize surveillance strategies.

Carcinoembryonic antigen (CEA) is the most widely used tumor biomarker for CRC in clinical practice and is routinely employed for postoperative monitoring [5]. However, conventional CEA assessment relies on a static threshold (typically 5 ng/mL), which fails to capture the dynamic characteristics of tumor changes over time [6]. Recent studies suggest that

longitudinal CEA trajectories may provide more valuable prognostic information than single measurements [7, 8]. Du et al. [9] extracted longitudinal trajectory features of CEA and CA19-9 within 12 months after surgery using multivariate functional principal component analysis and constructed a MFPC-Cox dynamic prediction model, which increased the 60-month AUC from 0.727 to 0.787. Wang et al. [10] identified three CEA trajectory patterns using latent class growth mixed modeling and demonstrated that an increasing trajectory independently predicted worse survival outcomes. Furthermore, Hamfjord et al. [11] showed that early kinetics of CEA and ctDNA were significantly associated with radiological response and survival in patients with metastatic CRC, further supporting the clinical value of longitudinal biomarker monitoring. In locally advanced rectal cancer, Yilmaz et al. [12] confirmed that integrating dynamic changes in CEA and NLR after chemoradiotherapy significantly improved prognostic accuracy, with a combined AUC of 0.84.

Beyond CEA, inflammation-related biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have been shown to reflect host immune status and possess prognostic value in various malignancies [13, 14]. However, the optimal timing for measuring postoperative inflammatory markers remains controversial. A longitudinal study published in *Annals of Surgery* included 2,280 patients with colorectal cancer and confirmed that the optimal reassessment window for postoperative NLR and LMR is between 21 and 56 days after surgery [15]. During this period, the acute inflammatory response induced by surgical trauma has largely subsided, representing a post-recovery state that reflects the "tumor microenvironment" and best captures the patient's long-term immune-inflammatory status. Based on this evidence, the present study selected this time window for postoperative blood collection and aimed to investigate the role of inflammatory markers in the dynamic changes of CEA.

Given the above background, the present study developed a four-category CEA trajectory grouping method based on time-slope parameters in a large cohort of 1,126 patients with stage I-III colon cancer and systematically evaluated its prognostic value. We constructed three prediction models: a clinicopathological model, a CEA trajectory model, and a combined model. Model performance was comprehensively assessed using the C-index, time-dependent AUC, calibration curves, and decision curve analysis (DCA). We hypothesized that dynamic CEA trajectory would provide prognostic information complementary to clinicopathological factors and that the combined model would achieve superior predictive accuracy and clinical utility.

2. Methods

2.1 Study Design and Population

This single-center retrospective cohort study included patients with stage I–III colon cancer who underwent curative resection at Zhejiang Cancer Hospital between January 2010 and December 2025. Inclusion criteria were: (1) histopathologically confirmed colorectal cancer; (2) underwent R0 resection; (3) had at least two postoperative CEA measurements. Exclusion criteria were: (1) receipt of neoadjuvant therapy; (2) presence of other malignancies; (3) confirmed infection within 30 days post-surgery (fever > 38.5°C, positive blood culture, or imaging-confirmed infection focus); (4) chronic inflammatory diseases (e.g., inflammatory bowel disease, rheumatoid arthritis); (5) insufficient follow-up data. A total of 1,126 patients were ultimately enrolled. This study was approved by the Ethics Committee of Zhejiang Cancer Hospital, and informed consent was waived due to the retrospective design.

2.2 Data Collection

The following data were extracted from the electronic medical record system: (1) Demographic and clinical characteristics: age, sex, body mass index (BMI). (2) Tumor pathological characteristics: tumor size, tumor location, T stage (8th edition AJCC), N stage, differentiation, lymphovascular invasion, perineural invasion, macroscopic type, histological type, preoperative CA125 level, preoperative CA199 level. (3) Treatment information: surgical approach (laparoscopic/open), adjuvant chemotherapy (yes/no, regimen, and cycles), ESD/EMR (yes/no), number of harvested lymph nodes. (4) CEA dynamic data: preoperative CEA level (within one week before surgery) and all postoperative follow-up CEA values (with

measurement dates and corresponding values). (5) Inflammatory markers: complete blood count results obtained at the first postoperative follow-up (corresponding to postoperative days 21–56) were used to calculate: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; SII = platelet count $\times$ NLR. (6) Outcome measures: The primary outcome was overall survival (OS), defined as the time from the date of curative surgery to death or last follow-up. The secondary outcome was disease-free survival (DFS), defined as the time from surgery to first recurrence (local recurrence or distant metastasis) or last follow-up. Recurrence was confirmed by imaging (CT/MRI) or pathological biopsy.

2.3 CEA Trajectory Grouping Method

We initially attempted to explore latent trajectory classes using latent class growth mixture modeling (LCGMM); however, the model exhibited unstable convergence and resulted in extreme class imbalance. Therefore, we developed a more robust and interpretable four-category classification rule based on clinical knowledge and data distribution characteristics, using temporal slope parameters (including the short-term slope within 12 months post-surgery [slope_short] and the long-term slope after 12 months [slope_long]) and mean CEA levels for grouping: Sustained-high type: Mean CEA level ≥ 5 ng/mL. Early-rising type: Rate of CEA increase within 12 months post-surgery significantly higher than after 12 months (slope difference [slope_diff = slope_short – slope_long] >75 th percentile), suggesting a high risk of short-term recurrence. Late-rising type: Rate of CEA increase after 12 months post-surgery significantly higher than within 12 months (slope_diff < 25 th percentile), suggesting a high risk of long-term recurrence. Low-stable type: Patients who did not meet any of the above three criteria, characterized by consistently stable CEA levels with minimal fluctuation, indicating the lowest risk of recurrence. Kaplan–Meier curves were used to plot OS and DFS curves for patients in different trajectory groups, and differences between groups were compared using the log-rank test.

2.4 Survival Analysis and Cox Proportional Hazards Models

Kaplan-Meier curves were generated to visualize OS and DFS across the four CEA trajectory groups, and differences were compared using the log-rank test. To assess the independent prognostic value of CEA trajectories, we performed both univariate and multivariate Cox proportional hazards regression analyses. Variables with a P-value < 0.10 in univariate analysis were entered into the multivariate model. The proportional hazards assumption was verified using Schoenfeld residuals. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. The Low-stable CEA trajectory group served as the reference.

2.5 Model Development and Performance Evaluation

Three prognostic Cox regression models were constructed for both OS and DFS:

Model 1 (Clinicopathological model): Included clinically relevant variables (age, sex, T stage, N stage, differentiation, adjuvant chemotherapy, lymphovascular invasion, perineural invasion). Model 2 (CEA trajectory model): Included only the four CEA trajectory groups. Model 3 (Combined model): Included both clinicopathological variables and CEA trajectory groups.

