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Machine learning-based dynamic CEA trajectory and prognosis in gastric cancer

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Abstract

Background Static carcinoembryonic antigen (CEA) levels are well-established prognostic markers in patients with gastric cancer, but the significance of their dynamic trajectories over time has rarely been reported.

Methods We analysed the perioperative CEA levels (presurgery, early postsurgery, and late postsurgery) of 578 gastric cancer patients who underwent curative resection, with a median follow-up of 29 months. We used the entire cohort for k-means clustering. Survival differences between clusters were assessed using Kaplan–Meier analysis and Cox regression.

Results Of the 578 patients, 15.57% exhibited elevated CEA levels before surgery (median 2.07 ng/mL), which then decreased to 3.29% (median 1.74 ng/mL) after surgery. However, after six months, a slight rebound was observed (18.51% elevated, median 2.98 ng/mL). K-means clustering identified three CEA trajectories: high, medium, and low (Calinski–Harabasz index: 358). Survival analysis demonstrated that higher CEA trajectories were associated with worse disease-free survival (DFS) and overall survival (OS). With the low cluster as a reference, multivariate Cox regression analysis revealed that a higher CEA trajectory was an independent prognostic factor, with an elevated risk in the high cluster (HR 2.64, 95% CI: 1.37-5.0), indicating that the high cluster had more than twice the mortality risk of the low cluster and that the medium cluster had a moderately increased mortality risk (HR 1.69, 95% CI: 1.0-2.85).

Conclusion Higher CEA trajectories are associated with a worse prognosis, highlighting the importance of enhanced monitoring for this group of patients.

Highlights

- A machine learning-powered trajectory clustering algorithm employed.
- The trajectory cluster classification demonstrates a strong correlation with both disease-free survival and overall survival.

Keywords Trajectory analysis, Carcinoembryonic antigen, Gastric cancer, Survival

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Introduction

Gastric cancer is a leading cause of cancer-related mortality worldwide, with a particularly high incidence in China [1, 2]. Despite advances in treatment, the prognosis for patients with advanced gastric cancer remains poor, primarily due to late-stage diagnosis and high recurrence rates following curative resection. Surgical resection offers the best chance for a cure among patients with advanced disease; however, the risk of recurrence due to incomplete tumour removal necessitates close postoperative monitoring [3].

Carcinoembryonic antigen (CEA) is widely recommended as a monitoring tool for gastric cancer recurrence, such as in the National Comprehensive Cancer Network (NCCN) gastric cancer management guidelines and the Japanese Gastric Cancer Treatment Guidelines [4, 5]. Elevated CEA, a static marker, is associated with a poor prognosis, advanced tumour stage, and increased tumour burden [6, 7]. However, the prognostic significance of dynamic changes in CEA levels over time remains underexplored.

Trajectory analysis, a machine learning method that examines patterns of change in variables over time, has gained traction in oncology research, particularly for studying postoperative symptom dynamics [8]. This approach maximizes the use of longitudinal data by focusing on dynamic changes rather than static values. While trajectory analysis has been applied to tumour markers in other cancers [9–11], it has rarely been used for studying CEA dynamics in gastric cancer.

To address this gap, our study investigated dynamic changes in CEA levels at three critical time points: preoperative (baseline), early postoperative (within 90 days after surgery), and late postoperative (6 months or more after surgery). These time points, spanning the critical first year of gastric cancer treatment, encompass surgery and adjuvant therapy, during which CEA changes may reflect the tumour burden and correlate with prognosis. Specifically, preoperative CEA levels reflect the baseline tumour burden, as supported by studies revealing that CEA is associated with cancer stage and prognosis [12, 13]. Early postoperative levels indicate the extent of tumour removal, as noted in previous trajectory analyses, where CEA served as a reliable indicator of treatment response [14]. Furthermore, late postoperative levels reflect postchemotherapy dynamics and tumour burden changes, with studies highlighting the role of CEA in the early detection of recurrence [15, 16]. Collectively, these time points are well suited to capture the dynamic changes in tumour burden during the critical first year of treatment. To analyse these trajectories, traditional statistical methods such as Cox regression, which rely on static data, are inadequate. Therefore, we employed k-means clustering—a mature machine learning algorithm that excels in identifying patterns in time series data [17, 18]—to classify patients into distinct CEA trajectory clusters. We hypothesized that different trajectory clusters are associated with distinct survival outcomes, with higher trajectory groups indicating a worse prognosis.

This research has the potential to enhance our understanding of CEA as a prognostic indicator and support more personalized postoperative monitoring strategies for patients with gastric cancer. By examining dynamic CEA patterns, we aim to provide clinicians with a novel tool to assess recurrence risk and guide follow-up care.

Methods

Inclusion criteria

- ➢ Age 18–85 years;
- ➢ Histologically confirmed gastric or oesophagogastric junction adenocarcinoma;
- ➢ Underwent radical gastrectomy;
- ➢ No distant metastasis.

Exclusion criteria

- ➢ Received neoadjuvant therapy;
- ➢ Insufficient CEA test data;
- ➢ Insufficient clinical staging information or uncertain distant metastasis;
- ➢ Secondary concurrent malignancy;
- ➢ Mixed tumours with squamous cell carcinoma or neuroendocrine carcinoma cells.

