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Development of a biomarker-guided chemotherapy response model using combined CEA and CA19-9 profiles in esophageal cancer: A real-world pharmacotherapeutic study

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Abstract: **Background**: Esophageal adenocarcinoma is associated with poor survival despite advances in systemic therapy. Readily available serum biomarkers may improve risk stratification; however, their combined role in biomarker-guided treatment decisions remains insufficiently investigated. **Objectives**: To evaluate the prognostic significance of combined baseline carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels and explore their utility for biomarker-based risk stratification in patients with esophageal adenocarcinoma receiving systemic chemotherapy. **Methods**: This retrospective real-world cohort study included 38 patients with histologically confirmed esophageal adenocarcinoma who received systemic chemotherapy at a tertiary referral center between January 2016 and December 2021. Patients were classified into three exploratory biomarker-defined risk groups according to baseline serum CEA and CA19-9 levels. Overall survival was evaluated using Kaplan–Meier analysis and Cox proportional hazards regression, while treatment outcomes were explored across biomarker-defined groups and chemotherapy regimens. **Results**: Elevated baseline CEA and CA19-9 levels were associated with shorter overall survival. Patients with simultaneous elevation of both biomarkers demonstrated the poorest survival outcomes (multivariable hazard ratio = 2.22). Differences in survival were observed across chemotherapy regimen groups within biomarker-defined categories; however, these comparisons were exploratory and may have been influenced by treatment-selection bias and unmeasured clinical factors. Patients with distal or gastroesophageal junction adenocarcinoma showed more favorable outcomes than those with cervical or thoracic tuxzmors. **Conclusion**: Combined assessment of baseline CEA and CA19-9 may provide a practical and inexpensive approach for biological risk stratification in esophageal adenocarcinoma. However, these findings do not establish that the biomarkers can guide chemotherapy selection. Prospective multicenter studies with independent validation are required to determine their prognostic and predictive value before biomarker-guided treatment selection can be recommended in routine clinical practice.

Keywords: Biomarker-guided therapy; Carcinoembryonic antigen; Carbohydrate antigen 19-9; Chemotherapy; Esophageal adenocarcinoma; Overall survival; Precision medicine; Real-world study

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INTRODUCTION

Esophageal carcinoma is one of the fastest growing cancers of the GI tract and is heavily associated with high morbidity and mortality globally (Sung *et al*., 2021; Lordick *et al*., 2022). The survival statistics for these patients is poor, with the average five-year survivorship not exceeding 20-25%, despite multiple advances in diagnostic imaging procedures, surgical approaches and radiation therapy (Lordick *et al*., 2022). Additionally, due to the biological heterogeneity of this malignancy, the variability of treatment response tests and the tendency for patients to present with advanced disease at the time of diagnosis, these patients experience an unfavorable prognostic outcome. These findings have emphasized the importance of optimizing therapeutic decision-making in modern oncology (Lordick *et al*., 2022).

Systemic chemotherapy remains the cornerstone of treatment for locally advanced, recurrent, or metastatic esophageal cancer (Deboever *et al*., 2024). Recent international guidelines and randomized clinical trials have further expanded treatment strategies by incorporating immune checkpoint inhibitors and biomarker-guided approaches (Lordick *et al*., 2022; Ajani *et al*., 2022; Janjigian *et al*., 2021). Over the last ten years, we have moved away from using conventional platinum-based doublet regimens and towards more aggressive combinations with paclitaxel and triplet regimens (Ilson *et al*., 2023). This includes combinations of modified docetaxel-cisplatin-5-fluorouracil (MDCF), fluorouracil-leucovorin-oxaliplatin (FOLFOX), fluorouracil-leucovorin-oxaliplatin-docetaxel (FLOT), or irinotecan-based regimens. There are varying degrees of benefit across the different regimens; however, there is still considerable variation in treatment responses between patients with similar clinicopathological data (Al-Batran *et al*., 2019).

