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Novel surveillance protocol for gastric cancer based on CEA: a high-volume multi-center study

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Abstract

Tumor markers are commonly used in gastric cancer patients, but their effectiveness in monitoring recurrences is not optimal. This study aims to evaluate the recurrence predictive performance of carcinoembryonic antigen (CEA) across different baseline groups and establish a new surveillance protocol. We analyzed data from 1708 patients at Sun Yat-Sen University Cancer Center with stage I-III gastric adenocarcinoma. The research findings were subjected to longitudinal validation (expanded dataset comprising 6422 follow-up records of patients) and external validation (109 patients from the Sixth Affiliated Hospital, Sun Yat-Sen University). The 5-year disease-free survival (DFS) rate was 61.1% (95% CI: 57.4%-65.0%) for the normal baseline group and 42.1% (95% CI: 36.4%-48.6%) for the elevated baseline group. The normalization group had DFS similar to the persistently normal group ($p=0.117$). For recurrence prediction efficacy, the elevated baseline group showed significantly higher sensitivity than the normal baseline group (0.73 vs. 0.32, $p=0.001$), while the normal baseline group had superior specificity (0.87 vs. 0.59, $p=0.031$). These results were confirmed in longitudinal validation and external validation cohorts. Different monitoring strategy should be used for different CEA baseline patients. Incorporating CEA monitoring into gastric cancer surveillance protocols with the above method may be included in the surveillance protocols of NCCN gastric cancer guideline.

Keywords Gastric cancer, Tumor marker, Disease-free survival, Recurrence, Surveillance protocol

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Introduction

Gastric cancer is a prevalent disease worldwide, ranking as the fifth most common cancer and the third leading cause of cancer-related deaths. Each year, there are over one million new cases globally, resulting in approximately 700,000 deaths [1, 2]. Early diagnosis of gastric cancer is challenging due to the absence of notable early symptoms, often leading to advanced-stage diagnosis characterized by local spread or metastasis [3]. About 40% of locally advanced gastric cancer patients experience recurrence even after undergoing standard treatments such as surgery and chemotherapy. Recurrence can occur in different forms, including local recurrence (LR), peritoneal recurrence (PR), and distant metastasis (DM) [4–7]. The prognosis for gastric cancer patients remains unsatisfactory, emphasizing the importance of early detection and timely management of recurrence. Early identification and effective management of recurrence are crucial for improving prognosis and quality of life in individuals affected by gastric cancer.

Multiple studies have highlighted the role of serum tumor markers in the management of cancer patients due to their significance in various aspects, including preoperative diagnosis, postoperative evaluation, and follow-up [8]. Among these tumor markers, carcinoembryonic antigen (CEA) is of particular importance in gastric cancer and is widely used for auxiliary diagnosis, prognosis assessment, and recurrence monitoring in patients with gastric cancer [9, 10].

The NCCN Clinical Practice Guidelines in Oncology for Gastric Cancer (Version 2.2022) recommend follow-up examinations for gastric cancer patients, including medical history, physical examination, blood tests, enhanced CT scans, and endoscopy [11]. Although tumor markers are commonly employed in clinical practice, they are not explicitly mandated in these guidelines due to the limited efficacy in gastric cancer [12]. Previous studies have demonstrated the impact of baseline CEA on prognosis in gastric cancer patients. For instance, Lin et al. identified preoperative CEA as an independent risk factor for gastric cancer, with a hazard ratio (HR) of 1.196 (95% CI:1.043–1.371) for overall survival (OS) [13]. Similarly, Huang et al. found that patients with elevated postoperative tumor markers, including CEA, faced twice the risk of overall death rate (HR = 2.338; 95% CI:1.071–5.101) [14]. While these studies shed light on the prognostic significance of CEA, they lack exploration and practical application regarding the effectiveness of recurrence monitoring in gastric cancer patients.

The significant prognostic influence of both baseline and postoperative CEA levels in gastric cancer patients underscores the potential for personalized surveillance approaches. In this multicenter study, we analyzed a large patient cohort to evaluate CEA's recurrence-predictive performance while accounting for baseline variability. This investigation validates the integration of CEA monitoring into follow-up criteria and advances the development of more efficient, accurate, and noninvasive surveillance protocols.

Materials and methods

Study population and ethics

We collected data from gastric cancer patients who underwent curative gastrectomy at the Department of Gastric Surgery of Sun Yat-Sen University Cancer Center (SYSUCC, Guangzhou, China) and The Sixth Affiliated Hospital, Sun Yat-Sen University (SAH-SYSU, Guangzhou, China) between January 2008 and December 2020. Inclusion criteria comprised histologically confirmed gastric adenocarcinoma, curative gastrectomy with D2 lymph node dissection, absence of distant metastasis, and availability of complete clinical information and follow-up records. Exclusion criteria included the presence of other malignant tumors, receipt of neoadjuvant chemotherapy or radiotherapy, or lack of pre- or postoperative CEA data. A total of 1817 gastric cancer patients met the eligibility criteria, including 1708 patients from SYSUCC and 109 from SAH-SYSU. Tumor staging was conducted following the eighth edition of the AJCC Staging Manual [15].

