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The combination of CA125, CA199, CEA, and AFP is an effective diagnostic biomarker for gastric cancer in elderly individuals

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Abstract

Background Serum tumour markers (TMs) such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199) and CA125 have been established as prognostic indicators for gastric cancer (GC); however, the diagnostic value of these markers for GC in older adults has yet to be examined. Therefore, this study aimed to explore the diagnostic and prognostic significance of AFP, CEA, CA199 and CA125 for GC in elderly individuals.

Methods A total of 188 patients who visited The Sixth Affiliated Hospital, School of Medicine, South China University of Technology, from May 2021 to March 2024 were selected for this study. TMs, namely, CA199, CA125, CEA, and AFP, were examined in all patients. Comparisons of these TMs were conducted among the three groups, and TM levels were compared in patients with GC at various TNM stages. The diagnostic value of these TMs for GC was evaluated by calculating the area under the curve (AUC).

Results We selected 89 patients diagnosed with GC: 52 patients with benign gastric diseases and 47 healthy individuals for our study. The positivity rates of AFP, CA125, CEA and CA199 were significantly greater in the GC group (31.46%, 31.46%, 43.82% and 23.60%, respectively) than in the benign gastric disease group and healthy control group. The diagnostic sensitivities of CEA, CA125, CA199 and AFP for GC were 31.46%, 29.21%, 44.90% and 24.72%, respectively. The combination of these markers yielded a sensitivity of 65.17%, which was significantly greater than the sensitivity of each marker alone ($P < 0.05$). Additionally, patients with stage I-II disease had significantly lower serum levels of CEA, CA199, CA125, and AFP than did those with stage III-IV disease.

Conclusions The levels of serum TMs, including CA12-5, CEA, CA199 and AFP, are elevated in elderly individuals with GC, indicating a higher TNM stage. The combination of CEA, CA12-5, CA199 and AFP has enhanced diagnostic value for GC, thereby offering significant clinical guidance. However, this study is limited by its retrospective design and lack of external validation, which should be addressed in future prospective trials.

Keywords Gastric cancer, Elderly individuals, Tumour marker

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Introduction

According to global cancer statistics from 2022, approximately 20.0 million new cancer cases worldwide and 9.7 million fatalities linked to cancer were recorded in 2022. In that year, over 968,000 patients were diagnosed with gastric cancer (GC), and nearly 660,000 fatalities related to GC were reported. GC ranks fifth in both occurrence and fatality rates among all cancers globally [1]. According to reports in the literature, the incidence of GC is closely related to multiple factors, including race, *Helicobacter pylori* infection, sex, age, eating habits, reflux oesophagitis and heredity [2–4].

Endoscopic biopsy via the upper gastrointestinal tract is considered the gold standard for diagnosing GC. However, endoscopy is an invasive, time-consuming procedure and frequently results in considerable discomfort for patients [5]. Surgical intervention serves as the primary modality of treatment for GC in current clinical practice [2]. Early detection of GC can significantly increase the 5-year survival rate to approximately 90% [6]. However, many patients exhibit no symptoms in the initial phase, and efficient screening methods for the early detection of GC are lacking. Therefore, GC patients are frequently diagnosed at a later stage, preventing them from undergoing surgery within the ideal time frame, resulting in considerably poor therapeutic outcomes [7]. Therefore, early diagnosis and prompt treatment are important for patients with GC.

For early cancer screening globally, serum tumour marker (TM) testing is widely used [8]. In Japan, nine types of serum TMs have been approved for tumour surveillance, namely, carbohydrate antigen (CA)125, CA50, CA199, CA724, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), sialyl Tn antigen (STN), tissue polypeptide antigen (TPA) and inhibitor of apoptosis (IAP) [9]. TMs such as CEA, AFP, CA199 and CA125 have been established as prognostic indicators for GC [10–13];

however, their diagnostic value in elderly populations remains unclear. Previous studies evaluating tumour markers for GC diagnosis predominantly included mixed-age cohorts (e.g., 21–85 years) [14–17]. To our knowledge, no previous meta-analysis has specifically assessed the combined utility of CA125, AFP, CEA, and CA199 exclusively in elderly GC patients (≥ 60 years).