Model performance was evaluated using the following metrics in the training set (or full cohort, if no split-sampling was performed) with 500 bootstrap resamples to reduce overfitting. 1.Discrimination: We calculated Harrell's C-index for each model. Pairwise comparisons of C-indexes were performed to test for significant differences between models. Additionally, time-dependent area under the receiver operating characteristic curve (time-dependent AUC) was calculated at 12, 24, 36, 48, and 60 months to assess predictive accuracy over time. 2.Calibration: Calibration curves were plotted to compare the predicted 5-year survival probabilities against the observed 5-year Kaplan-Meier estimates. Model calibration was quantified using the integrated absolute error (IAE), where lower values indicate better agreement. 3.Clinical Utility: Decision curve analysis (DCA) was performed to evaluate the net benefit of each model across a range of clinically reasonable threshold probabilities.

2.6 Statistical Analysis

Continuous variables are presented as median (interquartile range, IQR) and were compared using the Mann-Whitney U or Kruskal-Wallis's test. Categorical variables are presented as frequencies (percentages) and were compared using the chi-square or Fisher's exact test. All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant. All analyses were conducted using R software (version [4.5.2], R Foundation for Statistical Computing, Vienna, Austria) with packages including survival, rms, timeROC, and rmda.

3. Results

3.1 Base lines of patient characteristics in this study.

A total of 1,126 eligible postoperative colon cancer patients were included. The median age was 66 years (range, 27–95 years), and 665 patients (59.1%) were male. The median follow-up time was 53.2 months (IQR, 35.9–81.5 months). During follow-up, 196 patients (17.4%) experienced disease recurrence and 167 (14.8%) died. Baseline characteristics stratified by CEA trajectory groups are presented in Table 1. Significant differences among the four trajectory groups were observed for stage, T stage, N stage, death, recurrence, and follow-up duration (all $P < 0.001$). No significant differences were found for sex, laparoscopic surgery, tumor location, differentiation, or chemotherapy administration.

Table 1
Baseline characteristics

Sex	Subgroup	Low-stable (N = 695)	Early-rising (N = 151)	Late-rising (N = 128)	Sustained-high (N = 152)	Total (N = 1126)	P value
	<i>Male</i>	402 (57.8%)	101 (66.9%)	79 (61.7%)	83 (54.6%)	665 (59.1%)	0.122
	<i>Female</i>	293 (42.2%)	50 (33.1%)	49 (38.3%)	69 (45.4%)	461 (40.9%)	
Stage	<i>1</i>	96 (13.8%)	31 (20.5%)	4 (3.1%)	2 (1.3%)	133 (11.8%)	< 0.001
	<i>2</i>	241 (34.7%)	47 (31.1%)	21 (16.4%)	26 (17.1%)	335 (29.8%)	
	<i>3</i>	358 (51.5%)	73 (48.3%)	103 (80.5%)	124 (81.6%)	658 (58.4%)	
T	<i>1</i>	51 (7.3%)	16 (10.6%)	2 (1.6%)	1 (0.7%)	70 (6.2%)	< 0.001
	<i>2</i>	70 (10.1%)	18 (11.9%)	9 (7.0%)	4 (2.6%)	101 (9.0%)	
	<i>3</i>	284 (40.9%)	49 (32.5%)	48 (37.5%)	38 (25.0%)	419 (37.2%)	
	<i>4</i>	290 (41.7%)	68 (45.0%)	69 (53.9%)	109 (71.7%)	536 (47.6%)	
N	<i>0</i>	337 (48.5%)	78 (51.7%)	25 (19.5%)	28 (18.4%)	468 (41.6%)	< 0.001
	<i>1</i>	286 (41.2%)	55 (36.4%)	65 (50.8%)	83 (54.6%)	489 (43.4%)	
	<i>2</i>	72 (10.4%)	18 (11.9%)	38 (29.7%)	41 (27.0%)	169 (15.0%)	
Laparoscopic surgery	<i>Yes</i>	467 (67.2%)	95 (62.9%)	94 (73.4%)	94 (61.8%)	750 (66.6%)	0.152
	<i>No</i>	228 (32.8%)	56 (37.1%)	34 (26.6%)	58 (38.2%)	376 (33.4%)	
Tumor location	<i>Left</i>	301 (43.3%)	62 (41.1%)	57 (44.5%)	64 (42.1%)	484 (43.0%)	0.872
	<i>Right</i>	348 (50.1%)	74 (49.0%)	66 (51.6%)	77 (50.7%)	565 (50.2%)	
	<i>Transverse</i>	41 (5.9%)	13 (8.6%)	5 (3.9%)	8 (5.3%)	67 (6.0%)	
	<i>Rectum</i>	3 (0.4%)	0 (0%)	0 (0%)	1 (0.7%)	4 (0.4%)	
Differentiation	<i>low</i>	193 (27.8%)	50 (33.1%)	30 (23.4%)	29 (19.1%)	302 (26.8%)	0.051
	<i>median-low</i>	209 (30.1%)	52 (34.4%)	46 (35.9%)	55 (36.2%)	362 (32.1%)	
	<i>median</i>	251 (36.1%)	39 (25.8%)	43 (33.6%)	63 (41.4%)	396 (35.2%)	
	<i>high-median</i>	20 (2.9%)	5 (3.3%)	7 (5.5%)	2 (1.3%)	34 (3.0%)	

Sex	Subgroup	Low-stable (N = 695)	Early-rising (N = 151)	Late-rising (N = 128)	Sustained-high (N = 152)	Total (N = 1126)	P value
	Male	402 (57.8%)	101 (66.9%)	79 (61.7%)	83 (54.6%)	665 (59.1%)	0.122
	<i>high</i>	1 (0.1%)	1 (0.7%)	0 (0%)	1 (0.7%)	3 (0.3%)	
Death	Yes	55 (7.9%)	6 (4.0%)	14 (10.9%)	92 (60.5%)	167 (14.8%)	< 0.001
	No	640 (92.1%)	145 (96.0%)	114 (89.1%)	60 (39.5%)	959 (85.2%)	
Recurrence	Yes	59 (8.5%)	18 (11.9%)	23 (18.0%)	96 (63.2%)	196 (17.4%)	< 0.001
	No	636 (91.5%)	133 (88.1%)	105 (82.0%)	56 (36.8%)	930 (82.6%)	
Chemotherapy	Yes	18 (2.6%)	5 (3.3%)	6 (4.7%)	7 (4.6%)	36 (3.2%)	0.836
	No	397 (57.1%)	80 (53.0%)	92 (71.9%)	117 (77.0%)	686 (60.9%)	
	Missing	280 (40.3%)	66 (43.7%)	30 (23.4%)	28 (18.4%)	404 (35.9%)	
Follow-up (months)	<i>Mean (SD)</i>	61.6 (36.8)	73.8 (32.9)	68.5 (30.8)	46.1 (32.1)	61.9 (35.8)	< 0.001
	<i>Median [Min, Max]</i>	51.7 [6.21, 180]	69.4 [21.6, 169]	61.7 [23.7, 164]	37.3 [5.58, 166]	53.2 [5.58, 180]	

3.2 CEA dynamic trajectory and survival analysis

3.2.1 CEA trajectory groups

Four distinct CEA trajectory patterns were identified (Fig. 1): Low-stable (n = 695, 61.7%), Early-rising (n = 151, 13.4%), Late-rising (n = 128, 11.3%), and sustained-high (n = 152, 13.4%).