One of the major obstacles to obtaining effective treatment for esophageal cancer is the lack of valid and

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accessible predictive biomarkers that could help identify subgroups of patients who will experience positive outcomes from various management strategies. As it stands, the choice of management is based on traditional factors, including tumor stage, functional status, coexisting medical conditions, and treatment protocols (Lordick *et al*., 2022). While these are important pieces of information, in general they do not adequately reflect the inherent biological variability present, which plays a large role in determining how well an individual will respond to therapy (sensitivity) or fail to accomplish their objective (resistance) (Lordick *et al*., 2022). As a result, many patients may receive intensive therapies associated with significant toxicity without any significant impact on their clinical outcomes; meanwhile, others may receive insufficiently aggressive therapy despite evidence of having an aggressive underlying disease process (Kelly *et al*., 2021).

Recent advances in precision oncology have increased interest in identifying clinically applicable biomarkers that improve risk stratification and support individualized treatment decisions. Emerging evidence also highlights the increasing role of multimodal biomarker integration, artificial intelligence and molecular profiling in improving prognostic assessment and therapeutic selection for patients with esophageal cancer. (Bian *et al*., 2026; Baum *et al*., 2026). However, many molecular biomarkers remain expensive or unavailable in routine clinical practice, particularly in resource-limited settings (Ilson *et al* 2023; Andre *et al*., 2024). Consequently, inexpensive and widely available serum tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) continue to attract clinical interest because they can be easily integrated into routine oncology practice and may complement emerging molecular biomarkers. Recent systematic evidence further supports the continued clinical relevance of serum tumor markers when used in combination with newer molecular and immunological biomarkers for risk stratification in gastrointestinal malignancies (Matsumoto *et al*., 2026).

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are well-established serum biomarkers that have been widely used in gastrointestinal malignancies for disease monitoring and prognostic assessment. Several studies have reported that elevated CEA and CA19-9 levels are associated with advanced disease stage, greater metastatic burden and poorer survival outcomes in patients with esophageal cancer. However, most previous investigations have evaluated these biomarkers independently and primarily focused on their prognostic significance. Consequently, the potential clinical value of combining baseline CEA and CA19-9 measurements for biological risk stratification and biomarker-guided chemotherapy assessment in patients with esophageal adenocarcinoma remains insufficiently investigated.

Recent evidence indicates that combining conventional serum biomarkers with emerging genomic and circulating biomarkers may improve prognostic assessment and support individualized treatment strategies. Contemporary studies have further emphasized that biomarker integration represents a key component of precision oncology and individualized treatment planning in esophageal adenocarcinoma (Pinto *et al*., 2026; Almars *et al*., 2026). Nevertheless, evidence supporting combined CEA and CA19-9 assessment for guiding chemotherapy selection remains limited, particularly in real-world cohorts of patients with esophageal adenocarcinoma. The present study was therefore designed to explore this unmet clinical question. Increased CEA levels have been associated with a more advanced stage of tumor, greater ability to invade surrounding tissue, and greater likelihood of metastasis (Zhang *et al*., 2024; Liu *et al*., 2024). In a similar manner, increased CA19-9 levels have been shown to correlate with aggressive tumor biology, predominantly with adenocarcinomas of the distal esophagus and gastroesophageal junction. Because CEA and CA19-9 may reflect different aspects of tumor biology, their combined assessment may provide complementary prognostic information compared with either biomarker considered individually (Hoshi *et al*., 2025).

Patients with unfavorable biomarker profiles may require closer clinical assessment and may be candidates for treatment strategies appropriate to their overall clinical status; however, whether biomarker-defined risk can predict benefit from specific chemotherapy regimens requires prospective investigation. Patients with unfavorable biomarker profiles may benefit from more intensive systemic chemotherapy. In contrast, those with favorable biological characteristics may achieve satisfactory outcomes with less intensive treatment while minimizing treatment-related toxicity. This approach is consistent with the principles of precision medicine, which integrates clinical and biological information to support individualized therapeutic decision-making.