These criteria ensured the selection of a well-defined study population and maintained data quality and relevance for analysis.

CEA detection methodology

- ➢ Assay Kit: Carcinoembryonic Antigen (CEA) Reagent Kit (Chemiluminescent Microparticle Immunoassay, CMIA), Abbott Laboratories.
- ➢ Platforms: ARCHITECT® and Alinity™ ci-Series automated analysers.

Post-operative staging

After the resection surgery, the pathological stage of each patient was determined according to the American Joint Committee on Cancer (AJCC) staging criteria [19].

Follow-up

After discharge from the hospital, we recommend regular follow-up assessments every 3 months initially, followed by subsequent appointments every 6 months. Each follow-up examination included a review of medical history, physical examination, routine blood tests,

comprehensive biochemical analyses, and CT scans. If a patient missed a scheduled follow-up, the hospital's follow-up office contacted them via telephone or mail to collect information on their health status and survival. Overall survival (OS) was defined as the time from the date of surgery to the date of death or the last follow-up. Disease-free survival (DFS) was defined as the time from the date of surgery to the date of recurrence or the last follow-up without recurrence. No imputation was performed for missing data. Patients with incomplete CEA data—specifically, those missing any CEA measurements at the preoperative, early postoperative, or late postoperative stages (as defined in the Data Collection section)—were excluded from the study (exclusion details are listed in Fig. 1).

Data analysis

Continuous variables were evaluated for normality. Normally distributed data are presented as the means ± standard deviations and were analysed using Student's t test. Nonnormally distributed data are presented as medians (upper quartile, lower quartile) and were analysed using nonparametric tests (Mann–Whitney tests for two groups and the Kruskal–Wallis test for three or more groups). Categorical variables were compared using the chi-square test.

Survival analysis was performed with the Kaplan–Meier method. Cox regression was used to calculate hazard ratios and assess the independent associations of variables with survival. A p value < 0.05 was considered statistically significant.

Software: All analyses were performed in R (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

CEA data collection and trajectory classification

CEA data were collected at three time frames: preoperative (within 30 days before surgery), early postoperative (within 90 days after surgery), and late postoperative (6 months or more after surgery). The first available measurement in each time frame was used to represent the CEA level, covering the perioperative period, including adjuvant chemotherapy and follow-up, to reflect dynamic CEA changes.

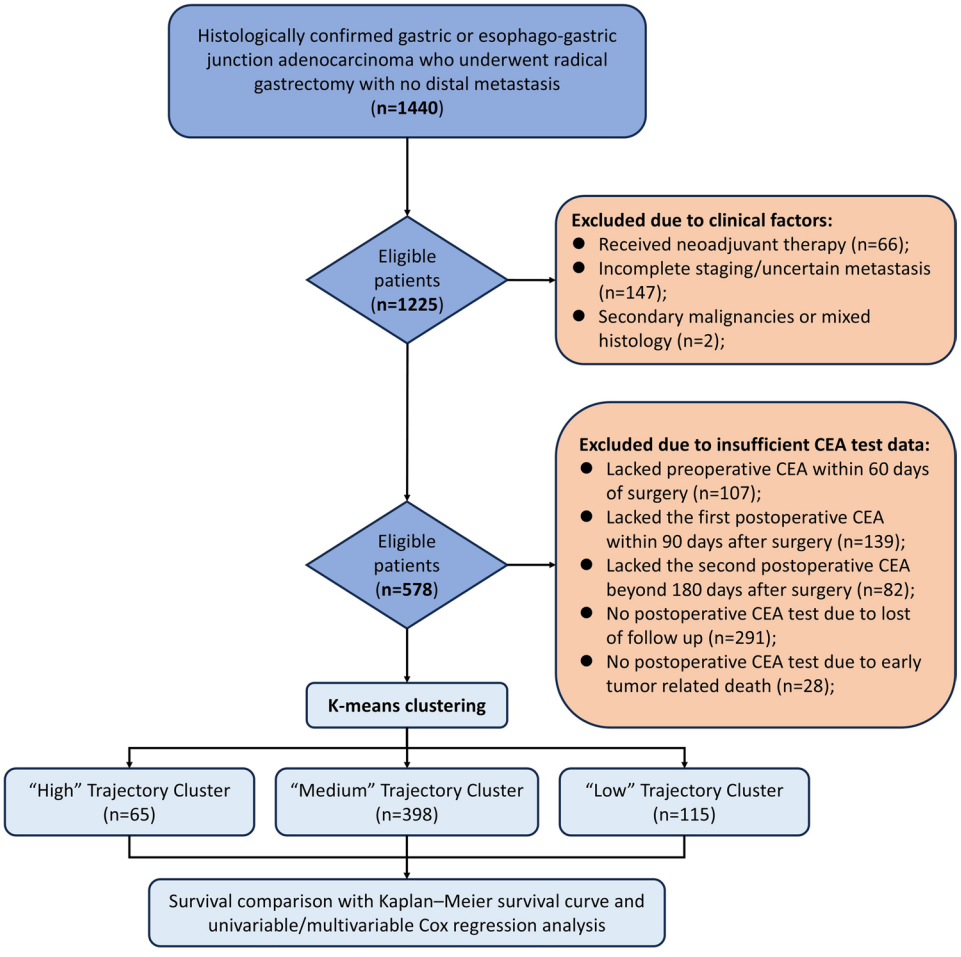

Fig. 1 Study flowchart showing the patient selection process and subsequent trajectory clustering based on perioperative CEA measurements