3.2.2 Survival analysis for the trajectory groups

Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) are shown in Fig. 2. The 5-year OS rates were 92.0% (Low-stable), 98.0% (Early-rising), 91.1% (Late-rising), and 34.9% (Sustained-high). The 5-year DFS rates were 91.6%, 88.8%, 83.0%, and 36.6%, respectively. The log-rank test showed significant differences among the four groups for both OS and DFS (both $P < 0.001$).

Multivariate Cox regression analysis adjusted for age and sex was performed with the Low-stable group as reference. For DFS, the Early-rising group showed no significant difference (HR = 1.28, 95% CI: 0.75–2.16, $P = 0.368$). The Late-rising group had a significantly higher risk (HR = 2.03, 95% CI: 1.26–3.29, $P = 0.004$). The Sustained-high group had the highest risk (HR = 11.81, 95% CI: 8.47–16.46, $P < 0.001$).

3.3 Univariate and multivariate Cox regression analysis

Results of univariate and multivariate analyses are shown in Table 2. In univariable analysis, older age, elevated CA19-9/CA125, larger tumor size, higher cancer nodule count, advanced T/N stage, vascular/nerve invasion, mucinous histology, moderate/high-moderate differentiation, laparoscopic surgery, postoperative chemotherapy, and Sustained-high CEA trajectory were associated with OS (all $P < 0.05$). Similar associations were observed for DFS. In multivariable analysis, age > 65 years, N1/N2 stage, and sustained-high CEA trajectory remained independent predictors for worse OS; cancer nodule

count, nerve invasion, and sustained-high CEA trajectory independently predicted worse DFS (all $P < 0.05$). Inflammatory markers (NLR, PLR, LMR, SII) were not significant in either analysis.

Table 2
Univariate and multivariate Cox regression

	Overall Survival (OS)				Disease-Free Survival (DFS)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age: ≤65	REF				REF			
Age: >65	2.051 (1.479–2.842)	< 0.001	1.796 (1.169–2.760)	0.0075	1.307 (0.984–1.735)	0.0647		
Sex: Male	REF				REF			
Sex: Female	0.957 (0.702–1.304)	0.779			0.870 (0.652–1.162)	0.3458		
BMI	1.033 (0.991–1.077)	0.124			1.034 (0.994–1.075)	0.0947		
Inflammatory markers								
NLR	1.006 (0.964–1.050)	0.784			1.011 (0.971–1.052)	0.6024		
PLR	1.000 (0.999–1.002)	0.935			1.000 (0.998–1.001)	0.8681		
LMR	0.949 (0.872–1.033)	0.227			0.979 (0.907–1.057)	0.5813		
SII	1.000 (1.000–1.000)	0.555			1.000 (1.000–1.000)	0.9933		
Laboratory markers								
Albumin	0.928 (0.898–0.959)	< 0.001	0.963 (0.923–1.005)	0.0841	0.960 (0.931–0.991)	0.0115	0.971 (0.938–1.006)	0.1014
Preoperative CEA	1.001 (1.000–1.002)	0.184			1.001 (1.000–1.002)	0.0643		
Preoperative CA199	1.000 (1.000–1.001)	0.004	1.000 (0.999–1.000)	0.6509	1.000 (1.000–1.000)	0.1236		
Preoperative CA125	1.007 (1.001–1.013)	0.023	1.002 (0.991–1.012)	0.7451	1.007 (1.002–1.013)	0.0085	1.004 (0.996–1.012)	0.3413
Tumor size	1.084 (1.017–	0.013	1.109 (0.998–	0.0539	1.014 (0.951–	0.6754		

	Overall Survival (OS)				Disease-Free Survival (DFS)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	1.156)		1.232)		1.080)			
Number of cancer nodules	1.325 (1.175–1.494)	< 0.001	1.156 (0.954–1.401)	0.1386	1.388 (1.265–1.523)	< 0.001	1.236 (1.087–1.406)	0.0012
T: T1	REF				REF			
T: T2	0.437 (0.073–2.617)	0.365	NE	0.9934	1.025 (0.171–6.132)	0.9788	0.554 (0.091–3.383)	0.5225
T: T3	2.863 (0.887–9.241)	0.079	0.783 (0.153–4.004)	0.769	5.536 (1.351–22.681)	0.0174	1.258 (0.289–5.481)	0.7603
T: T4	5.005 (1.591–15.741)	0.006	0.784 (0.154–3.983)	0.7694	9.548 (2.363–38.579)	0.0015	1.397 (0.320–6.094)	0.6563
N: N0	REF				REF			
N: N1	3.680 (2.393–5.658)	< 0.001	2.786 (1.589–4.883)	< 0.001	3.188 (2.168–4.688)	< 0.001	1.526 (0.971–2.399)	0.0669
N: N2	4.017 (2.407–6.703)	< 0.001	2.196 (1.061–4.545)	0.0341	5.064 (3.290–7.792)	< 0.001	1.613 (0.917–2.840)	0.0972
Tumor location: Left colon	REF				REF			
Tumor location: Right colon	1.046 (0.762–1.436)	0.78			0.955 (0.714–1.278)	0.7577		
Tumor location: Transverse colon	0.672 (0.309–1.465)	0.318			0.957 (0.523–1.751)	0.8857		
Tumor location: Rectum	2.480 (0.344–17.882)	0.367			NE	0.9919		
Vascular invasion: No	REF				REF			
Vascular invasion: Yes	1.517 (1.088–2.115)	0.014	1.386 (0.877–2.191)	0.1619	2.053 (1.536–2.745)	< 0.001	1.213 (0.832–1.769)	0.315
Nerve invasion: No	REF				REF			
Nerve invasion: Yes	2.089 (1.517–2.877)	< 0.001	0.831 (0.533–1.294)	0.4122	2.951 (2.213–3.937)	< 0.001	1.489 (1.051–2.109)	0.0251
Histology: Adenocarcinoma	REF				REF			

	Overall Survival (OS)				Disease-Free Survival (DFS)			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Histology: Mucinous adenocarcinoma	1.741 (1.079–2.807)	0.023	1.245 (0.572–2.711)	0.5803	1.280 (0.778–2.104)	0.3314		
Histology: Signet-ring cell carcinoma	NE	0.992	NE	NA	NE	0.9934		
Differentiation: Low	REF				REF			
Differentiation: Median-low	0.971 (0.545–1.730)	0.921	0.849 (0.401–1.794)	0.6672	1.001 (0.576–1.741)	0.9961	0.952 (0.497–1.821)	0.8814
Differentiation: Median	0.541 (0.313–0.936)	0.028	0.506 (0.245–1.045)	0.0656	0.649 (0.384–1.097)	0.1062	0.947 (0.502–1.787)	0.8664
Differentiation: High-median	0.278 (0.092–0.839)	0.023	0.533 (0.155–1.836)	0.3184	0.355 (0.130–0.968)	0.0431	0.883 (0.296–2.636)	0.8236
Differentiation: High	0.301 (0.040–2.283)	0.246	2.044 (0.212–19.702)	0.5362	NE	0.9897	NE	0.9939
Laparoscopic surgery: No	REF				REF			
Laparoscopic surgery: Yes	0.635 (0.465–0.866)	0.004	0.714 (0.467–1.090)	0.1187	0.928 (0.692–1.245)	0.6203		
EMR/ESD: No	REF				REF			
EMR/ESD: Yes	0.719 (0.295–1.751)	0.467			0.446 (0.166–1.200)	0.1098		
Postop chemo: No	REF				REF			
Postop chemo: Yes	4.343 (2.291–8.230)	< 0.001	0.973 (0.425–2.229)	0.9489	8.243 (3.876–17.527)	< 0.001	2.331 (0.985–5.521)	0.0543

HR, Hazard Ratio; CI, Confidence Interval; REF, Reference group; NE, Not estimable; NA, Not available.