Demographic and clinicopathologic characteristics of the patients, such as sex, age at diagnosis, body mass index, tumor size, Bormann type, Lauren type, degree of differentiation, tumor marker value, and TNM stage, were recorded for analysis.All patients provided written informed consent authorizing the use of their medical data for research purposes This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at SYSUCC and SAH-SYSU.

Measurement of tumor markers

The CEA levels were measured within two-week before surgery and were used as the baseline tumor marker value. Comparatively, postoperative CEA levels were measured at multiple time points after the surgery. CEA level measurements were based on a standardized protocol in clinical laboratory settings using double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), and the normal level reference range was established as 0 to 5 ng/mL [16]. Based on their baseline tumor marker levels, the patients were categorized into a normal group (range 0 to 5 ng/mL) and an elevated group (> 5 ng/mL).

Study cohort and design

The study cohort had a long follow-up time, with each patient having different recurrence statuses and current tumor marker records at different follow-up time points.

To optimize the utilization and enhance the accuracy of the follow-up results, we conducted separate analyses on three distinct study cohorts, comprising the main study cohort (cohort 1), the longitudinal cohort (cohort 2), and the external study cohort (cohort 3).

The main study cohort (cohort 1) consisted of 1708 patients from SYSUCC. For patients who experienced recurrence, their postoperative tumor marker values were recorded as the measurements taken within two weeks before the confirmed diagnosis of recurrence. In cases where patients did not experience recurrence, their postoperative tumor marker values were recorded as the earliest measurements obtained at least two months after surgery. Figure 1 illustrates the study design flowchart. To account for variations in the frequency and number of postoperative follow-ups among patients, we established Cohort 2 (longitudinal cohort) incorporating multi-time-point monitoring-level statistics to enhance analytical robustness. For Cohort 1, we documented each patient follow-up as discrete data points, capturing recurrence status and tumor marker values at every visit. This approach enabled us to assemble a longitudinal dataset comprising 6,422 patient follow-up records (Figure S1). The external study cohort (cohort 3) comprised 109 patients from SAH-SYSU, and the same methodology as applied in cohort 1 was employed. Cohort 3 served as an independent validation cohort for comparative analysis, enabling us to further validate the findings obtained in cohort 1 (Figure S2).

Follow-up investigation

All enrolled patients underwent regular follow-up examinations following the institutional standard protocols for gastric cancer management, which is based on the NCCN Guidelines [11]. Within the first two years after surgery, patients were followed up every 3–6 months. From 3 to 5 years after surgery, the follow-ups occurred every 6–12 months and were conducted annually thereafter. The median follow-up time in our study was 48.9 months, ranging from 1 to 180 months. During the follow-up visits, patients underwent various examinations to determine their survival and recurrence status, which included physical examination (i.e., anal digital examination and abdominal examination), measurement of tumor markers, computed tomography (CT) scans with oral and IV contrast, ultrasound examinations, endoscopy, and positron emission tomography-computed tomography (PET-CT). Radiologic images were carefully reviewed, and the diagnosis of LR, peritoneal recurrence or distant metastasis was established based on the detection of new lesions on CT, PET-CT or confirmation through endoscopy. In this study, overall recurrence (OR) referred to the occurrence of LR, PR, or DM after curative resection. The primary endpoint of the study was disease-free survival (DFS), which was calculated from the date of curative resection to the date of recurrence, death or the last follow-up.