Owing to the presence of extreme values in the CEA data, we applied a natural logarithmic transformation [log(test value + 1)] to normalize the values and approximate a normal distribution. K-means clustering for longitudinal data was subsequently applied to classify the CEA trajectories using the 'kml' package in R [17]. The optimal number of clusters was determined using the elbow method, where the within-cluster sum of squares was plotted against different cluster numbers. The point at which the rate of decrease sharply slows—forming an "elbow"—was selected as the ideal number of clusters. Additionally, the clinical relevance of the findings was also taken into consideration. The clustering process was repeated until a result that was both statistically significant and clinically interpretable was achieved. The quality and sensitivity of this k-means clustering was validated by the following metrics.

Calinski–harabasz index

This index measures the ratio of between-cluster to within-cluster dispersion, with higher values indicating more distinct and compact clusters. It also reflects the sensitivity of the clustering to underlying data patterns, ensuring robust cluster separation.

Jaccard index from the bootstrap method

This index evaluates cluster stability across repeated sampling, with values ranging from 0 (low stability) to 1 (perfect stability). Higher values signify consistent and reliable cluster assignments while also demonstrating sensitivity to data variability.

Results

Patient characteristics

From November 2012 to March 2023, we identified 1,440 patients who underwent curative gastrectomy, with the patient selection process detailed in Fig. 1. Of these, 578 eligible patients were included in the final analysis. As shown in Table 1, the cohort consisted mostly of male patients (374/578, 64.7%), with a median age of 58 years. The tumours were mostly undifferentiated or poorly differentiated adenocarcinomas (410/578, 70.9%), with the majority at clinical stage T3 (361/578, 62.5%) and over half classified as stage N2 or higher. All patients underwent gastrectomy, including 286 total gastrectomies, 275 distal gastrectomies, and 17 proximal gastrectomies. Approximately half of the surgeries were open procedures (293/578, 50.7%), whereas the other half were laparoscopic (285/578, 49.3%).

Perioperative CEA trajectory and classification

Figure 2 illustrates the CEA level trajectories of the initial 1,440 patients, showing each patient's consecutive CEA levels from before surgery to one year postsurgery. While most trajectories remain within a certain range and follow a postsurgical decline, subsequent variations suggest underlying patterns worthy of further exploration. However, not all patients underwent consistent CEA monitoring, with some having limited tests or falling outside our defined time intervals, leading to exclusions. Ultimately, 578 eligible patients were included in the final analysis, with CEA levels assessed at three key time points: preoperative, early postoperative (within 3 months), and late postoperative (after 6 months). The median preoperative CEA level was 2.07 ng/mL, with 15.57% of patients exceeding the reference value (>5 ng/mL). This value decreased significantly to 1.74 ng/mL in the early postoperative period ($p < 0.01$), with only 3.29% above the reference value. By the late postoperative period, the median CEA level had rebounded to 2.98 ng/mL ($p < 0.01$ vs. early postoperative), with 18.51% exceeding the reference value. This decline–rebound pattern is shown in Fig. 2.

The k-means method was used to identify trajectory clusters, with the elbow method applied to determine the optimal number of clusters. Three distinct CEA trajectories were identified (Fig. 3): high (elevated preoperative levels with a partial postoperative decline), medium, and low (both consistently below the reference level but at different magnitudes). All trajectories exhibited a postsurgical decline followed by a rebound. The nonoverlapping 95% confidence intervals of the merged trajectories confirmed the statistical significance of this clustering. The quality and sensitivity of the k-means clustering were supported by a Calinski–Harabasz index of 358, indicating compact and well-defined clusters, and a Jaccard index of 0.8186, reflecting high stability and reproducibility across bootstrap samples. Together, these results demonstrate that the k-means clustering model reliably captured the distinct CEA level change patterns in our patient cohort.

Survival analysis

Survival analysis of the cohort, with a median follow-up of 29 months, revealed a significant association between CEA trajectory groups and prognosis, with higher trajectories linked to worse disease-free survival (DFS) and overall survival (OS) (Fig. 4). Among the 578 patients, 454 (78.5%) were censored and 124 (21.5%) experienced an event (tumour-related death) during the study period. At the 29-month median follow-up time point, 220 patients (38.1%) were censored and 77 patients (13.3%) had experienced an event. The high cluster had the poorest survival, with a median DFS of 27 months and a median OS of 44 months, whereas the median survival for the medium and low clusters was not reached. Initial univariable Cox regression analysis indicated an elevated risk for the high cluster (HR 3.15, 95% CI: 1.69–5.87) and a moderately increased risk for the medium cluster (HR 1.81, 95% CI: 1.10–2.98) compared with the low