3.4. Model predictive performance evaluation

3.4.1 Discrimination

(1)C-index

C-indexes for OS and DFS are presented in Table 3. For OS, Model 1 (clinicopathological variables) had a C-index of 0.736 (95% CI: 0.709–0.790); Model 2 (CEA trajectory) had 0.773 (95% CI: 0.733–0.810); Model 3 (combined) had 0.841 (95% CI: 0.816–0.876). The difference between Model 2 and Model 1 was not significant ($\Delta = 0.037$, $P = 0.314$). Model 3 was

significantly higher than both Model 1 ($\Delta = 0.105$, $P < 0.001$) and Model 2 ($\Delta = 0.068$, $P < 0.001$). For DFS, Model 1 C-index was 0.735 (95% CI: 0.716–0.782); Model 2: 0.738 (95% CI: 0.701–0.778); Model 3: 0.819 (95% CI: 0.797–0.858). Model 2 was not significantly different from Model 1 ($\Delta = 0.002$, $P = 0.802$). Model 3 was significantly higher than both Model 1 ($\Delta = 0.084$, $P < 0.001$) and Model 2 ($\Delta = 0.082$, $P < 0.001$).

Table 3
C-indexes of three Cox models

OS	Model	C-index (95% CI)	Δ vs Model 1 (95% CI)	P	Δ vs Model 2 (95% CI)	P
	Model 1	0.736 (0.709–0.790)	–	–	–	–
	Model 2	0.773 (0.733–0.810)	0.037 (-0.025–0.073)	0.314	–	–
	Model 3	0.841 (0.816–0.876)	0.105 (0.067–0.132)	< 0.001	0.068 (0.051–0.102)	< 0.001
DFS	Model 1	0.735 (0.716–0.782)	–	–	–	–
	Model 2	0.738 (0.701–0.778)	0.002 (-0.058–0.039)	0.802	–	–
	Model 3	0.819 (0.797–0.858)	0.084 (0.055–0.105)	< 0.001	0.082 (0.059–0.119)	< 0.001

(2)Time-dependent AUC

Time-dependent AUC values at 12, 24, 36, 48, and 60 months are shown in Fig. 3. For OS, Model 2 achieved AUCs ranging from 0.773 to 0.813; Model 1 from 0.620 to 0.709; Model 3 from 0.825 to 0.856. For DFS, Model 2 AUCs ranged 0.724–0.778; Model 1 0.723–0.762; Model 3 0.811–0.865.

3.4.2 Calibration

Calibration curves for 5-year survival predictions are displayed in Fig. 4. Integrated absolute errors (IAE) for OS were 0.016 (Model 1), 0.022 (Model 2), and 0.018 (Model 3). For DFS, IAE values were 0.017 (Model 1), 0.007 (Model 2), and 0.018 (Model 3). All IAE values were below 0.03.

3.4.3 Decision Curve Analysis, DCA

Decision curves for overall survival (OS) and disease-free survival (DFS) are presented in Fig. 5. For OS prediction, when the threshold probability exceeded 0.1, Model 2 achieved the highest net benefit, followed by Model 3 and then Model 1. For DFS prediction, a crossover point was observed at a threshold probability of approximately 0.2: below 0.2, Model 1 yielded the highest net benefit, whereas above 0.2, Model 2 became the best-performing model. Model 3 demonstrated intermediate net benefit across most threshold ranges.

4. Discussion

This study developed a four-category carcinoembryonic antigen (CEA) trajectory grouping method based on time-slope parameters and systematically evaluated its prognostic value in a large retrospective cohort of 1,126 patients with stage I–III colon cancer. Three key findings emerged. First, the four CEA trajectory groups (low-stable, early-rising, late-rising, and sustained-high) exhibited significantly different survival outcomes, with the persistently high group showing the worst prognosis (5-year overall survival rate: 34.9%; 5-year disease-free survival rate: 36.6%). Second, the CEA trajectory model alone demonstrated non-inferior performance in predicting overall survival and disease-free survival compared with a clinicopathological model incorporating eight variables. Third, a combined model integrating CEA trajectories and clinicopathological factors significantly improved predictive performance across all evaluated metrics, achieving a C-index of 0.841 for overall survival and 0.819 for disease-free survival, with time-dependent area under the curve values ranging from 0.811 to 0.865.

4.1. Prognostic Value and Clinical Application of Longitudinal CEA Trajectories

Our findings extend and contextualize previous research on longitudinal CEA monitoring. First, we developed a slope parameter-based four-category classification method, which offers greater clinical interpretability than purely data-driven latent class approaches and circumvents common issues associated with latent class growth mixture models, such as convergence instability and extreme class imbalance [16]. Second, we performed a comprehensive model evaluation using multiple complementary metrics (C-index, time-dependent AUC, calibration curves, and decision curve analysis [DCA]), thereby assessing not only predictive accuracy but also clinical utility [17, 18].

The persistently high carcinoembryonic antigen (CEA) trajectory group, accounting for 13.4% of our study population, exhibited an extremely poor prognosis, with a 5-year overall survival (OS) rate of 34.9% and an adjusted hazard ratio (HR) for disease-free survival (DFS) of 11.81. This finding is consistent with previous reports that persistently elevated postoperative CEA levels indicate residual or micrometastasis disease [19] or the presence of therapy-resistant tumor clones. Clinically, such patients should be considered for intensified surveillance, early systemic therapy, or enrollment in clinical trials of novel agents.

The late elevation group also showed significantly lower DFS compared with the low-stable group (HR = 2.03), suggesting that delayed CEA elevation may reflect late recurrence or the emergence of chemotherapy-resistant clones [20]. This pattern aligns with the concept of tumor dormancy, wherein disseminated tumor cells remain quiescent for months to years before being reactivated. Mechanisms underlying late recurrence include immune evasion, angiogenic switching, and acquired resistance mutations. Our findings underscore the need for extended follow-up beyond three years, as 11% of patients exhibited CEA elevation after an initial period of normal levels.