Beyond the biomarker status, anatomical location of the tumor is an important consideration for therapeutic management. For example, tumors located in the cervical region have different biological behavior, lymphatic spread patterns, surgical approach accessibility, and response to systemic therapy compared to tumors located in the thoracic and distal esophageal regions. In addition, the distal esophagus and gastroesophageal junction tumors are increasingly showing characteristics similar to gastric adenocarcinoma. They may differ in their response to modern chemotherapeutics when compared with the cervical and thoracic lesions. Thus, incorporating anatomical factors into the biomarker-based treatment model may provide a better way to stratify therapy.

Another important issue is the substantial difference between clinical trial outcomes and what is typically seen in everyday clinical practice. Patients enrolled in clinical trials tend to be very homogeneous populations, with good performance status and fewer comorbidities. On the other hand, real-world patients tend to be older, more heterogeneous populations and have complex clinical characteristics that may impact how the patient tolerates and responds to treatment. Therefore, the use of real-world evidence to evaluate the effectiveness of pharmacotherapy is increasingly recognized as an important part of pharmacotherapy research because it indicates the barriers that patients experience when receiving routine patient care (Deboever *et al*., 2024).

Although previous investigations have established the prognostic significance of individual serum biomarkers, limited evidence is available regarding the combined assessment of baseline CEA and CA19-9 for biological risk stratification and chemotherapy response evaluation in real-world clinical practice. Therefore, further investigation is needed to determine whether combined biomarker assessment may improve prognostic evaluation and support individualized treatment planning for patients with esophageal adenocarcinoma (Dorman *et al*., 2023).

The present study aimed to evaluate the prognostic significance of combined baseline CEA and CA19-9 levels in patients with esophageal adenocarcinoma receiving systemic chemotherapy in routine clinical practice. In addition, the study explored whether combined biomarker assessment could improve biological risk stratification and provide an exploratory framework for individualized chemotherapy decision-making. The findings are intended to generate hypotheses for future prospective studies evaluating biomarker-guided treatment strategies rather than to establish a validated clinical decision model.

MATERIALS AND METHODS

Study design and setting

This was a retrospective, single-center, real-world cohort study conducted at Medipol Bahçelievler Hospital, Istanbul, Turkey. The study evaluated the association between baseline serum CEA and CA19-9 levels, chemotherapy treatment, and clinical outcomes among patients with histologically confirmed esophageal adenocarcinoma. All consecutive eligible patients diagnosed and treated between January 1, 2016, and December 31, 2021, were assessed from institutional medical records. Because the study used all eligible patients available during the predefined study period, no formal sample-size calculation was performed.

The primary objective was to evaluate the association between baseline serum CEA and CA19-9 levels and overall survival in patients with esophageal adenocarcinoma receiving systemic chemotherapy. A secondary exploratory objective was to assess whether biomarker-defined risk groups were associated with differences in treatment response and outcomes across chemotherapy regimens. The study complied with the principles of the Declaration of Helsinki and was approved by the Medipol University Non-Interventional Clinical Research Ethics Committee, Istanbul, Turkey (Approval No.: E-10840098-772.02-2021/356). All patient information was anonymized before analysis and patient confidentiality was maintained throughout the study in accordance with institutional and national ethical standards.

Study population

The population has been selected based on an analysis of medical records from patients with histologically confirmed esophageal carcinomas. All eligible patients included in the study had:

• Age ≥ 18 years at the time of diagnosis
• Histologically diagnosed esophageal cancer
• Received systemic chemotherapy as part of their treatment plan
• Documented baseline serum levels of CEA and CA19-9 prior to starting chemotherapy
• Received follow-up care that documented their response to chemotherapy and survival status.