Table 1 Patients baseline characteristics of different trajectory subtypes

Characteristic (%)	Overall (*n* = 578)	"High" Trajectory Cluster (*n* = 65)	"Medium" Trajectory Cluster (*n* = 398)	"Low" Trajectory Cluster (*n* = 115)	*p*-value
Sex*					
Female	204 (35.3)	14 (21.5)	120 (30.2)	70 (60.9)	< 0.001
Male	374 (64.7)	51 (78.5)	278 (69.8)	45 (39.1)	
Age	58 [49, 64]	61 [55, 68]	59 [51, 64]	50 [37, 59]	< 0.001
Location					
Lower	287 (49.7)	25 (38.5)	200 (50.3)	62 (53.9)	0.008
Middle	110 (19.0)	9 (13.8)	73 (18.3)	28 (24.3)	
Upper	181 (31.3)	31 (47.7)	125 (31.4)	25 (21.7)	
Differentiation					
Undifferentiated	410 (70.9)	38 (58.5)	280 (70.4)	92 (80.0)	0.008
Differentiated	168 (29.1)	27 (41.5)	118 (29.6)	23 (20.0)	
Resection extend					
Distal gastrectomy	275 (47.6)	24 (36.9)	187 (47.0)	64 (55.7)	0.039
Proximal gastrectomy	17 (2.9)	0 (0.0)	15 (3.8)	2 (1.7)	
Total gastrectomy	286 (49.5)	41 (63.1)	196 (49.2)	49 (42.6)	
Resection approach					
Laparoscopic	285 (49.3)	26 (40.0)	207 (52.0)	52 (45.2)	0.123
Open	293 (50.7)	39 (60.0)	191 (48.0)	63 (54.8)	
T stages					
T1	46 (8.0)	0 (0.0)	30 (7.5)	16 (13.9)	< 0.001
T2	52 (9.0)	3 (4.6)	39 (9.8)	10 (8.7)	
T3	361 (62.5)	38 (58.5)	248 (62.3)	75 (65.2)	
T4a	109 (18.9)	19 (29.2)	76 (19.1)	14 (12.2)	
T4b	10 (1.7)	5 (7.7)	5 (1.3)	0 (0.0)	
N stages					
N0	136 (23.5)	12 (18.5)	92 (23.1)	32 (27.8)	0.005
N1	155 (26.8)	17 (26.2)	98 (24.6)	40 (34.8)	
N2	141 (24.4)	10 (15.4)	104 (26.1)	27 (23.5)	
N3a	90 (15.6)	19 (29.2)	61 (15.3)	10 (8.7)	
N3b	56 (9.7)	7 (10.8)	43 (10.8)	6 (5.2)	
Comprehensive stages					
Stage I	45 (7.8)	2 (3.1)	13 (11.3)	30 (7.5)	0.004
Stage II	249 (43.1)	23 (35.4)	62 (53.9)	164 (41.2)	
Stage III	284 (49.1)	40 (61.5)	40 (34.8)	204 (51.3)	
CEA Levels at different time points**					
Pre-surgery	2.07 [1.56, 3.61]	14.19 [8.24, 36.19]	2.22 [1.73, 3.25]	0.98 [0.64, 1.19]	< 0.001
Early post-surgery	1.74 [1.42, 2.51]	3.66 [2.74, 5.83]	1.87 [1.73, 2.46]	0.93 [0.69, 1.15]	< 0.001
Late post-surgery	2.98 [2.07, 4.33]	5.72 [2.92, 10.13]	3.24 [2.39, 4.42]	1.78 [1.25, 2.24]	< 0.001

* Values in parentheses represent percentages (%), where n is the count and the denominator is the total number of patients in the respective subgroup

** For numerical variables, values are presented as median [Q1, Q3], where Q1 and Q3 are the first and third quartiles, respectively

cluster, as shown in Fig. 4. To account for baseline differences in sex, age, and T/N stage (Table 1), a multivariable Cox regression analysis was performed (Table 2), adjusting for these covariates. The results confirmed the independent prognostic value of the trajectory groups, with the high cluster (HR 2.64, 95% CI: 1.37–5.09, $p = 0.004$) and medium cluster (HR 1.69, 95% CI: 1.00-2.85, $p = 0.049$) remaining significant predictors of worse survival, independent of other factors. Subgroup analysis (Fig. 5) underscored the classification's relevance in men, patients under 60 years, patients with oesophagogastric junction cancer, patients with differentiated carcinoma, and patients with advanced nodal stages (N1 or higher). However, these subgroup findings should be interpreted cautiously because of the risk of inflated type I error from multiple comparisons, as no adjustments (e.g., Bonferroni correction) were applied.