Notably, the early elevation group (accounting for 13.4% of the study population) had survival outcomes comparable to those of the low-stable group, with a 5-year OS rate of 98.0%, a 5-year DFS rate of 88.8%, and an adjusted HR of 1.28 ($P = 0.368$). This seemingly counterintuitive finding may have several explanations. First, early CEA elevation in some patients may be attributable to benign causes, such as postoperative inflammation, liver dysfunction (e.g., fatty liver, biliary obstruction), or smoking, leading to false-positive results [21, 22]. Second, patients with early CEA elevations may have received more intensive surveillance and earlier interventions, thereby achieving better outcomes [23]. Third, the limited number of events (only six deaths) in this group resulted in statistical instability and a lack of precision in the HR estimate, warranting cautious interpretation of the findings.

Another important finding is that the CEA-trajectory-alone model achieved a C-index of 0.773 for OS and 0.738 for DFS, which was non-inferior to the eight-variable clinicopathological model (OS: 0.736; DFS: 0.735). This indicates that the prognostic information captured by dynamic CEA monitoring is at least comparable to that of multiple traditional clinicopathological factors. Similar observations have been reported in other solid tumors; for example, longitudinal alpha-fetoprotein trajectories in hepatocellular carcinoma were superior to baseline values in predicting survival [24].

The combined model integrating CEA trajectories and clinicopathological factors significantly improved discrimination compared with either model alone. Relative to the clinicopathological model, the combined model showed increases in C-index of 0.105 for OS and 0.084 for DFS (both $P < 0.001$). Time-dependent AUC analyses further supported this finding, with the combined model achieving AUC values exceeding 0.80 for both OS and DFS at all time points. These results suggest that CEA trajectories provide complementary prognostic information not fully captured by traditional clinicopathological variables [25].

All three models demonstrated good calibration, with integrated absolute error (IAE) values below 0.03 for both OS and DFS. Notably, the CEA-trajectory-alone model exhibited excellent calibration for DFS prediction (IAE = 0.007), suggesting that in certain clinical scenarios, CEA trajectories alone may suffice for predicting DFS.

The DCA revealed clinically important threshold-dependent differences. For OS prediction, the CEA-trajectory-alone model provided the highest net benefit across most clinically relevant threshold probabilities (> 0.1), suggesting it may be the preferred model for OS prediction. For DFS prediction, the optimal model varied by threshold: the clinicopathological model was superior at low thresholds (< 0.2), whereas the CEA-trajectory-alone model became optimal at higher thresholds (> 0.2). This crossover phenomenon has been reported in other decision curve analyses [26] and reflects the differential applicability of models across clinical decision contexts. The combined model consistently performed intermediately across all thresholds, indicating that more parsimonious models may be preferable in some clinical scenarios [27].

4.2. Analysis of negative results

Contrary to some prior studies [13, 14], in the multivariable analysis of the present study, none of the inflammatory markers—including NLR, PLR, LMR, and SII—significantly predicted overall survival (OS) or disease-free survival (DFS). Several factors may account for this discrepancy.

First, the complete blood count results used in this study were obtained from the first follow-up visit (postoperative days 21–56), whereas most previous studies employed preoperative measurements or values from different postoperative time points [11]. Regarding the temporal dynamics of postoperative inflammatory markers, existing evidence indicates that following curative resection for colorectal cancer, markers such as LMR, NLR, PLR, and SII exhibit substantial fluctuations across different follow-up time points. Notably, LMR at 12 months post-surgery demonstrated the highest predictive value for 5-year survival (AUC = 0.717). This suggests that the prognostic significance of postoperative inflammatory markers is highly dependent on the timing of measurement. Although our blood collection time point avoided the immediate postoperative acute phase, it may still fall within a “gray zone” of postoperative recovery, during which confounding factors—such as nutritional status, physical activity levels, subclinical infections (e.g., urinary or respiratory tract infections), and medication use (e.g., antibiotics, nonsteroidal anti-inflammatory drugs)—could compromise the stability of these inflammatory indices. Moreover, the prognostic value of preoperative versus postoperative inflammatory markers differs substantially. A 2023 study demonstrated that preoperative SII and NLR had predictive value for anastomotic leakage and overall complications after colorectal cancer surgery, whereas postoperative markers exhibited considerably greater heterogeneity [28]. Further corroborating this, a 2024 study published in *Pathology and Oncology Research* confirmed that preoperative systemic inflammatory response markers (e.g., CRP, modified Glasgow Prognostic Score) were significantly associated with poor prognosis and aggressive phenotypes in patients with colorectal cancer [29]. Thus, our negative findings may be partially attributable to a “suboptimal” timing of blood sampling.

Second, in a patient cohort undergoing curative resection and standard adjuvant therapy, the prognostic impact of inflammatory markers may be partially attenuated. Previous studies have shown that in patients with non-metastatic colorectal cancer after curative surgery, the pan-immune-inflammation value (PIV) correlates significantly with T stage, TNM stage, differentiation grade, and perineural invasion. The 5-year OS rates in the high- versus low-PIV groups were 46.3% and 88.7%, respectively ($P < 0.001$) [30]. However, most of these studies used preoperative measurements and did not uniformly include patients receiving standardized adjuvant therapy. Adjuvant therapy itself may modulate systemic inflammation and thereby partially offset the prognostic effect of baseline inflammatory markers.

Third, although composite markers such as NLR, PLR, and SII are convenient to calculate, they are essentially ratios of various blood cell counts and thus lose absolute count information. For instance, an elevated NLR could result from increased neutrophils, decreased lymphocytes, or both—each of which may correspond to distinct prognostic implications. Recent studies have suggested that absolute lymphocyte or absolute neutrophil counts alone may offer superior predictive value compared with their ratios. More importantly, the present study did not measure cytokine profiles (e.g., IL-6, IL-8, TNF- α , and high-sensitivity CRP), which might reflect tumor-related inflammation more directly than blood count-derived ratios. Therefore, the negative results of this study do not refute the well-established conclusion that inflammation is associated with colorectal cancer prognosis. Instead, they suggest that, in this specific cohort, the prognostic utility of blood count-derived composite inflammatory indices is limited.

Another notable interpretation is that the dynamic trajectory of CEA may have inherently “encoded” the inflammatory signals. Biologically, tumor-related systemic inflammation can promote CEA expression and release through multiple mechanisms: (i) the inflammatory cytokine TNF- α upregulates CEACAM1 expression via activation of NF- κ B and β -catenin signaling pathways; and (ii) CEA interacts with immune cells in the tumor microenvironment, inducing the release of inflammatory mediators such as IL-1 β and TNF- α , activating NF- κ B and chemokine cascades, and thereby constructing an immunosuppressive microenvironment [31]. Thus, dynamic changes in serum CEA levels may be viewed, to some extent, as an integrated downstream signal reflecting the interplay between host inflammatory response and tumor burden. A recent study on locally advanced rectal cancer further supports this notion: the combined assessment of post-chemoradiotherapy changes in NLR and CEA significantly enhanced survival prediction, with patients showing decreases in both parameters having the best prognosis and those with increases in both the worst prognosis (OS: $P < 0.0001$; DFS: $P = 0.00019$) [12]. In other words, the CEA trajectory may already integrate inflammatory signals, implying potential informational redundancy between the two. In our study cohort, once the strong predictor—CEA trajectory—was included in the model, the incremental prognostic information provided by inflammatory markers was extremely limited. This aligns with the concept of “informational redundancy” in multivariable prediction models: when a strong predictor is already included, the independent contribution of weaker predictors approaches zero.