Exclusion criteria were

• Patients with incomplete biomarker data
• Patients who were lost to follow-up immediately following diagnosis
• Patients who have had any treatments outside of this centre
• Patients with insufficient information to document therapeutic outcomes.

Data collection

Clinical information from electronic records was collected using a standard data collection form.

The data collected included:

- Demographic Data
- Age at diagnosis
- Sex
- Comorbid Conditions

Tumor data

- Histology
- Tumor location (Cervical, thoracic, distal gastro-esophageal junction)
- Clinical stage according to the American Joint Committee on Cancer (AJCC) 8th edition staging system for esophageal and esophagogastric junction cancers (Rice *et al*., 2017)
- Biomarkers
- Serum CEA
- Serum CA19-9
- Laboratory reference range per institution (Elevated CEA = > 5 ng/mL; Elevated CA19-9 = > 37 U/mL)

Chemotherapy information

The chemotherapy regimens were classified into four primary treatment groups. Chemotherapy regimens were grouped according to their principal therapeutic backbone and expected treatment intensity to facilitate comparison among patients. Although individual regimens within each group differed slightly in drug composition and dosing schedules, they were considered clinically comparable for exploratory analyses because of the limited sample size.

- Modified Docetaxel-Cisplatin-5-Fluorouracil
- FOLFOX/FLOT
- FOLFIRI/XELIRI
- Cisplatin/Etoposide

Treatment duration, dose modifications, treatment delays and chemotherapy-related toxicities were recorded whenever these data were available in the medical records. Information regarding previous oncological treatments and Eastern Cooperative Oncology Group (ECOG) performance status was not consistently available because of the retrospective design. Therefore, it was not included in the final statistical analysis.

Exploratory biomarker-based risk stratification

Baseline serum CEA and CA19-9 levels were combined to define exploratory biomarker-based risk categories for subsequent analysis of overall survival and treatment outcomes.

Patients were classified into three exploratory biomarker-defined risk categories:

- Group A: Low biomarker risk — normal CEA and normal CA19-9
  - Normal CEA
  - Normal CA19-9
- Group B: Intermediate biomarker risk — elevation of either CEA or CA19-9
  - Elevated CEA or CA19-9
- Group C: High biomarker risk — simultaneous elevation of CEA and CA19-9
  - Elevated CEA and CA19-9

Simultaneous elevation of both CEA and CA19-9

The purpose of this exploratory model was to evaluate whether biomarker-defined biological risk was associated with differences in chemotherapy response and survival outcomes. Because of the limited sample size, no internal or external validation procedures were performed and the model should be considered hypothesis-generating rather than clinically validated.

The biomarker categories were used for exploratory comparisons of survival and treatment outcomes and were not used prospectively to determine chemotherapy selection.

Pharmacotherapy assessment framework

To implement principles of precision medicine, assessment of treatment outcome was based on both biomarker status and prescribed chemotherapy regimen.

The pharmacotherapy assessment framework included evaluation of:

- Treatment response by biomarker group
- Overall survival by biomarker group
- Survival by chemotherapy regimen
- Interaction between biomarker status and chemotherapy intensity
- Potential value of biomarkers in assisting with choosing chemotherapy regimen

This exploratory assessment examined whether treatment outcomes differed across chemotherapy intensity groups within the biomarker-defined risk categories. Because treatment allocation was not randomized, observed differences could reflect treatment-selection bias and other unmeasured clinical factors.

Measures of outcomes

Primary measure

Overall Survival (OS) was the primary measure. This was defined as the time from the diagnosis to death from any cause, or to the last documented follow-up.

Secondary measures

The secondary measures included the following:

- Chemotherapy response, i.e. Chemotherapy Response, or CR
- Progression-Free Interval, i.e. PFI
- Toxicity of Chemotherapy
- Survival differences by biomarker association
- Exploratory association between biomarker-defined risk groups and treatment outcomes.