Discussion

Carcinoembryonic antigen (CEA) is a glycoprotein produced during foetal development that is typically present at very low levels in adult blood. It serves as a tumour

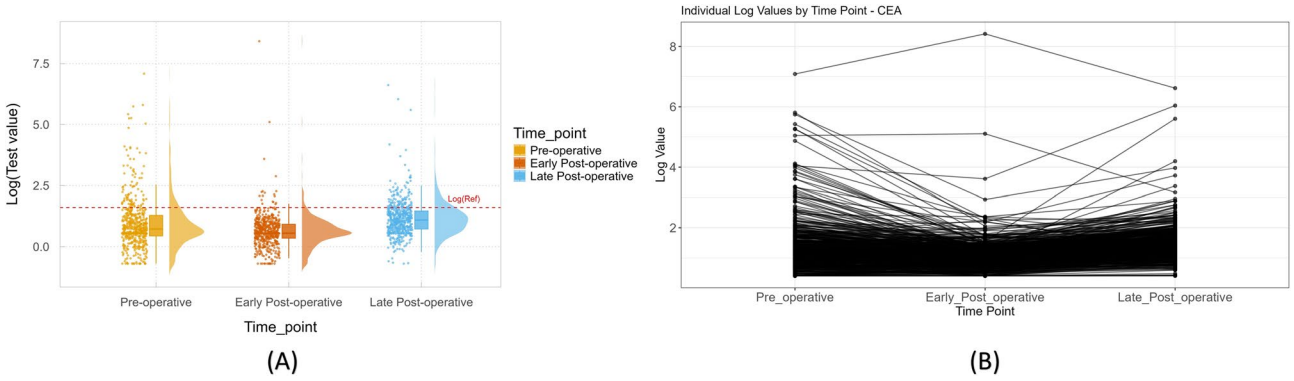

Fig. 2 Log-transformed CEA Levels Over Different Time Periods (**A**) Scatter plot and distribution of log-transformed CEA levels at three time points: preoperative (first CEA test before surgery), early postoperative (first CEA test after surgery within 3 months), and late postoperative (first test 6–12 months after surgery). The box plots and violin plots illustrate the data distribution. Preoperative CEA levels varied widely (median original value of 2.07 ng/mL). After surgery, it significantly decreased in the early postoperative period (median original value of 1.74 ng/mL), followed by a rebound in the late postoperative period (median original value of 2.98 ng/mL). The CEA levels shown in the figure were log transformed (**B**) Trajectories of individual log-transformed CEA levels over time for each patient, connected by lines. The overall pattern shows an initial decline postoperatively followed by a subsequent rebound in many cases

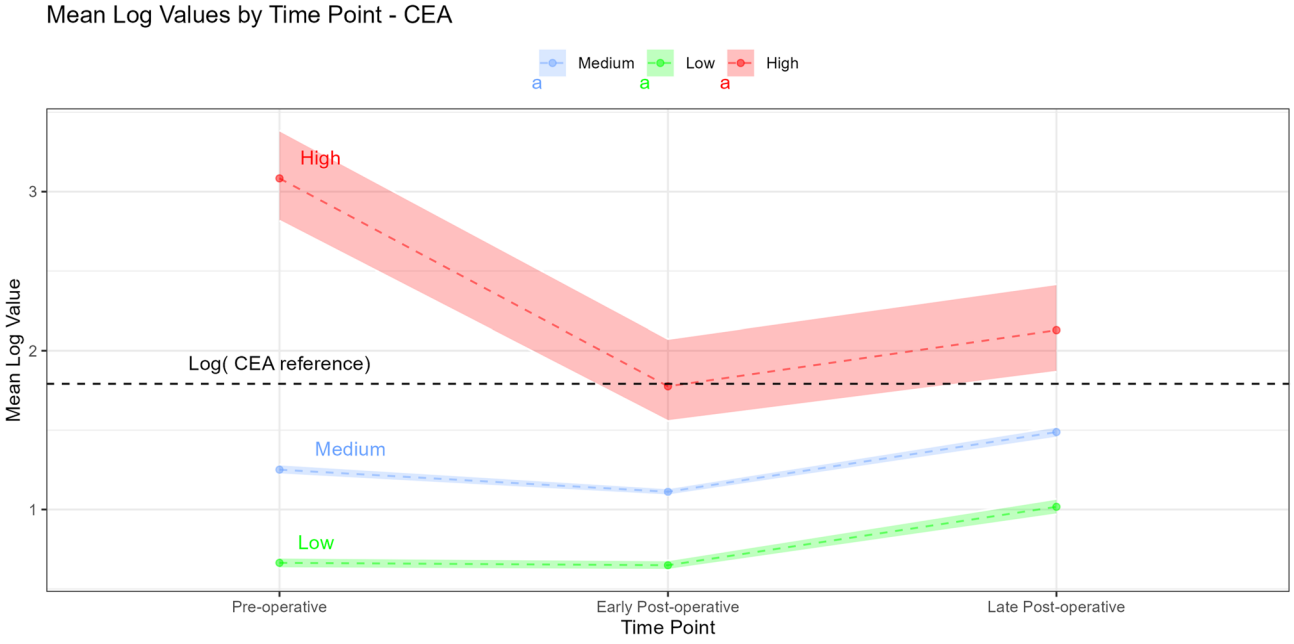

Fig. 3 Merged CEA Trajectories for 3 Clusters Identified by K-means Clustering. K-means clustering identified three distinct CEA-level trajectory clusters: high, medium, and low. The dots represent the mean CEA values for each cluster at each time point and are connected by lines to depict the merged trajectory. The transparent ribbons show 95% confidence intervals for each cluster. The high-level cluster consistently ranged above the reference level, whereas the medium- and low-level clusters remained below it. The absence of overlapping confidence intervals indicates statistically significant differences between the trajectories

marker, primarily for digestive tract carcinomas [20], although elevated levels can also occur in lung, breast, and ovarian cancers. The reference threshold is commonly set at 5 ng/mL. Elevated CEA levels may suggest the presence of cancer but lack specificity for diagnosis alone, making it more valuable for assessing treatment response and monitoring for recurrence [21].