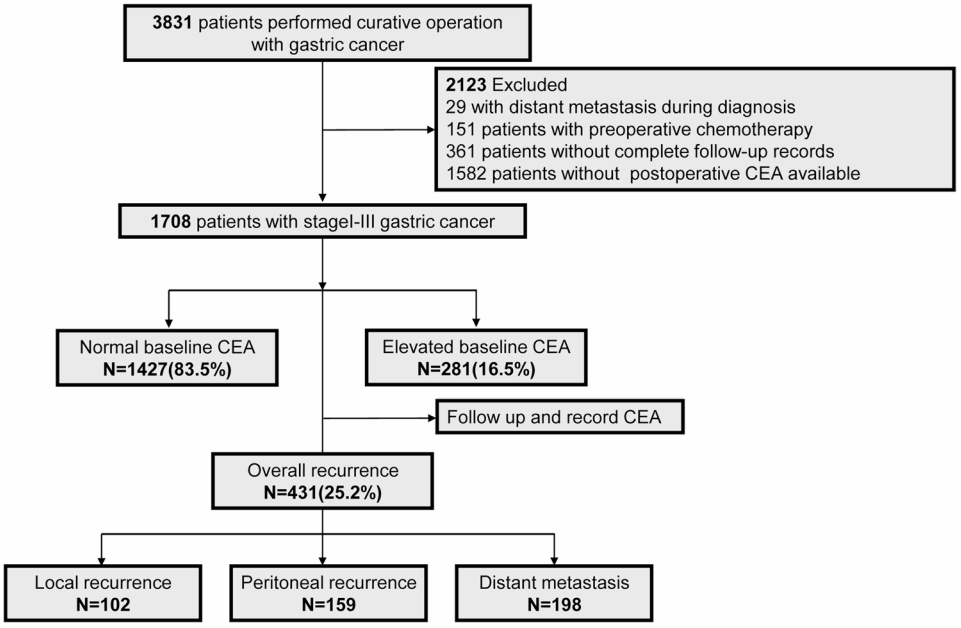

Fig. 1 Study design and flowchart of the main study cohort (cohort 1). A total of 1708 patients who received curative resection and were diagnosed with stage I-III gastric adenocarcinoma were included. All patients were grouped based on their baseline CEA level and recurrence status. *Abbreviations: CEA, carcinoembryonic antigen*

Statistical analysis

The data analysis and graph generation were conducted using R software (version 4.0.4, Revolution Analytics, USA). Categorical variables were analyzed using the chi-square test or Fisher's exact test, and the results were presented as numbers and percentages. Continuous variables were assessed using t-tests, and the findings were reported as medians with interquartile ranges (IQR). Survival analysis for DFS was performed using the Kaplan-Meier method, and differences in survival times were evaluated using the log-rank test. A value of $p < 0.05$ was considered significant. To account for the baseline imbalance observed between the two patient groups and to mitigate the potential influence of the baseline imbalance on the study outcomes, we conducted subgroup adjustment analysis on key variables, specifically the TNM stage. The performance of CEA in determining recurrence during patient follow-up was assessed using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to evaluate the accuracy of CEA.

Results

Patient characteristics

A total of 1708 patients diagnosed with gastric cancer were included in this study, comprising 1125 (65.9%) male and 583 (34.1%) female patients. Most patients (67.4%) had a low degree of differentiation, and Bormann III type was the most common among the Bormann classifications (59.4%). The distribution of each type in the Lauren classification was relatively balanced. In terms of cancer stage, 451 (26.4%) patients had stage I gastric cancer, while 1257 (73.6%) patients had advanced gastric cancer. Based on the baseline CEA measurements, patients were divided into a normal group ($N = 1427$) and an elevated group ($N = 281$). Table 1 summarizes the clinical characteristics of all patients in each group. The results indicated that patients in the elevated group were relatively older, had higher postoperative CEA levels, and exhibited more advanced TNM staging than the normal group. However, no significant differences were observed in tumor size or BMI between the two groups.

Recurrence status and postoperative CEA values

During the entire follow-up period, a total of 431 patients (25.2%) experienced recurrence, including 102 cases (5.9%) of LR, 159 cases (9.3%) of PR and 198 cases (11.6%) of DM. It's worth noting that some patients had multiple recurrence patterns, as mentioned above. Figure 2A demonstrates that postoperative CEA values were significantly higher in patients who experienced recurrence compared to those without recurrence. The analysis of postoperative CEA values for different types of recurrence patterns is illustrated in Fig. 2B. Patients with LR, PR and DM had higher postoperative CEA values than those without recurrence (all $p < 0.001$). However, there was no significant difference in CEA values among the various types of recurrence patterns (all $p > 0.05$).

Survival analysis for different baseline and postoperative CEA levels

The 5-year DFS rate for the entire cohort was 55.3% (95% CI: 52.1%–58.7%). When stratified by cancer stage, the 5-year DFS rates were 89.2% (95% CI: 85.0%–93.5%) for stage I, 68.5% (95% CI: 62.1%–75.5%) for stage II, and 34.2% (95% CI: 30.1%–38.9%) for stage III patients. The 5-year DFS rates were 61.1% (95% CI: 57.4%–65.0%) for the normal baseline group and 42.1% (95% CI: 36.4%–48.6%) for the elevated baseline group. The difference in DFS between the two groups was significant (HR: 1.74, 95% CI: 1.47–2.07, $p < 0.001$), as shown in Fig. 3A.

To further investigate the prognostic differences among patients with different baseline and postoperative CEA statuses, we categorized them into four groups: persistently normal (normal baseline and postoperative CEA), normalization (elevated baseline and normal postoperative CEA), elevation (normal baseline and elevated postoperative CEA), and persistently elevated (elevated baseline and postoperative CEA). The 5-year DFS rates for the patients in the four groups were as follows: 64.7% (95% CI: 60.7%–68.4%) for the persistently normal group, 52.6% (95% CI: 41.7%–66.2%) for the normalization group, 36.8% (95% CI: 29.4%–45.9%) for the elevation group, and 22.4% (95% CI: 14.6%–34.4%) for the persistently elevated group. Figure 3B-D depicts the survival comparisons among the stratified groups. The persistently normal group had the best survival outcome, while the persistently elevated group had the poorest survival outcome. The normalization group showed DFS comparable to the persistently normal group (HR: 1.36, 95% CI: 0.94–1.79; $p = 0.117$). Stratification by TNM staging confirmed this pattern persisted in advanced gastric cancer patients. Specifically, in advanced gastric cancer, the survival outcomes of the normalization and persistently normal groups were even more similar (HR: 1.02, 95% CI: 0.73–1.42, $p = 0.927$), and both groups exhibited significantly better survival than the elevation and persistently elevated groups (log-rank $p < 0.001$).