Chemotherapy response assessment

Treatment response was assessed using routine clinical evaluation together with radiological imaging. Whenever adequate radiological measurements were available, treatment response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Eisenhauer *et al*., 2009). For patients without sufficient quantitative measurements for formal RECIST assessment because of the retrospective nature of the study, treatment response was based on the treating oncologist's documented radiological assessment. For patients lacking complete RECIST measurements because of the retrospective nature of the study, treatment response was determined from the treating oncologist's documented radiological assessment.

Response categories included:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

For the purposes of comparative pharmacotherapeutic analyses, the objective response rate and disease control rates were determined for each chemotherapy regimen and biomarker-defined subgroup.

Statistical analysis

IBM SPSS Statistics (Version 26.0) and R Statistical Software (Version 4.1.2) were used for the statistical analyses. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies (von Elm *et al*., 2007). The completed STROBE checklist is provided as a supplementary document.

Continuous variables were summarized using mean ± standard deviation, whereas categorical variables were summarized using frequencies and percentages.

For overall survival analysis, the Kaplan-Meier method was applied, and differences between survival curves were analyzed with the log-rank test (Kaplan and Meier, 1958).

To determine factors influencing survival outcomes, Cox regression analysis (Cox, 1972) with proportional hazard assumption was performed on the following set of variables:

- Age
- Tumor site
- CEA status
- CA19-9 status
- Biomarker combined status
- Chemotherapy type

Given the limited sample size and number of candidate variables, the multivariable Cox regression analysis was considered exploratory, and the resulting effect estimates were interpreted cautiously because of the potential for model overfitting and imprecision.

The hazard ratio (HR) along with the 95% confidence interval (CI) is provided. Two-sided p-values <0.05 were considered statistically significant.

Proposed clinical application of the model

After completion of statistical analysis, a decision model was proposed to help translate the results into clinical practice.

The model would establish criteria for:

- Standard-intensity patients
- Individually-treated patients
- Triplet chemotherapy application

The proposed framework is intended to illustrate the potential clinical application of the observed biomarker associations. It should be regarded as an exploratory decision-support framework that requires prospective external validation before implementation in routine clinical practice.

Figure 1 summarizes the participant-selection process, including screening of preliminary records, exclusion of patients with missing information or loss to follow-up, and inclusion of the final cohort of 38 patients. The flow diagram is provided to transparently describe participant selection in accordance with STROBE reporting recommendations.

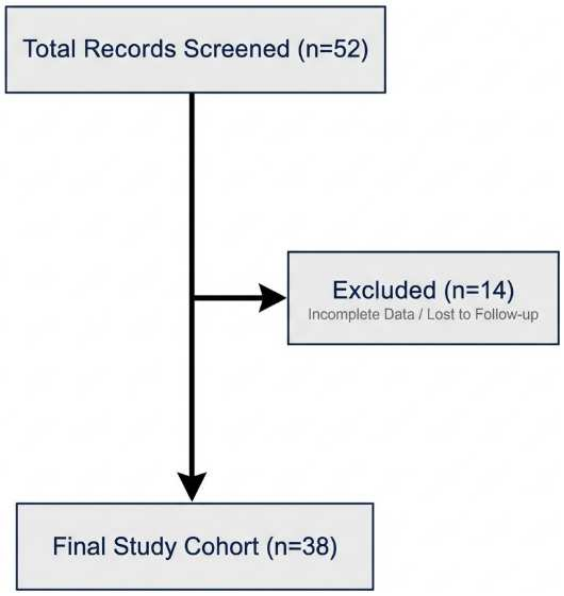

Fig. 1: Flow diagram of patient selection. Fifty-two potentially eligible patient records were screened, 14 patients were excluded because of missing information or loss to follow-up, and 38 patients were included in the final retrospective cohort.