With advancing age, metabolic function declines, oxidative stress increases, and mitochondrial dysfunction worsens. These changes not only impair the physiological functions of normal cells but may also create a favourable environment for tumour cell growth and metastasis. Moreover, cellular senescence and chronic inflammation during aging contribute to tumour development through the secretion of various inflammatory mediators and growth factors. In terms of cancer therapy, older adults, who have reduced metabolic reserves and weakened immune function, may have poorer tolerance and response to treatments, thus necessitating more personalized therapeutic strategies. These distinctions highlight the importance of considering age-related factors in cancer research and clinical practice, guiding the development of more precise and effective interventions [18–21].

Therefore, the aim of the current study was to evaluate the diagnostic value of C125, AFP, CEA and CA199 for GC among elderly individuals and to explore the potential link between these serum TMs and the clinical stage of GC lesions. In our study, the serum levels of C125, AFP, CEA and CA199 were detected in 89 patients with GC, 52 patients with benign gastric diseases, and 47 healthy individuals. We subsequently performed a statistical analysis to assess the diagnostic accuracy of these markers for detecting GC in elderly individuals.

Materials and methods

Patient samples

This study used a retrospective design. Ethics approval for our study was obtained from the Ethics Committee of The Sixth Affiliated Hospital, School of Medicine, South China University of Technology (permit number: 20190106). Written informed consent was obtained from the patients involved in the study. A total of 188 subjects who visited The Sixth Affiliated Hospital, School of Medicine, South China University of Technology, from May 2021 to March 2024 were selected for this study. No significant differences were observed in the baseline characteristics, such as sex and age, among the three groups ($P > 0.05$).

Among them, the 89 patients with GC (GC group) included 35 females and 54 males. The average age of the participants was 69.09 years, ranging from 60 to 87 years. The GC group was further classified on the basis of TNM staging [22], with 28 patients having stage I to II disease and 35 patients having stage III to IV disease.

Additionally, 52 patients with benign gastric lesions (benign gastric lesion group), including 20 females and 32 males, who visited the hospital during the same period were enrolled. The average age of the participants was 68.10 years, with ages ranging from 60 to 85 years.

Furthermore, 47 healthy individuals who underwent physical examinations during the corresponding period composed the healthy control group. This group included 19 females and 28 males, ranging in age from 60 to 87 years, with an average age of 69.00 years.

Inclusion and exclusion criteria

The inclusion criteria were as follows. (1) All patients in the GC group were definitively diagnosed with GC by means of histopathology, whereas those in the benign gastric lesion group were diagnosed with benign gastric diseases. The patients in the healthy group did not

have any gastric symptoms, nor did they have a history of gastric diseases or malignancies. (2) All participating patients voluntarily signed informed consent forms. (3) All pertinent clinical information was preserved and complete.

The exclusion criteria were as follows: (1) patients with malignant tumours at sites other than the stomach; (2) patients who had undergone radiotherapy or chemotherapy due to malignancy; (3) patients with severe dysfunction of vital organs such as the lungs, heart, liver, brain, or kidneys; and (4) patients who failed to follow medical advice during treatment and could not complete the planned treatment, resulting in incomplete or unanalysable data.

Measurement of serum CEA, AFP, CA199 and CA125

All three groups of patients received 5.0 ml of venous blood drawn on an empty stomach in the morning, and the samples were left to stand at ambient temperature. After centrifugation at a speed of 4000 revolutions per minute for 4 min, the serum portion was separated and then stored at 2 °C to 8 °C. Under these conditions, the serum samples remained stable for 12 h. If the duration exceeded 12 h, the samples were first aliquoted and then stored at -20 °C for up to 30 days. Additionally, it is essential to avoid subjecting the serum to more than two cycles of freezing and thawing.

For testing, magnetic particle chemiluminescence assays for CEA, CA199, AFP and CA125 were performed via the Maglumi 4000 fully automated chemiluminescence analyser from New Industry, which was paired with the corresponding TM reagent kits from the same manufacturer. All the experimental steps were conducted in strict compliance with the instrument operation guidelines and reagent kit instructions. Furthermore, the internal quality control (QC) was confirmed to be satisfactory prior to the experiments. The cut-off values of the TMs were established on the basis of the manufacturer-provided ranges: CA19-9 > 37 IU/mL; CA125 > 35 IU/mL; CEA > 5.093 ng/mL; and AFP > 7 IU/mL.