4.3 Clinical Significance

The clinical significance of this study is fourfold. First, for patients with stage I–III colon cancer undergoing curative resection, postoperative routine monitoring of dynamic carcinoembryonic antigen (CEA) changes alone enables effective risk stratification for recurrence. This simplifies follow-up protocols, reduces unnecessary blood tests, lowers healthcare costs, and improves patient adherence. Second, CEA trajectory–guided individualized follow-up is recommended: high-risk trajectory (Sustained-high group) patients should receive more intensive surveillance and stronger adjuvant therapy, such as shorter intervals of imaging (e.g., CT every 3–6 months), whereas low-risk trajectory (Low-stable group) patients may extend intervals to every 12 months. The Early-rising group shows favorable prognosis, suggesting that not all early CEA rises warrant excessive concern and may be managed with low-risk strategies. Moreover, the choice of predictive model should be grounded in clinical decision contexts—the CEA trajectory model is better suited for decisions regarding overall survival prognosis and high-risk disease-free survival (DFS), whereas the clinicopathological model retains value in low-risk DFS scenarios. Third, our findings indicate that inflammatory markers do not predict recurrence or differentiate CEA trajectories. This negative finding cautions clinicians and researchers against indiscriminately applying inflammation-based prognostic models from other solid tumors to the post-resection colon cancer population without validation in the specific disease stage, treatment context, and timing of blood sampling.

4.4 Study Limitations

1. Study Design and Bias

This was a retrospective, single-center study, which is subject to selection and information biases. Consequently, external validity is limited, and the findings require validation in independent multicenter cohorts.

2. Data Collection and Standardization

CEA measurements were obtained during routine clinical practice, leading to heterogeneity in sampling frequency and timing across patients.

3. Variable and Biomarker Limitations

The study did not assess high-specificity inflammatory markers (e.g., high-sensitivity CRP, IL-6, sIL-2R). Furthermore, potential confounders such as comorbidities, performance status, and detailed chemotherapy regimens were not fully

accounted for.

4.5. Future Directions

1. Conduct a multicenter prospective cohort study to validate whether risk-adaptive surveillance and treatment strategies based on CEA trajectory can improve patient outcomes.
2. Since dynamic changes in circulating tumor DNA (ctDNA) are more sensitive than CEA, combining CEA trajectory with ctDNA kinetics for joint modeling may further enhance predictive accuracy [32, 33].
3. Given that inflammatory markers were measured only once in this study, future research could similarly analyze longitudinal trajectories of NLR, PLR, and other inflammatory indicators to examine whether they act synergistically with or complementarily to CEA trajectories.

5. Conclusion

In conclusion, dynamic CEA trajectory provides prognostic information complementary to clinicopathological factors in patients with stage I–III colon cancer. The combined model integrating CEA trajectory with clinicopathological variables achieved excellent predictive performance for both overall survival (OS) and disease-free survival (DFS). The choice of the optimal model for clinical decision-making depends on the threshold probability, with the CEA trajectory model demonstrating superior clinical utility in predicting OS and at high-risk DFS decision thresholds. These findings support the integration of dynamic CEA monitoring into routine postoperative risk assessment for patients with colon cancer.

Declarations

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CRedit authorship contribution statement

Yiyun Hu: Data curation, Formal analysis, Visualization, Writing – original draft. Yimin Wu: Conceptualization, Data curation, Methodology, Writing – review & editing. Junbo Yuan: Conceptualization, Funding acquisition, Resources, Writing – review & editing. Dening Ma: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – review & editing. Shunv Cai: Conceptualization, Funding acquisition, Writing – review & editing.

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Conflicts of Interest Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Statement

This study was approved by the Ethics Committee of Zhejiang Cancer Hospital (Approval No.: IRB-2025-866(IIT)). All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Data availability statement

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Figures

CEA Trajectories by Group

Solid line: median; Shaded area: interquartile range; Numbers: median (IQR)

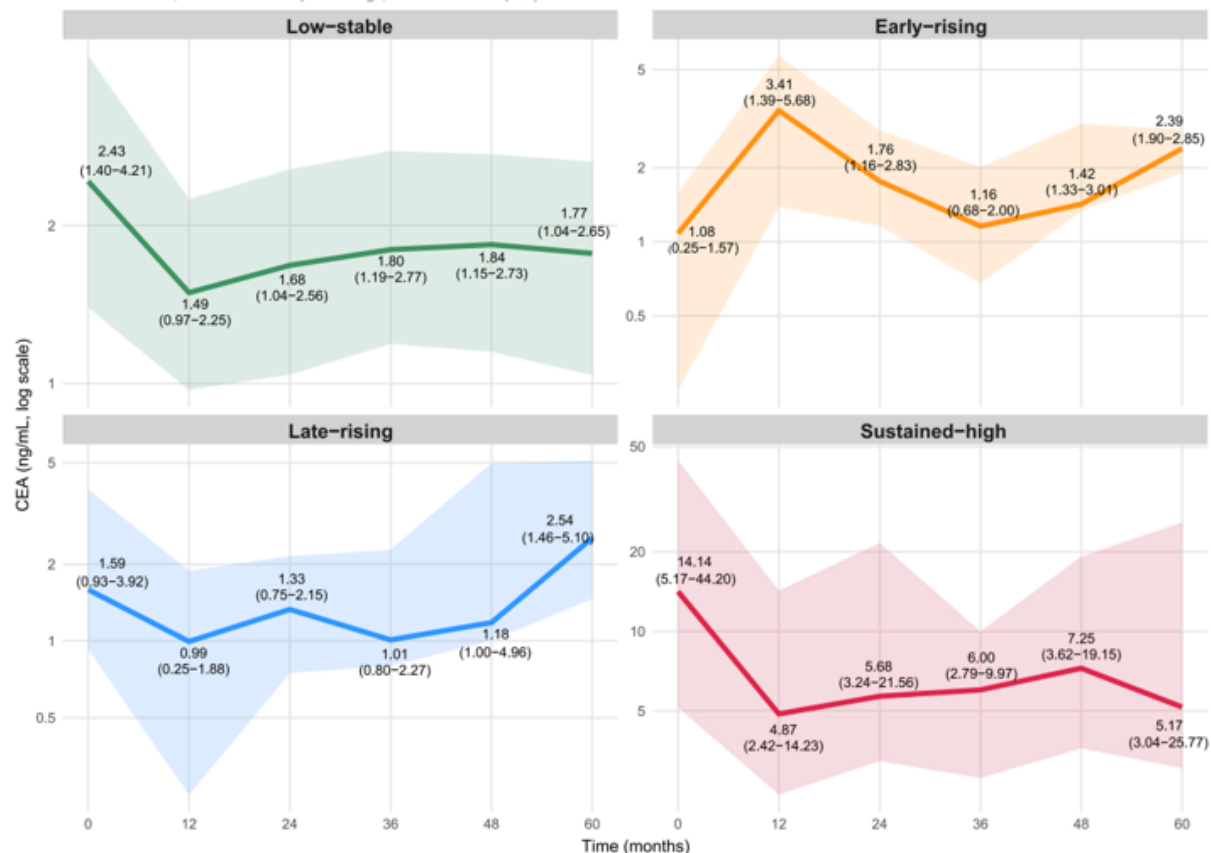
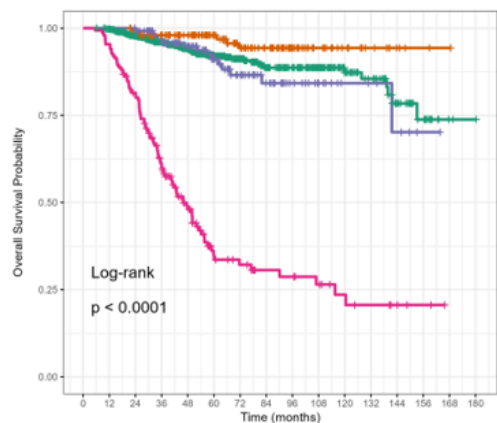