RESULTS

Demographic distribution and clinical profile

The study cohort consisted of 38 patients with a mean age of 63.5 ± 11.4 years (range, 41–82 years). Twenty-nine patients (76.3%) were male and nine (23.7%) were female. Most patients presented with stage III or IV disease and received systemic chemotherapy. Clinically significant comorbidities, primarily hypertension and type 2 diabetes mellitus, were present in 15% of patients. Tumor location was distributed as follows: distal esophagus/gastroesophageal junction in 18 patients (47.3%), thoracic esophagus in 15 patients (39.5%) and cervical esophagus in 5 patients (13.2%).

Table 1 summarizes the baseline demographic and clinical characteristics of the study cohort. Of the 38 patients, 29 (76.3%) were male and 9 (23.7%) were female. Distal esophagus/gastroesophageal junction tumors were observed in 18 patients (47.3%), thoracic tumors in 15 patients (39.5%) and cervical tumors in 5 patients (13.2%). Elevated baseline CEA and CA19-9 levels were present in 16 (42.1%) and 14 (36.8%) patients, respectively.

Table 1: Baseline demographic and clinical characteristics of the study cohort (N=38).

Characteristic	Category	n (%)	Mean ± SD
Age (years)	-	-	63.5 ± 11.4
Gender	Male	29 (76.3%)	-
	Female	9 (23.7%)	-
Tumor location	Cervical	5 (13.2%)	-
	Thoracic	15 (39.5%)	-
	Distal/GEJ	18 (47.3%)	-
CEA level	Normal (≤5 ng/mL)	22 (57.9%)	-
	Elevated (>5 ng/mL)	16 (42.1%)	-
CA 19-9 level	Normal (≤37 U/mL)	24 (63.2%)	-
	Elevated (>37 U/mL)	14 (36.8%)	-

Fig. 2 illustrates the age and sex distribution of the study cohort.

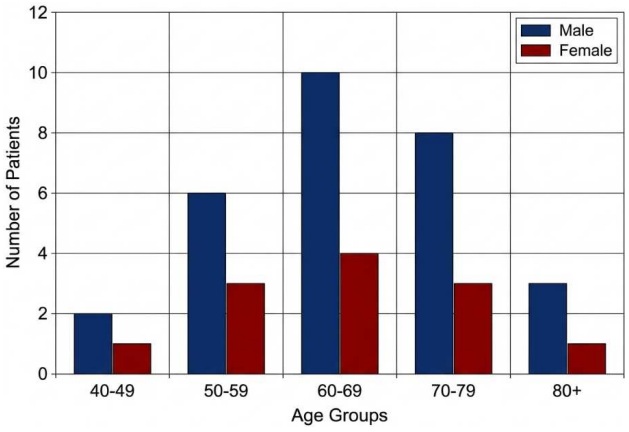

Fig. 2: Age and gender distribution histogram.

Fig. 3 presents the distribution of tumor location within the study cohort.

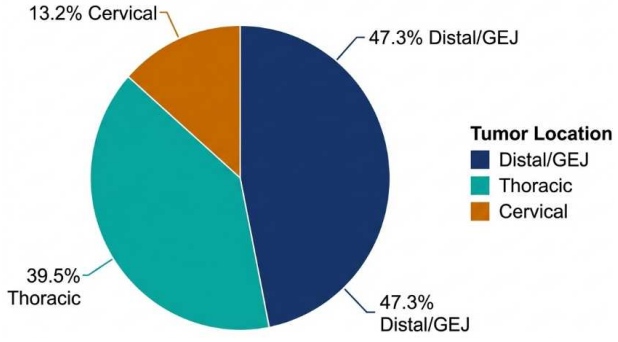

Fig. 3: Tumor location distribution pie chart.

Prognostic significance of CEA levels

Elevated baseline CEA levels (>5 ng/mL) were observed in 16 patients (42.1%). Median overall survival was 18.4 months in patients with normal baseline CEA levels and 11.2 months in patients with elevated baseline CEA levels (log-rank p = 0.042). CEA concentrations greater than 20 ng/mL were observed only in patients presenting with metastatic disease. In the multivariable Cox regression analysis, elevated baseline CEA remained independently associated with overall survival.