Quality control and calibration

To ensure interlaboratory consistency and reproducibility, QC procedures were strictly implemented according to the Clinical and Laboratory Standards Institute (CLSI) Guideline C24. For each marker (CEA, CA125, CA19-9, and AFP), controls were run in a singlicate daily and whenever a new reagent lot or calibrator was introduced. Control materials (Snibe, REF: 160201220MT) were matched to the corresponding reagent lot numbers, and values outside predefined ranges triggered recalibration and systematic troubleshooting (e.g., verifying reagent expiration dates, maintenance logs, and protocol adherence). External QC validation was performed periodically using standardized panels to minimize variability across batches.

Performance evaluation

The levels of serum tumour markers were used to construct the ROC curve, and the diagnostic performance was assessed by calculating the AUC value. If the AUC was 0.5 or less, the diagnostic method was deemed ineffective and lacked meaningful diagnostic value. If the AUC exceeded 0.5, a higher AUC value, approaching 1, indicated a better diagnostic outcome. An AUC ranging from 0.5 to 0.7 suggested relatively poor diagnostic accuracy, an AUC value above 0.9 indicated extremely high diagnostic precision, and an AUC value between 0.71 and 0.90 suggested good diagnostic precision.

Statistical analysis

The data were statistically analysed by means of SPSS 25.0 software. Differences among multiple groups were assessed by one-way analysis of variance (ANOVA), whereas between-group differences were analysed using an independent samples t test. Statistical significance was considered at $P < 0.05$. A power analysis (G*Power3.1.9.7) revealed 80% power to detect significant differences in AUC values ($\alpha = 0.05$, effect size = 0.25), supporting the robustness of our findings. We performed a multivariate logistic regression analysis to evaluate the independent contribution of each TM (CEA, CA199, CA125, and AFP) to the diagnosis of cancer, adjusting for age and sex.

Results

Comparison of the positivity rates of TMs among the three groups of patients

The positivity rates for each TM are presented in Table 1. The positivity rates of CA125, CEA, AFP and CA199 in the healthy group were 0.00%, 2.13%, 2.13% and 0.00%, respectively. The positivity rates of CA125, CEA, AFP and CA199 in the benign gastric lesion group were 5.77%, 1.92%, 3.85% and 0.00%, respectively. The positivity rates of CA125, CEA, AFP and CA199 in the GC group were 43.82%, 31.46%, 23.60% and 31.46%, respectively. Compared with both the healthy control group and the group with benign gastric lesions, the GC group had significantly higher positivity rates for CA125, CA199, CEA, and AFP ($P < 0.05$). Conversely, there were no significant differences in the levels of these serum tumour markers between the benign gastric lesion group and the healthy control group ($P > 0.05$) (Table 1).

Comparison of the positivity rates of TMs in patients with different TNM stages of GC

The positivity rates of the TMs in patients with different TNM stages of GC are presented in Table 2. The positivity rates of CA125, CEA, AFP and CA199 in patients

Table 1 Comparison of the positivity rates of CEA, CA199, AFP, and CA25 among the three groups

Groups		CEA		CA199		CA125		AFP	
	N	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Healthy	47	46	1	47	0	47	0	46	1
Benign gastric lesion	52	51	1	52	0	49	3	50	2
Gastric cancer	89	61	28	61	28	50	39	68	21
P		*0.52		*1		*0.278		*>0.93	
		#<0.001		#<0.001		#<0.001		#0.003	
		^<0.001		^<0.001		^<0.001		^0.005	

*Comparison between the benign lesion group and the control group, #Comparison between the control group and the gastric cancer group, ^Comparison between the benign lesion group and the gastric cancer group

Table 2 Comparison of C125, CA199, CEA and AFP positivity rates in patients with different TNM stages of GC

Groups	*N*	CEA		CA199		CA125		AFP	
		Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
I~II	28	26	2	27	1	22	6	28	0
III~IV	61	35	26	34	27	28	33	40	21
P		0.002		< 0.001		0.008		0.001	