Carcinoembryonic antigen (CEA) has been widely utilized in the management and surveillance of gastric cancer across various disease stages. In the preoperative stage, Shimada et al. [22] demonstrated through a systematic review that CEA levels are closely related to cancer stage, providing valuable information for initial assessment. Deng et al. [23] further reinforced this finding with a meta-analysis of 14,651 patients, confirming that elevated pretreatment CEA levels significantly correlate with a poorer prognosis. After treatment, CEA continues to play a crucial role in patient monitoring.

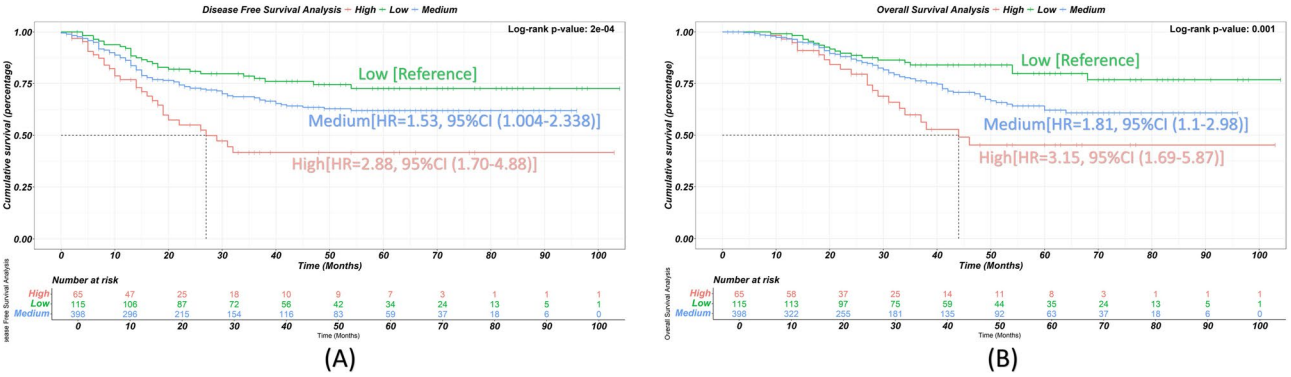

Fig. 4 Kaplan–Meier Curves Highlighting Survival Differences Across CEA Trajectory Clusters (**A**) Disease-free survival (DFS) and (**B**) overall survival (OS) show significant overall prognostic differences among trajectory groups (log-rank $p < 0.01$ for both, as annotated). Using the low trajectory group as a reference, univariable Cox regression-derived hazard ratios (HRs) were annotated, indicating that patients with higher CEA level trajectories (medium and high) had significantly worse survival outcomes

Table 2 Multivariable Cox regression analysis of prognostic factors to address the baseline characteristic imbalance

Characteristic	Hazard ratio (95% Confidence Interval)	*p*-value
Sex		
Female	1.30 (0.87–1.94)	0.195
Male	Reference	Reference
Age		
>=70	1.69 (1.04–2.76)	0.035
< 70	Reference	Reference
Location		
Upper	1.18 (0.77–1.80)	0.445
Middle	1.52 (0.96–2.40)	0.075
Lower	Reference	Reference
Differentiation		
Differentiated	0.81 (0.53–1.25)	0.343
Undifferentiated	Reference	Reference
Pathological stages		
Stage I	0.23 (0.07–0.73)	0.013
Stage II	0.46 (0.31–0.68)	<0.001
Stage III	Reference	Reference
Trajectory Cluster group		
High trajectory cluster	2.64 (1.37–5.09)	0.004
Medium trajectory cluster	1.69 (1.00-2.85)	0.049
Low trajectory cluster	Reference	Reference

Marrelli et al. [24], Choi et al. [25], and Takahashi et al. [26] highlighted the effectiveness of CEA in detecting recurrence following gastric cancer resection. Building on the concept of marker combinations, Liang et al. [27] investigated the enhanced diagnostic value of CEA when used alongside CA19-9 and CA72-4, demonstrating improved utility in patient management. Notably, Feng et al. [28] extended the application of CEA to early gastric cancer, highlighting its potential for both diagnosis and prognosis even in the initial stages of the disease. In summary, CEA is a well-established biomarker in gastric cancer that is useful for staging, prognostic assessment, posttreatment surveillance, and early detection, particularly when combined with other markers.

While prior research has focused on CEA levels at specific time points, understanding the dynamic trajectory of CEA throughout treatment is crucial. In other cancer types, trajectory-based analyses have demonstrated significant prognostic value. For example, Li et al. [9] conducted a multicentre study on colorectal cancer and reported that persistent CEA elevation was associated with a poor prognosis. Similarly, Yang et al. [11] examined dynamic CEA changes in patients with advanced non-small cell lung cancer receiving immunotherapy and demonstrated that certain marker trajectories (e.g., sustained increases or delayed normalization) were linked to shorter progression-free and overall survival. Parikh et al. [10] revealed that trajectory-based models outperformed single-time-point assessments in predicting outcomes across various cancers. In gastric cancer, related studies exist but differ in focus: Chen et al. [14] explored CEA trajectories to predict the response to neoadjuvant chemotherapy, whereas Zheng et al. [29] used CA72-4 dynamics to predict survival in patients with triple-negative gastric cancer. However, perioperative CEA trajectory analysis has rarely been applied in patients with gastric cancer.