Figure 1

Solid lines represent median CEA levels; shaded areas represent interquartile ranges (IQR); numbers indicate median (IQR) at each time point. Patients were classified into four trajectory groups: Low-stable, Early-rising, Late-rising, and Sustained-high. CEA levels are shown on a log10 scale. Time 0 indicates preoperative CEA level.

A Overall Survival by Trajectory Group

Group: Low-stable, Early-rising, Late-rising, Sustained-high

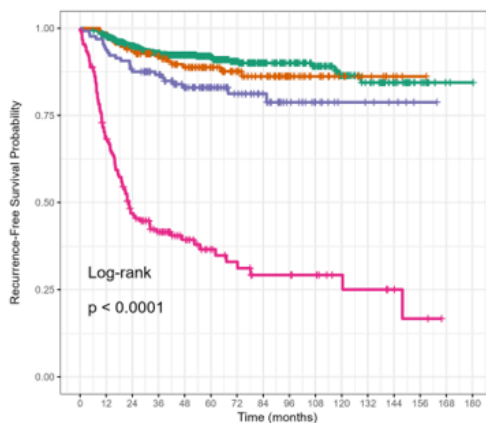


Number at risk

Time (months)	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
Group=Low-stable	695	686	608	515	394	290	204	156	131	99	62	46	29	15	2	1
Group=Early-rising	151	151	147	133	116	89	72	57	36	23	15	9	4	2	1	0
Group=Late-rising	128	128	127	112	94	66	50	35	21	13	8	7	5	1	0	0
Group=Sustained-high	152	145	120	82	52	27	22	16	15	12	8	6	4	2	0	0

B Recurrence-Free Survival by Trajectory Group

Group: Low-stable, Early-rising, Late-rising, Sustained-high



Number at risk

Time (months)	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180
Group=Low-stable	695	671	582	486	369	271	186	143	119	89	56	40	26	13	2	1
Group=Early-rising	151	149	139	125	105	80	65	50	32	22	14	8	3	1	0	0
Group=Late-rising	128	120	111	101	83	58	45	33	21	13	8	7	5	1	0	0
Group=Sustained-high	152	101	66	49	34	22	18	13	13	11	7	6	4	2	0	0

Figure 2

The Kaplan-Meier curves for overall survival (OS) and disease-free survival (DFS) stratified by CEA trajectory groups.

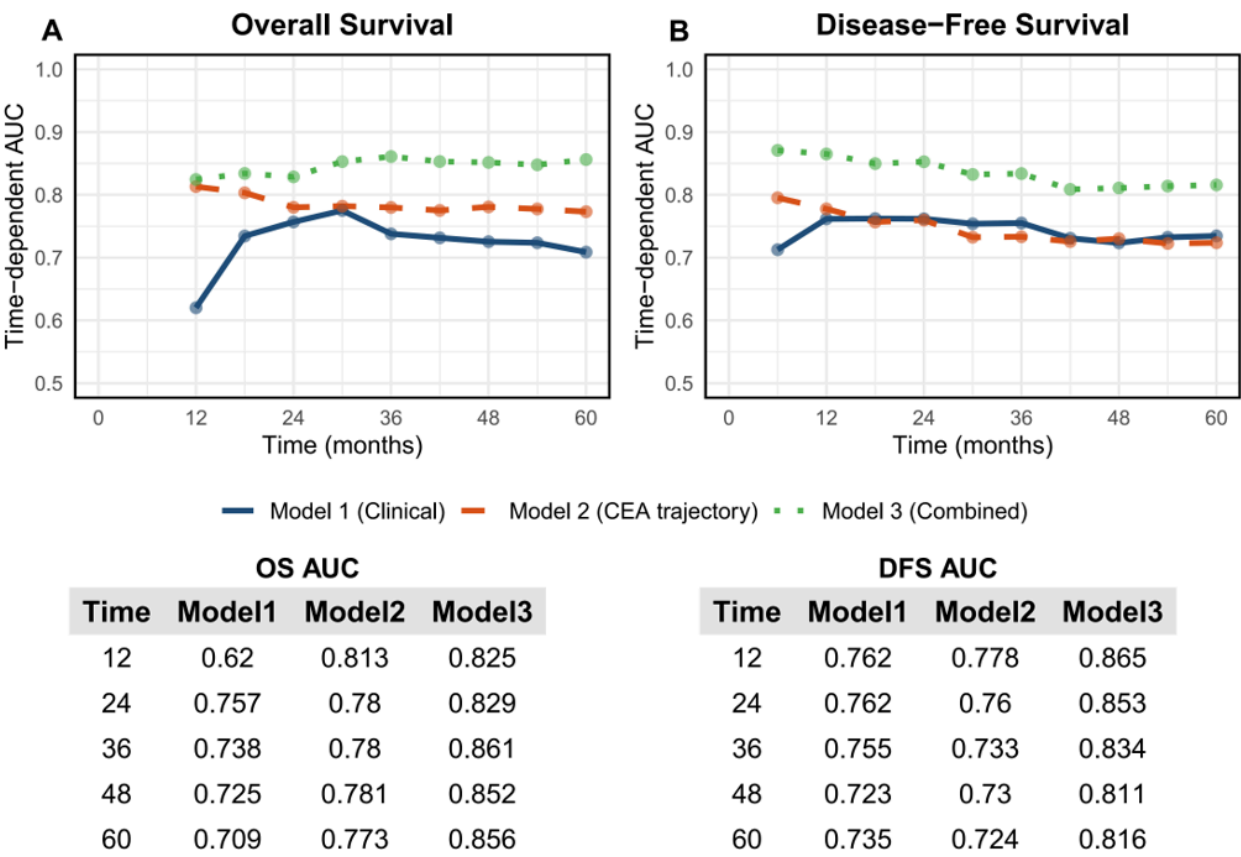


Figure 3

Time-dependent AUC curves for OS (A) and DFS (B) prediction of the clinicopathological model, CEA trajectory model, and combined model at 12, 24, 36, 48, and 60 months post-surgery.