Table 3 Diagnostic value of C125, CA199, CEA and AFP in GC

Tumour marker	Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value(%)	Negative predictive value(%)
CA199	37.00IU/mL	29.21	100	100	42.73
	5.305 IU/mL	91.01	87.23	93.1	83.67
CEA	5.09 ng/mL	31.46	97.98	96.55	42.99
	3.07 ng/mL	53.93	82.98	85.71	48.75
CA125	35.00 IU/mL	44.94	100	100	48.96
AFP	7.00 IU/mL	24.72	97.87	95.65	40.71
	7.20 IU/mL	24.72	100	100	41.23
Combination		65.17	95.74	96.67	59.21
	0.741	98.85	85.11	92.63	85.56

with stage I ~ II GC were 21.43%, 7.14%, 0.00% and 3.57%, respectively. The positivity rates of CA125, CEA, AFP and CA199 in patients with stage III ~ IV GC were 54.10%, 42.62%, 34.43% and 44.26%, respectively. When the positivity rates of serum CEA, CA199, CA125, and AFP in GC patients at different TNM stages were compared, patients with stage I-II disease had significantly lower levels of these markers than did those with stage III-IV disease ($P < 0.05$), as shown in Table 2.

Diagnostic value of individual and combined detection of serum indicators in gastric cancer among elderly patients.

First, we used the normal reference range of our institution to determine the cut-off values. Consequently, we observed that the sensitivities of CA125, CA199, CEA, and AFP for detecting GC were 44.94%, 29.21%, 31.46%, and 24.72%, respectively. However, when these markers were combined for detection, the sensitivity increased to 65.17%. We subsequently utilized the ROC curve to establish the diagnostic cut-off values for CA125, CA199, CEA, and AFP, which were 35.00 IU/mL, 5.305 IU/mL, 3.07 ng/mL, and 7.20 IU/mL, respectively. By using the optimal cut-off values, we found that the sensitivities of CEA and CA199 in the diagnosis of GC were 53.93% and 91.01%, respectively. The negative predictive values of CEA and CA19-9 were 83.67% and 83.67%, respectively (Table 3).

As shown in Fig. 1, the AUCs for the diagnosis of GC when CEA, CA199, CA125, and AFP were used as single tests and in combination were 0.727 (95% CI: 0.643–0.812), 0.949 (95% CI: 0.914–0.984), 0.709 (95% CI: 0.625–0.793), 0.372 (95% CI: 0.278–0.467), and 0.981 (95% CI: 0.961–1.000), respectively. The diagnostic significance of the combined diagnostic test was significantly greater than that of the single diagnostic test ($P < 0.001$).

After adjusting for age and sex, CEA (OR = 1.33, $P = 0.039$) and CA199 (OR = 1.09, $P < 0.001$) remained independently associated with cancer risk, whereas AFP and CA125 lost significance (Fig. 2). Notably, the confidence intervals for some of these estimates are relatively wide, indicating variability in the results. Additionally, while the combination of markers showed improved diagnostic accuracy (AUC = 0.981), this model should be interpreted with caution as it does not imply causality but rather an association. Regarding the association between sex and cancer risk, our analysis revealed an odds ratio of 1.96 (95% CI: 0.86–4.48) with a p-value of 0.109, indicating that this association is not statistically significant.