Postoperative CEA diagnostic performance for recurrence

To comprehensively assess the diagnostic efficacy of elevated postoperative CEA in detecting gastric cancer recurrence, we systematically compared sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) across the entire cohort, normal-baseline CEA patients, and elevated-baseline CEA patients. We also examined the diagnostic performance of elevated postoperative CEA in different recurrence

Table 1 General characteristics of 1708 patients with gastric cancer grouped by baseline CEA levels

Variable	Normal group $N=1,427$[1]	Elevated group $N=281$[1]	*p*-value[2]
Gender			< 0.001
Male	905 (63%)	220 (78%)	
Female	522 (37%)	61 (22%)	
Age (years)	55 (47, 63)	60.5 (54, 67)	**< 0.001**
BMI (kg/m^2)	22.3 (20.0, 24.3)	21.7 (19.5, 23.9)	0.133
Tumor size (cm)	4.0 (3.0, 6.0)	5.0 (3.0, 6.0)	0.072
Bormann type			**< 0.001**
I	191 (13%)	17 (6.0%)	
II	369 (26%)	49 (17%)	
III	810 (57%)	205 (73%)	
IV	57 (4.0%)	10 (3.6%)	
Lauren type			**< 0.001**
Diffuse type	605 (42%)	81 (29%)	
Intestinal type	472 (33%)	125 (44%)	
Mixed type	350 (25%)	75 (27%)	
Degree of differentiation			**< 0.001**
Low	998 (70%)	153 (54%)	
Medium	412 (29%)	126 (45%)	
High	17 (1.2%)	2 (0.7%)	
Pre CEA (ng/mL)	2.1 (1.1, 3.2)	10.2 (6.4, 26.3)	**< 0.001**
Post CEA (ng/mL)	2.6 (1.6, 4.2)	6.7 (3.0, 10.2)	**< 0.001**
PN			**< 0.001**
N0	369 (26%)	35 (12%)	
N1	80 (5.6%)	7 (2.5%)	
N2	53 (3.7%)	3 (1.1%)	
N3	925 (64.8%)	236 (84.6%)	
PT			**< 0.001**
T1	370 (26%)	34 (12%)	
T2	170 (12%)	19 (6.8%)	
T3	464 (33%)	129 (46%)	
T4	423 (30%)	99 (35%)	
TNM			**< 0.001**
I	411 (29%)	40 (14%)	
II	355 (25%)	54 (19%)	
III	661 (46%)	187 (67%)	

Abbreviations: *BMI* Body mass index, *TNM* Tumor, Lymph node, Metastasis, *IQR* Interquartile range

[1] n (%); Median (IQR)

[2] Pearson's Chi-squared test; Fisher's exact test

patterns, including OR, LR, PR and DM (Fig. 4). The predictive performance of postoperative CEA status for recurrence differed significantly among the total cohort, normal baseline group and elevated baseline group, particularly in terms of sensitivity and specificity. For OR, the sensitivity of the elevated baseline group was significantly higher than that of the normal baseline group (0.73 versus 0.32, $p=0.001$), while the normal baseline group exhibited higher specificity (0.87 versus 0.59, $p=0.031$). Similar results were observed for the surveillance of local recurrence (sensitivity: 0.86 versus 0.29, $p=0.001$; specificity: 0.84 versus 0.51, $p=0.022$), peritoneal recurrence (sensitivity: 0.59 versus 0.31, $p=0.013$; specificity: 0.84 versus 0.49, $p=0.022$), and distant metastasis (sensitivity: 0.74 versus 0.35, $p=0.001$; specificity: 0.86 versus 0.56, $p=0.035$). Interestingly, regarding the recurrence pattern, we found that postoperative CEA status exhibited high sensitivity for local recurrence (0.86) but relatively lower sensitivity for peritoneal recurrence (0.59).

Internal validation and external validation

To ensure the reliability of our results, we conducted longitudinal and external cohort validation. In the longitudinal analysis of 6422 records (Figure S1), we observed that the sensitivity for recurrence prediction was higher in the normal baseline group compared to the elevated baseline