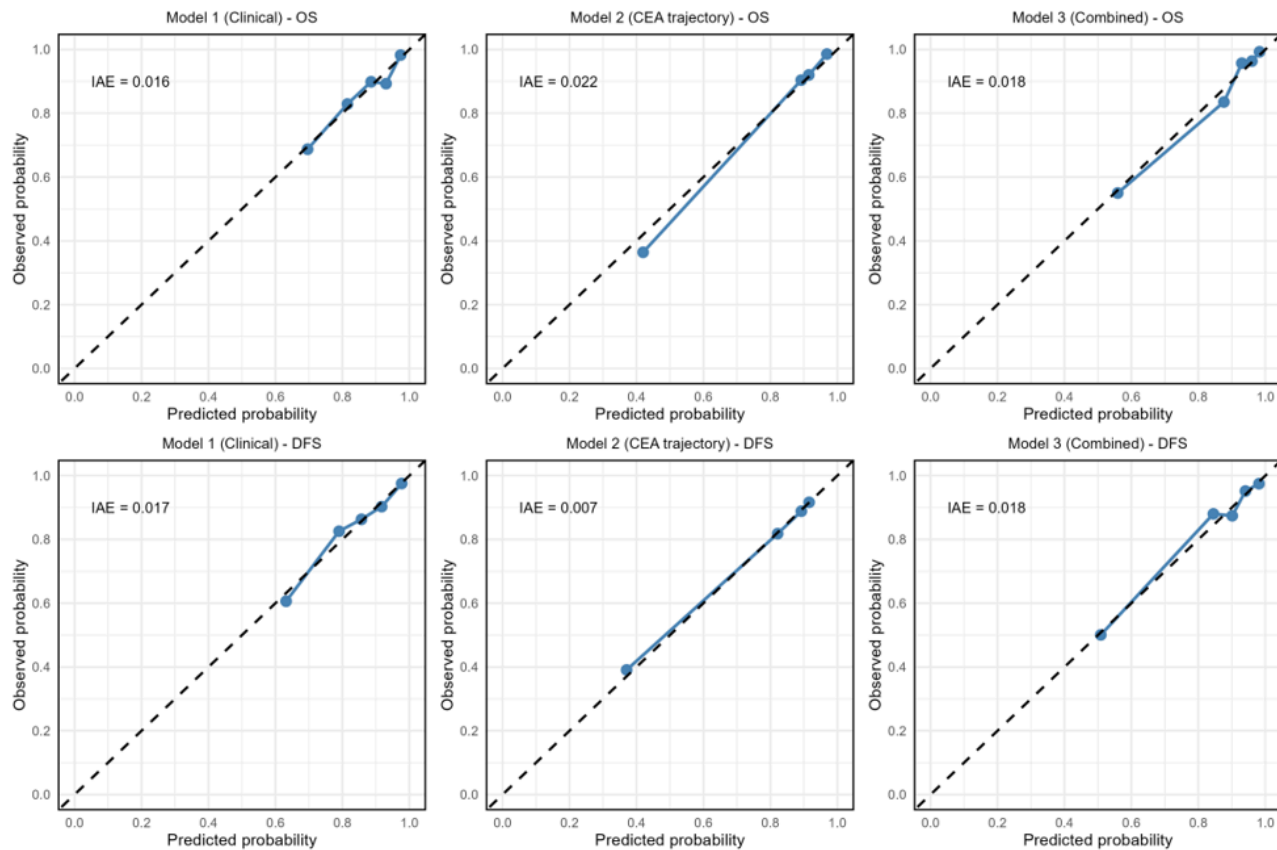


Figure 4

Calibration curves for 5-year survival predictions of three models. Each panel shows the calibration of predicted 5-year probabilities (x-axis) against observed 5-year Kaplan-Meier estimates (y-axis).

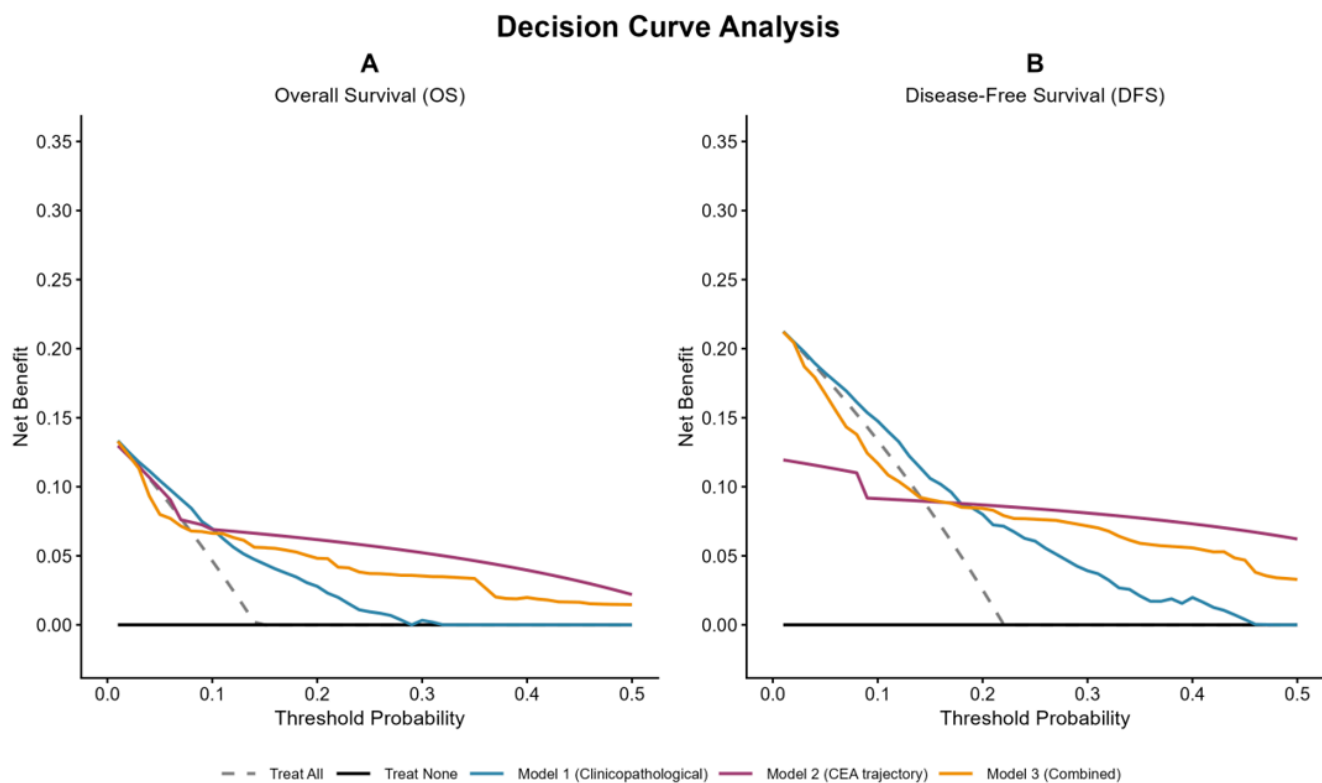


Figure 5

Decision curve analysis for OS (A) and DFS (B) prediction.