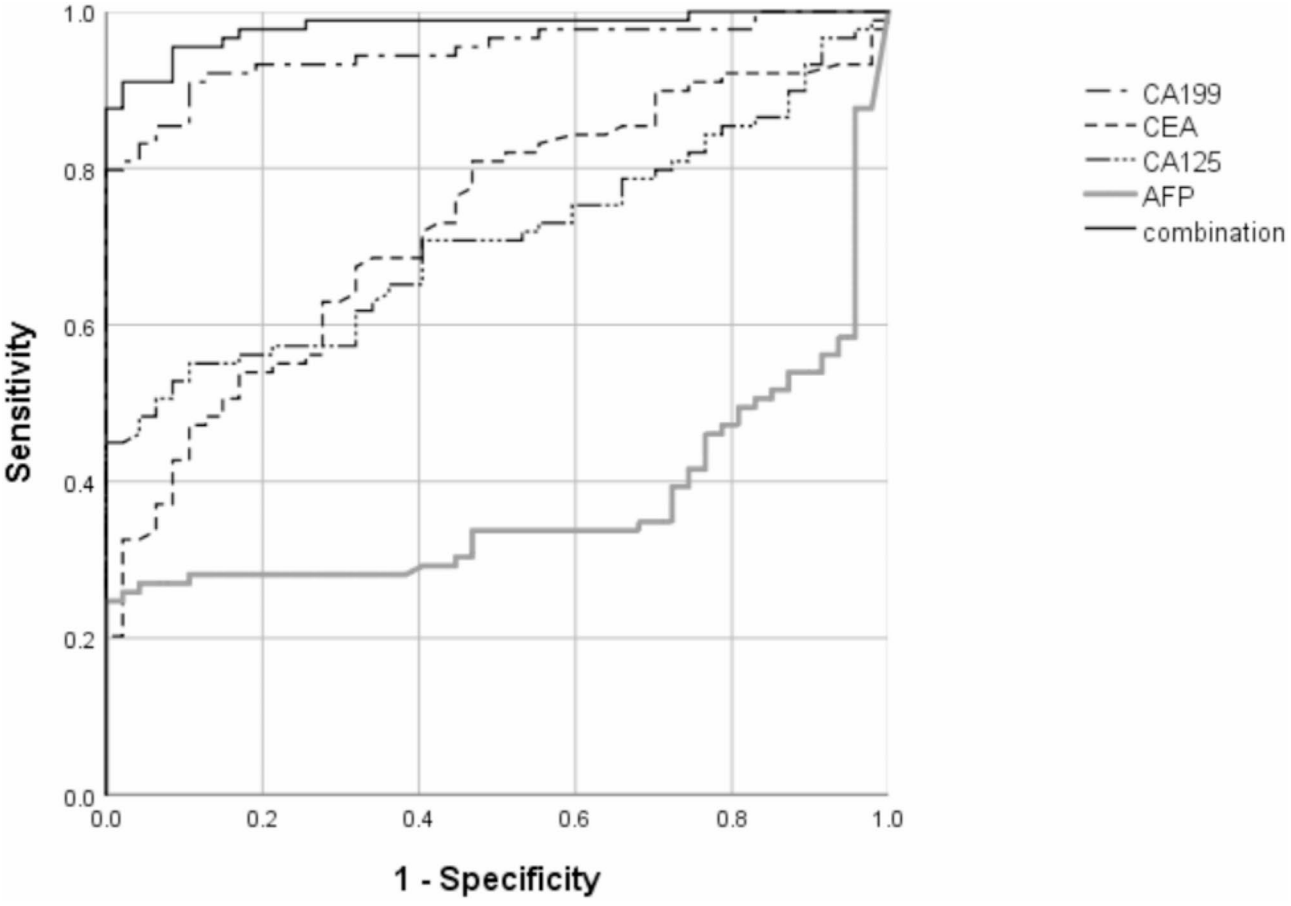

Fig. 1 Diagnostic value of individual and combined detection of serum indicators in elderly patients with GC