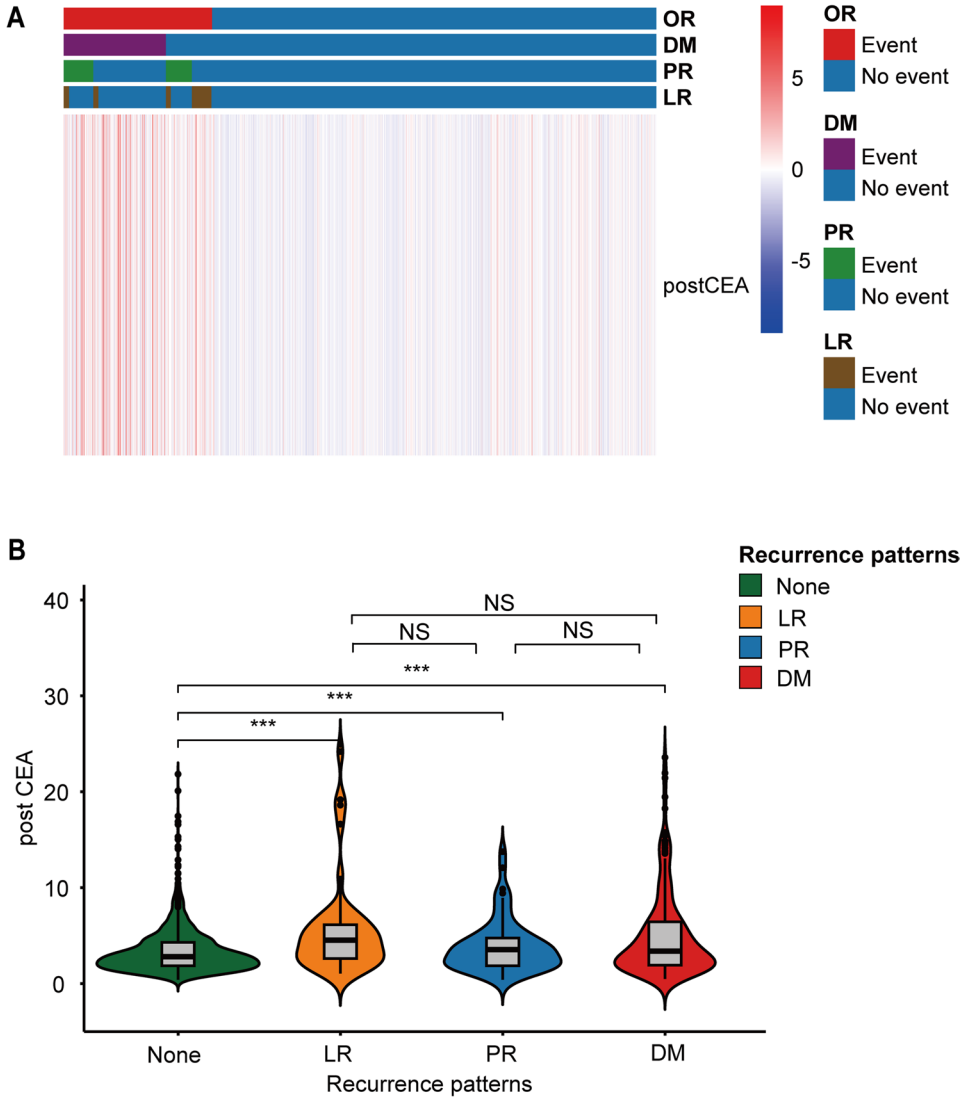

Fig. 2 The relationship between recurrence patterns and postoperative tumor marker levels in gastric cancer patients. **A** Heatmap of the relationship between recurrence patterns and postoperative CEA levels in gastric cancer patients. Tumor marker levels are presented as relative expression values, with values higher than the mean represented by red shades (relative expression value > 0) and values lower than the mean represented by blue shades (relative expression value < 0). **B** Violin plots of postoperative CEA levels for different recurrence patterns. NS indicates no significant difference in the measured values between the two groups ($p > 0.05$). *** indicates a significant difference in the measured values between the two groups ($p < 0.001$). *Abbreviations: OR,overall recurrence; LR, local recurrence; PR, peritoneal recurrence; DM, distant metastasis.*

group (0.73 versus 0.34, $p = 0.001$). Conversely, the elevated baseline group exhibited higher specificity than the normal baseline group (0.85 versus 0.53, $p = 0.025$).

Next, we included an independent external cohort consisting of 109 patients from SAH-SYSU to further validate our findings (Table S1). The 5-year DFS rate for the external cohort was 33.1% (95% CI: 24.6%–44.5%), and the proportion of OR was 29.3%. Similar to the results in the main study cohort, we found that the sensitivity for recurrence prediction was higher in the normal baseline group compared to the elevated baseline group (0.64 versus 0.14, $p < 0.001$), while the specificity was higher in the elevated baseline group compared to the normal baseline group (1.00 versus 0.52, $p < 0.001$) (Figure S2). Taken together, the consistency of the results obtained from both the longitudinal cohort validation and the external cohort validation methods further confirms the reliability and robustness of our findings.