In this study, we explored the prognostic value of CEA level dynamics in gastric cancer patients over a one-year perioperative period, aiming to uncover hidden prognostic information within these trajectories. We selected three time points—preoperative, within 3 months postsurgery, and 6 months or more postsurgery—to capture key stages of treatment, including surgery and adjuvant therapy. However, approximately 60% of the initial 1,440 patients were excluded because of incomplete CEA data across these time points, which we acknowledge was largely due to follow-up compliance, inconsistent testing schedules, and missing records. We recognize that

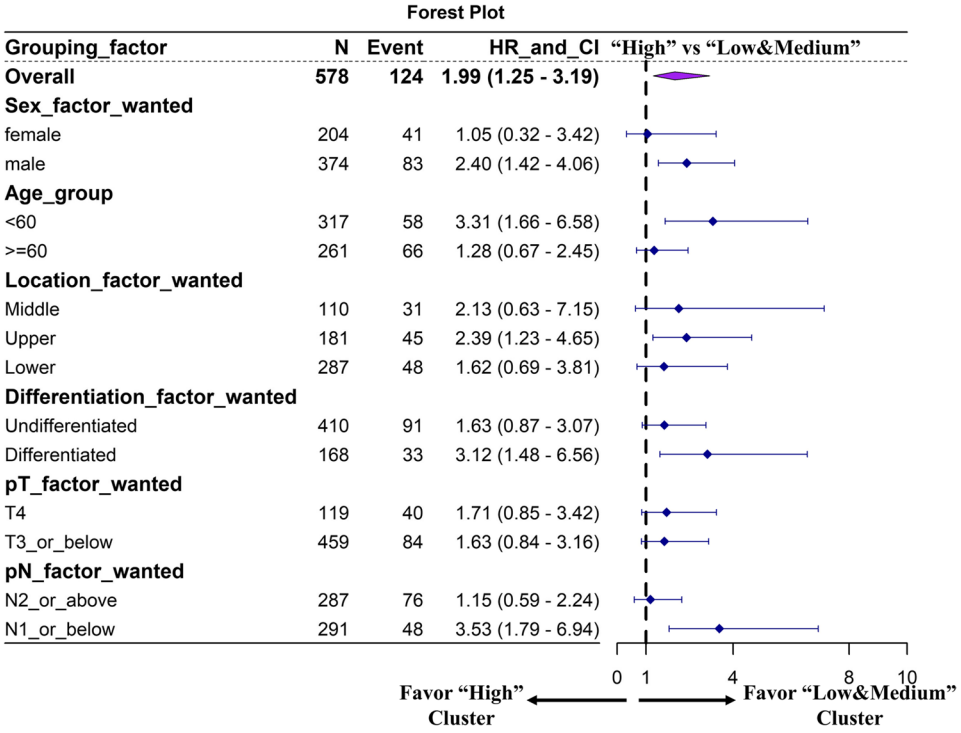

Fig. 5 Forest plot of subgroup analysis for the association between CEA trajectory and overall survival. The hazard ratios and confidence intervals were calculated by cox regression in the respective subgroups

this high exclusion rate, although only 4.3% were due to early postoperative death, may limit our insights into late recurrences and requires cautious interpretation of the findings.

In this study, we employed k-means clustering, a mature machine learning algorithm that excels in identifying patterns in time series data such as CEA trajectories, and offers clear, interpretable risk stratification for clinical use. Alternative clustering methods were considered but deemed less suitable. Hierarchical clustering requires subjective decisions to determine the number of clusters, which can introduce bias and undermine the objectivity needed for clinical applications. Similarly, Gaussian mixture models (GMMs) assume a Gaussian distribution, an assumption that does not hold for CEA trajectory data, which often exhibit skewed distributions or outliers. Latent class mixed models, while powerful, require larger sample sizes and significant computational resources, making them less practical for our dataset and less interpretable in a clinical context. After careful evaluation, we selected k-means clustering as the most robust and practical method for this study.

Using k-means clustering, we identified three distinct CEA trajectory types in the final analysis: "high," "medium," and "low" groups. This trajectory analysis captured both CEA values at different time points and their patterns of change, offering more comprehensive insights than static values alone. Notably, this classification was significantly associated with disease-free survival and overall survival, with higher trajectories linked to poorer outcomes. Multivariate Cox regression analysis (Table 2) confirmed the independent prognostic value of these trajectory groups after adjusting for baseline differences in sex, age, and T/N stage, with the high cluster (HR 2.64, 95% CI: 1.37–5.09, $p = 0.004$) and medium cluster (HR 1.69, 95% CI: 1.00–2.85, $p = 0.049$) showing significant associations with worse survival. Thus, higher CEA trajectories generally indicate a worse prognosis. The underlying mechanism may involve higher CEA levels, reflecting not only greater tumour burden but also chemotherapy resistance, a critical factor given the role of chemotherapy as a primary antitumour therapy alongside surgical resection. A recent meta-analysis revealed that pretherapeutic serum CEA levels > 5 ng/mL were significantly associated with a poorer pathological response to neoadjuvant chemotherapy [30] and that elevated CEA may promote chemotherapy resistance in gastric cancer cells via the CEA–KRT1–PI3K/AKT axis [31]. However, the wide confidence intervals in our model suggest limited precision, which should be noted.