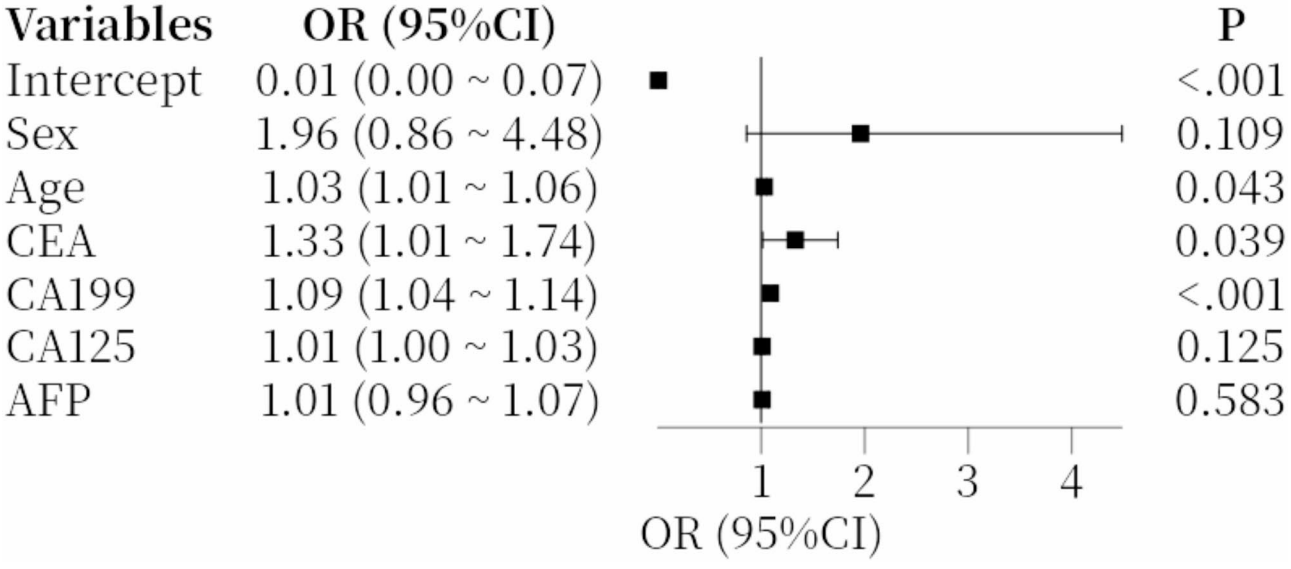

Fig. 2 Forest Plot of the Multivariate Logistic Regression Analysis. OR: odds ratio, CI: confidence interval

Therefore, we cannot conclude that sex is a significant risk factor based on these results.

Discussion

To date, the importance of various serum tumour markers in diagnosing and predicting the outcome of patients with GC has been investigated in numerous studies [23–25]. Thus far, the prognostic significance of serum tumour markers for GC in elderly patients remains unexplored. Hence, the aim of the current study was to evaluate the value of CA125, CA199, CEA, and AFP in the diagnosis of GC among elderly patients by analysing the data of 89 GC patients, 52 patients with benign gastric lesions and 47 healthy people.

The results of our study revealed that the positivity rates of CA125, CA199, CEA, and AFP in GC patients were notably higher than those in patients with benign stomach disease and those in the control group. These findings indicate that CA125, CA199, CEA, and AFP are markedly elevated in individuals with GC and serve as supplementary clinical diagnostic indicators. The positivity rates of CA125, CEA, CA199 and AFP expression in early-stage (I-II) GC are notably lower than those in later-stage (III-IV) GC. On the basis of the aforementioned results, we propose that these tumour markers do not have a notable effect on early-stage GC. Monitoring the levels of CA125, CA199, CEA and AFP is beneficial for clinically distinguishing the emergence and progression of GC in elderly individuals. Combining these markers enhances diagnostic sensitivity and correlates with TNM staging, making them clinically relevant.

Stratification revealed that the increases in CEA and CA199 levels in stage I-II GC patients in our study were 7.14% and 3.57%, respectively. These findings are consistent with those from other studies, suggesting that the positivity rates of CA199 and CEA are low in patients with early-stage GC [14, 15]. The AFP positivity rate in our study was 23.60% in GC patients: it was 0% in patients with stages I-II disease and 34% in patients with stages III-IV disease. These findings suggest that AFP is more likely to be positive in advanced-stage GC than in early-stage GC, which is consistent with previous findings [26].

In our study, we observed that the positivity rates of CA125, CA1995, CEA and AFP were 43.82%, 31.46%, 31.46% and 23.6%, respectively, and the positivity rates of CA125, CA199 and CEA were similar to those reported in previous studies [9, 14, 16–17]. However, importantly, AFP has lower diagnostic sensitivity, raising concerns about its usefulness as a standalone marker for GC detection. The low sensitivity of AFP can be attributed to tumour heterogeneity and the specific subtypes of GC. For example, AFP-producing GC (AFPGC) is a distinct subtype characterized by high serum AFP levels and aggressive behaviour, including a high incidence of liver metastasis [27]. The variability in AFP expression across different GC subtypes highlights the need for a comprehensive approach for diagnosis, particularly in elderly individuals, where advanced-stage GC is more common. However, the positivity rate of AFP was higher than that reported in previous studies [28]. This may be caused by multiple factors, including variations in detection methods, heterogeneity among patient populations, and sample size, among others.

To address the limitations of AFP as a standalone marker, we emphasize the importance of integrating AFP with other TMs, such as CA125, CA199, and CEA. Our results indicated that the combination of these biomarkers could further improve the diagnostic precision for GC. These findings indicate that the combination of several tests could significantly improve the diagnostic accuracy of GC in elderly individuals, which aligns with the findings of previous studies [11, 29–30]. The multivariate logistic regression analysis revealed that CEA and CA199 are independent predictors of cancer diagnosis, even after adjustment, whereas CA125 and AFP did not significantly differ.