Discussion

Tumor markers play a crucial role in diagnosing, predicting outcomes, and monitoring cancer progression in various types of cancers [17, 18]. In the context of gastric cancer, CEA is widely used as a tumor marker in clinical practice [19]. Previous studies have predominantly focused on preoperative tumor marker levels and their

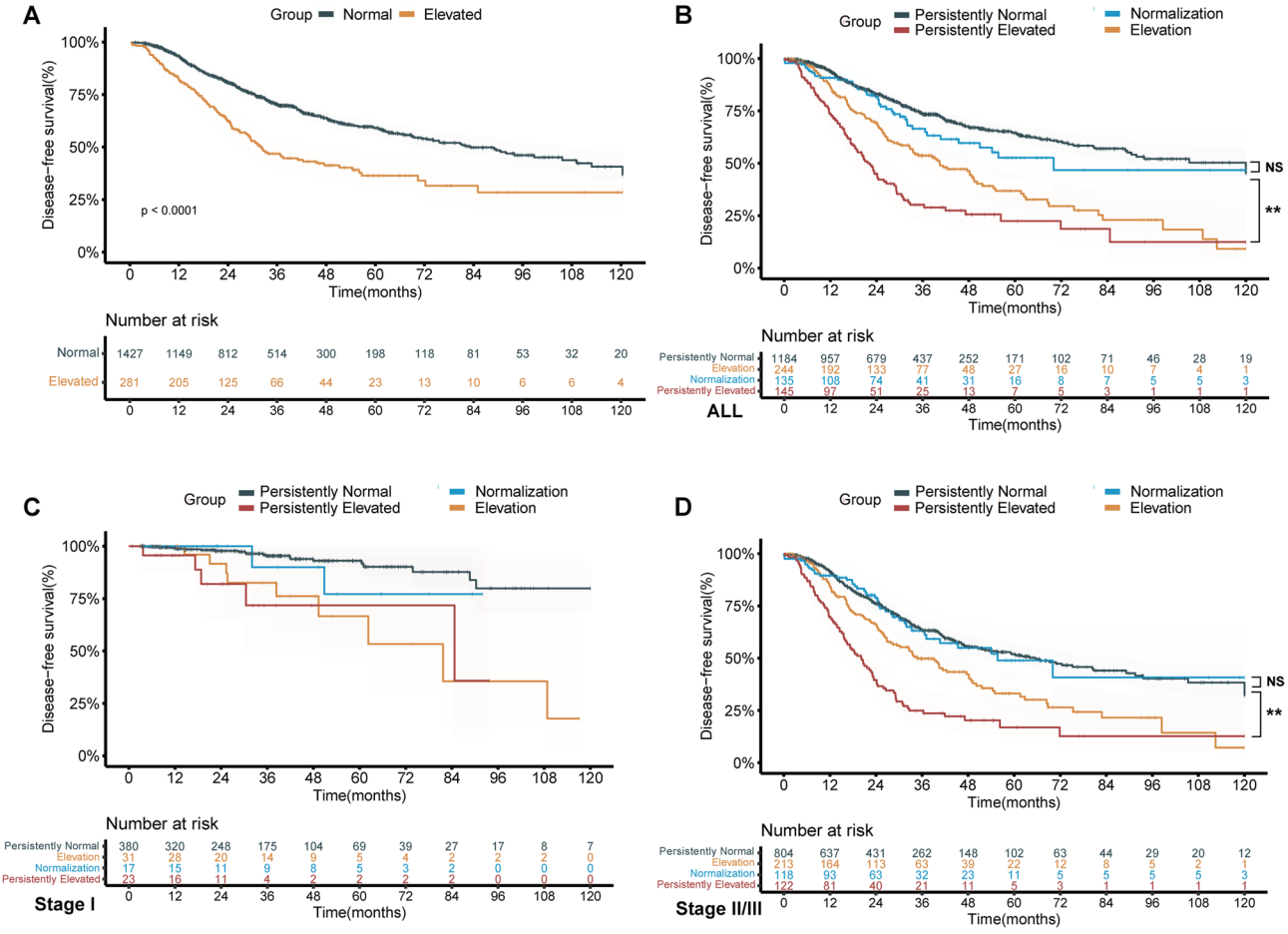

Fig. 3 Kaplan–Meier DFS analysis for gastric cancer patients. **A** Comparison according to the baseline CEA status in the normal and elevated groups. **B** Comparison according to the baseline and postoperative CEA status by persistently normal, elevation, normalization and persistently elevated groups. **C-D** Comparison according to the baseline and postoperative CEA status in stage I and stage II/III gastric cancer patients ** indicates that the *p*-value of the log-rank test between each pair of groups is less than 0.01. ** indicates that the p-value of the log-rank test between each pair of groups is less than 0.01

correlation with prognosis in gastric cancer patients [20, 21]. However, the predictive performance of CEA in this context has not yet reached an optimal level [22]. Thus, the main objective of this study was to evaluate the effectiveness of postoperative CEA as a tool for monitoring recurrence in gastric cancer patients. To achieve this, we stratified patients based on their baseline CEA levels.

The positive rates of baseline CEA have been reported to vary in previous studies, ranging from 15–30% [23, 24]. In this present study, the positive rate of baseline CEA was 16.5%, which is similar to the results of the previous study. Consistent with previous research findings, the baseline normal group showed a longer DFS time than the baseline elevated group [13, 25]. In both the overall patient population and specifically in advanced-stage gastric cancer patients, the normalization group showed DFS comparable to that of the persistently normal group. This suggests patients with initially elevated CEA levels that normalized following surgery may have similarly favorable prognosis as those with consistently normal CEA levels.