In this study, we observed that CEA levels generally declined after surgery—likely reflecting a reduced tumour burden—but subsequently rebounded in some patients, especially those in the high-trajectory cluster

(Fig. 3). This rebound may result from multiple mechanisms; on the basis of a review of the literature, we consider the progression of microscopic residual disease (MRD) to be the primary factor. Despite curative resection, MRD may persist in the peritoneal cavity, lymph nodes, or bone marrow, contributing to delayed CEA rebound. Previous studies have shown that patients with incomplete resection often experience early recurrence and shorter recurrence-free survival—typically within 18 months—which is directly associated with elevated CEA levels [32, 33]. Other factors, such as chemotherapy resistance, may also contribute [30, 31].

With respect to clinical interpretation, we propose that the high-trajectory group requires heightened diligence in monitoring. In accordance with the National Comprehensive Cancer Network (NCCN) guidelines, postoperative patients should undergo follow-up every 3–6 months during the first year, which includes a medical history, physical examination, and abdominal imaging, such as contrast-enhanced CT. For patients in the high-trajectory group, we recommend adhering to the guideline's framework but suggest increasing the frequency of exams to every 3 months. Additionally, CEA levels should be checked at each visit to monitor for any sustained elevation. If contrast-enhanced CT raises a suspicion of recurrence, further evaluation with PET–CT is advised to facilitate early detection and intervention. For the low-trajectory group, the follow-up interval could be extended to every 6 months, which is consistent with the guideline's recommendations. These proposed frequencies are fully aligned with the NCCN guideline framework [4].

This study has several limitations that warrant consideration. Its single-centre, retrospective design, while ensuring consistency in CEA measurement and follow-up, introduces potential selection bias, as patients with more frequent follow-up may have been more likely to be included, thus limiting generalizability. Additionally, the retrospective nature of our study restricts causal inference, and prospective validation is necessary to confirm these findings. The relatively small sample size further reduces the statistical power, potentially weakening the reliability of the results for direct clinical decision-making. The median follow-up of 29 months is sufficient to capture early- to midterm recurrences but may miss late recurrences—particularly in early-stage or low CEA trajectory patients—due to a high censoring rate (78.5%). Moreover, the lack of data on postoperative adjuvant therapy, which is a potential confounding factor of survival outcomes, and the lack of an external validation cohort further constrain the findings' applicability and robustness. With respect to the machine learning approach, k-means clustering, while insightful, is sensitive to initial values, relies on means that may not fully reflect individual CEA variability, and introduces complexity that hinders interpretability and clinical usability. Furthermore, k-means clustering failed to identify distinct prognostic subgroups with transitions from high to low or low to high CEA values due to limited sample sizes and potential algorithmic constraints. Additionally, there is a risk of overfitting, as the model was trained and tested on the same dataset without external validation, which may overestimate its predictive performance. Future research with larger, prospective cohorts, complete follow-up, and external validation is essential to address these limitations, strengthen the conclusions, and enhance the clinical relevance.

Despite these limitations, our findings provide valuable insights into the prognostic significance of CEA trajectories in gastric cancer, potentially informing more personalized treatment strategies and follow-up protocols.

Conclusions

We demonstrated that higher CEA trajectories are associated with a worse prognosis, suggesting that CEA trajectory monitoring may serve as an early indicator of recurrence risk in patients with gastric cancer, warranting more intensive surveillance for high-trajectory patients.

Abbreviations

CEA	Carcinoembryonic Antigen
NCCN	National Comprehensive Cancer Network
AJCC	American Joint Committee on Cancer
DFS	Disease-Free Survival
OS	Overall Survival
HR	Hazard Ratio
ng/mL	Nanograms per milliliter
CI	Confidence Interval
CA19-9	Carbohydrate Antigen 19 – 9
CA72-4	Carbohydrate Antigen 72 – 4
GMM	Gaussian Mixture Models
MRD	Microscopic Residual Disease
PET-CT	Positron Emission Tomography-Computed Tomography

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Chen YH and Lian L designed the study. Chen YH collected and cleaned the data, created the tables and figures, and drafted the initial manuscript. Liu D contributed to data collection and manuscript writing. Wang Z performed data analysis. Lin Y, Jiang XH, and Liu JJ contributed to data collection. All

authors read and approved the final manuscript. Chen YH, Liu D, and Wang Z contributed equally to this work.

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Data availability
The data that support the findings of this study are available from Dr. Yonghe Chen (E-mail: chenyhe@mail2.sysu.edu.cn) upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was reviewed and approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No.2024ZSLYEC-454) and conducted in accordance with the Declaration of Helsinki.
Informed consents were obtained from all study participants or their legal guardians prior to study by the follow-up office.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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