When the cut-off values obtained from the ROC curve were applied, an improvement in diagnostic sensitivity was observed, with the cut-off values for CEA and CA199 being lower than those used in clinical practice (Table 3). This finding indicates that suitably reducing the cut-off values of CEA and CA199 could be beneficial for enhancing their diagnostic value in GC, yet the optimal cut-off values should be determined by future studies with larger sample sizes. The integration of these markers into clinical screening protocols can enhance early detection and cost-effectiveness. Early detection is crucial for improving patient outcomes, and the combined use of these TMs can increase diagnostic accuracy. This approach is cost-effective compared with more invasive diagnostic procedures, as blood tests are relatively inexpensive and can be easily incorporated into routine health checkups. The total reagent cost for our four-marker panel CA125 + CA199 + CEA + AFP) is ¥170, which is considerably lower than the cost of gastroscopy (¥777 per procedure). This cost difference results in a direct savings of ¥607 per screened case while maintaining 65.17% sensitivity for GC detection.

However, it is important to consider the potential risks of overdiagnosis and unnecessary endoscopic procedures when lowering the cut-off values. While lower cut-off values can increase sensitivity, it may also lead to an increase in false positives, thereby prompting further invasive investigations and interventions that might not be necessary. Therefore, clinicians should carefully balance the sensitivity and specificity of these tests when applying them in real-world settings. The decision to

proceed with additional diagnostic procedures should be based on a comprehensive assessment of the patient's clinical history, symptoms, and other relevant diagnostic information, rather than relying solely on tumour marker levels.

Studies have shown that the use of the G8 score to screen elderly GC patients can optimize chemotherapy safety and that muscle mass assessment is valuable in personalized treatment. These findings support the integration of biomarkers and multidimensional health assessments in the diagnosis and management of GC in elderly individuals to improve diagnostic and therapeutic precision [31–32].

However, our study has certain limitations. First, the sample size was relatively small, which may limit the generalizability of our findings. The small sample size might have affected the statistical power and ability to detect significant differences in some subgroups. Future studies with larger cohorts are needed to validate our results and further explore the diagnostic and prognostic value of these serum TMs in elderly patients with GC. Second, we did not assess the prognostic significance of postoperative TM levels for the recurrence patterns and prognosis of early GC patients. Second, owing to the limitations of our retrospective study design, we encountered significant challenges in obtaining complete follow-up data, including information on survival rates and recurrence. Consequently, we were unable to assess the prognostic significance of postoperative TM levels for the recurrence patterns and prognosis of early GC patients. We recognize that this is a major limitation of our study and plan to address it in future prospective studies with more rigorous follow-up protocols to collect comprehensive long-term outcome data.

Further research should be conducted to delve deeper into the diagnostic significance of postoperative serum tumour marker levels. Finally, we did not investigate the correlation between the tumour site and tumour markers. In the future, we plan to explore the relationships between the tumour site and tumour markers.

Conclusions

In summary, the levels of CA125, CA199, CEA, and AFP are closely related to the occurrence of gastric cancer and also to the extent of gastric cancer progression. Monitoring the levels of CA125, CA199, CEA and AFP is beneficial for clinically distinguishing the occurrence and development of GC in elderly individuals.

In the future, the diagnostic significance of postoperative serum TM levels and the correlation between the tumour site and TMs still need to be explored in depth to realize the clinical application of TMs with greater value. Additionally, while this study provides meaningful insights into GC diagnostics in elderly individuals, validation in larger, prospective, and multicentre studies is necessary before these findings can be implemented in routine practice.

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Author contributions
Jia- hao Feng, De bing Huang, Hui-ling Ye and Ping Chen coordinated and performed all sample analyses. Xiao-wen Yuan and Lv Dengdrafted and revised the manuscript. All the authors read and approved the final manuscript.

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Data availability
Sequence data that support the findings of this study have been deposited in a secure data repository at South China University of Technology.The datasets generated and/or analysed within this study are not publicly available because of the need to safeguard the participants' anonymity. However, they can be obtained from the corresponding author upon justifiable request.

Declarations

Ethics approval and consent to participate
The present study was authorized by the Ethical Committee of The Sixth Affiliated Hospital, School of Medicine, South China University of Technology (permit number: 20190106). Written informed consent was obtained from the patients involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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