Although previous studies have investigated the use of CEA monitoring for detecting recurrence in gastric cancer patients [26] they reported low predictive value and limited clinical relevance. Importantly, there has been a noticeable gap in analyzing patient stratification based on baseline CEA levels [26–28]. This present study addressed these limitations and observed a significant disparity in predictive performance between the normal and elevated baseline groups. Specifically, the sensitivity for the elevated baseline group was 0.73, indicating a moderate ability to correctly identify cases of recurrence. In contrast, the specificity for the normal baseline group was 0.87, demonstrating a high level of accuracy in correctly identifying cases without recurrence. These results were consistent across all types of recurrence patterns, with local recurrence showing the highest predictive efficacy and peritoneal recurrence exhibiting relatively lower

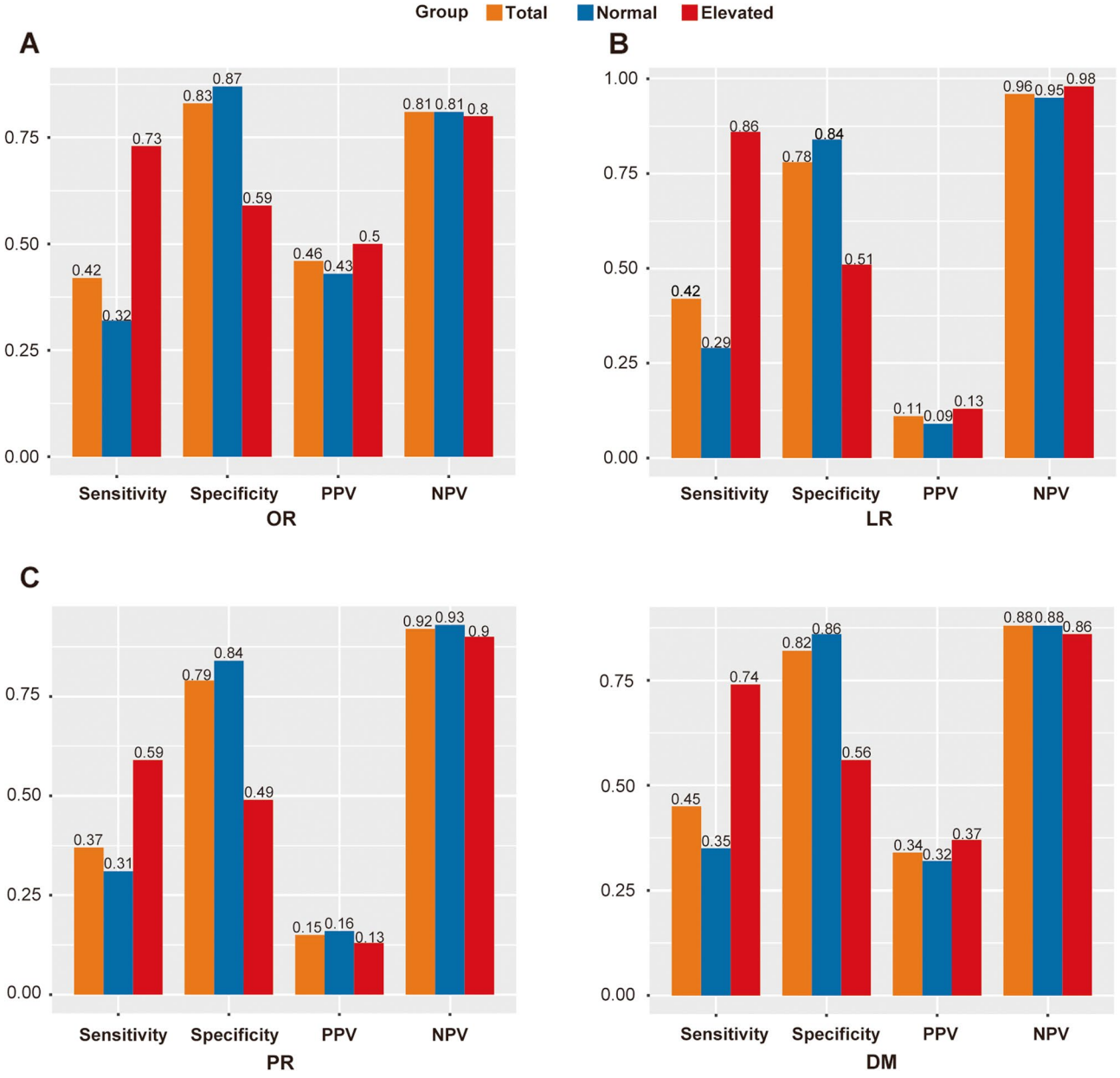

Fig. 4 Predictive performance of postoperative CEA status for recurrence in gastric cancer patients. Patients were grouped by whether baseline CEA levels were within the reference range, resulting in normal and elevated groups. **A-D** Predictive performances for OR, LR, PR and DM. *Abbreviations: PPV, positive predictive value; NPV, negative predictive value*

predictive performance. Furthermore, our study demonstrated superior clinical efficacy compared to previous research [29].

The significant intergroup differences and elevated predictive values following CEA-based stratification demonstrate critical implications for gastric cancer surveillance, necessitating distinct monitoring strategies for patients with normal versus elevated baseline CEA levels. This novel CEA-guided follow-up strategy holds substantial clinical potential by enabling more effective, risk-adapted patient management. In the NCCN guidelines for colorectal cancer, regular monitoring of CEA is recommended as part of the follow-up protocol. However, in the NCCN guidelines for gastric cancer, tumor markers are not currently included as a follow-up requirement. Instead, the guidelines primarily emphasize imaging follow-up requirements, such as chest/abdomen/pelvis CT scans with oral and IV contrast every 6 months for the first 2 years, followed by annual scans for up to 5 years [11, 30, 31]. Based on our study findings, we propose the implementation of a novel surveillance strategy for gastric cancer, utilizing CEA baseline grouping as a

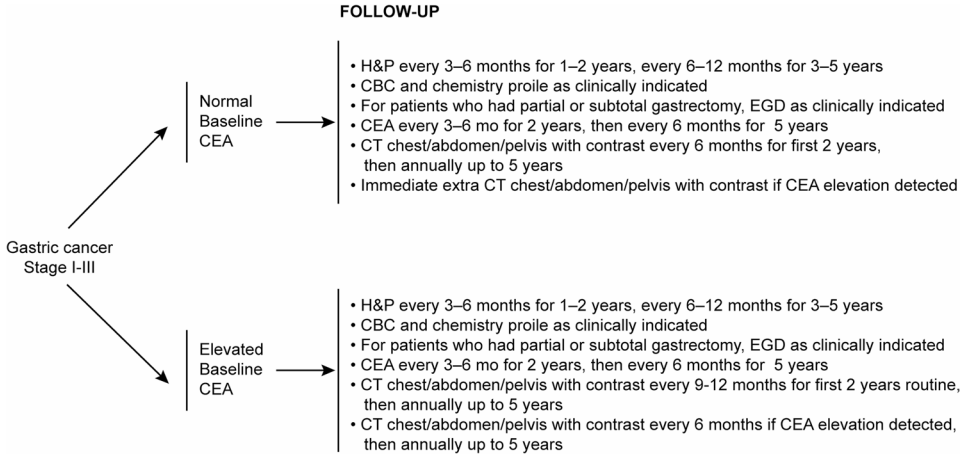

Fig. 5 Follow-up recommendations for gastric cancer patients based on baseline CEA status. Tumor marker detection can be added to routine follow-up. For patients in the normal group, if CEA elevation is detected during follow-up, simultaneous imaging examination is recommended. For patients in the elevated group, if CEA normalization is detected, the frequency of imaging examination could be reduced

key component. The proposed strategy is an improved version based on the existing NCCN guidelines and is illustrated in Fig. 5. Elevated CEA levels can serve as a high-sensitivity predictor for recurrence, enabling a reduction in the frequency of imaging follow-up for gastric cancer patients. On the other hand, in the normal CEA group, additional imaging examinations should be conducted when elevated CEA levels are detected due to their higher specificity. Implementing this proposed surveillance strategy has the potential to enhance the effectiveness of recurrence monitoring, while also reducing unnecessary tests and associated harm. Tumor marker surveillance offers several advantages, including its speed, cost-effectiveness, and less invasive nature, making it highly suitable for monitoring tumor recurrence.

Conclusion

Significant differences were observed in survival outcomes and the efficacy of predicting recurrence between patients with normal and elevated baseline CEA levels. Building upon these research findings, we propose the development of a novel surveillance strategy for gastric cancer patients that includes CEA testing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-14790-w.

Supplementary Material 1: Figure 1. Internal validation analyses by longitudinal cohort (cohort 2). (A) Study design and flowchart of the longitudinal cohort (cohort 2), including 6422 records of recurrence and tumor marker measurement information. (B-E) Predictive performances of postoperative CEA for OR, LR, PR and DM.

Supplementary Material 2: Figure 2. Validation analyses of the external study cohort (cohort 3). (A) Study design and flowchart of the external study cohort (cohort 3), including 109 gastric cancer patients from SAH-SYSU. (B)Predictive performance of postoperative CEA in overall recurrence

Supplementary Material 3.

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Clinical trial number

Not applicable.

Authors' contributions

YB.C, SC and RC.N conceptualized the study and devised the study protocol. RP.Z, XJ.C and GM.C participated in the study design and manuscript writing.ZK.Z, CZ.W, FY.Z, JL, ZW.C and CY.F developed the methodology and statistical analysis.ZK.Z, ZM.L and YL participated in data collection. All authors participated in the review and edit of this article. All authors approved the final version of the manuscript. YB.C, SC and RC.N have full access to, and verify, the underlying data and accept responsibility to submit or publication.

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Data availability

The original clinical data can be requested from the corresponding author with reasonable justification.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board and Human Ethics Committee of SYSUCC. Written consent to use the samples for research purposes was obtained from all the patients before surgery.

Competing interests

The authors declare no competing interests.

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