Fig. 4 presents the Kaplan–Meier survival curves according to baseline CEA status.

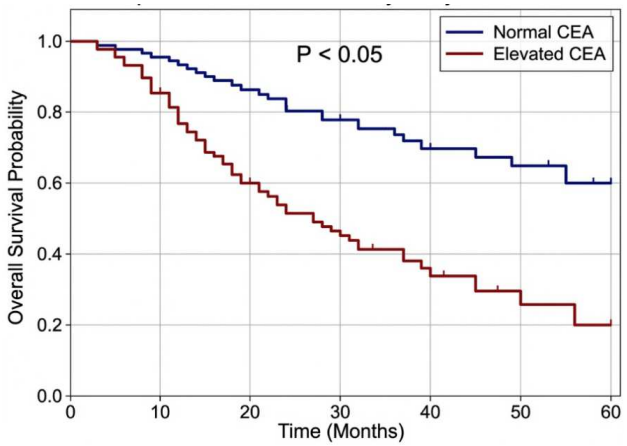

Fig. 4: Kaplan-Meier survival curve of CEA.

Fig. 5 illustrates the distribution of baseline CEA concentrations according to tumor stage.

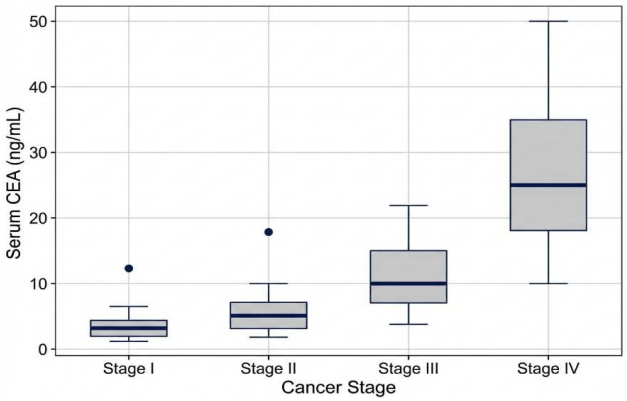

Fig. 5: CEA levels boxplot by tumor stage.

Prognostic significance of CA 19-9 levels

Elevated baseline CA19-9 levels (>37 U/mL) were observed in 14 patients (36.8%). Median overall survival was 19.1 months in patients with normal baseline CA19-9 levels and 10.5 months in patients with elevated baseline CA19-9 levels (log-rank p = 0.038). Elevated CA19-9 levels were observed more frequently among patients with adenocarcinoma histology and distal/ gastroesophageal junction tumors.

Fig. 6 presents the Kaplan–Meier survival curves according to baseline CA19-9 status.

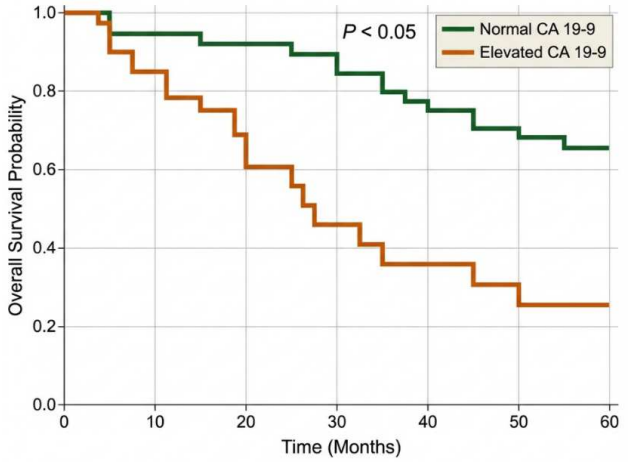

Fig. 6: Kaplan-Meier survival curve of CA 19-9.

Fig. 7 illustrates the relationship between baseline serum CEA and CA19-9 concentrations.

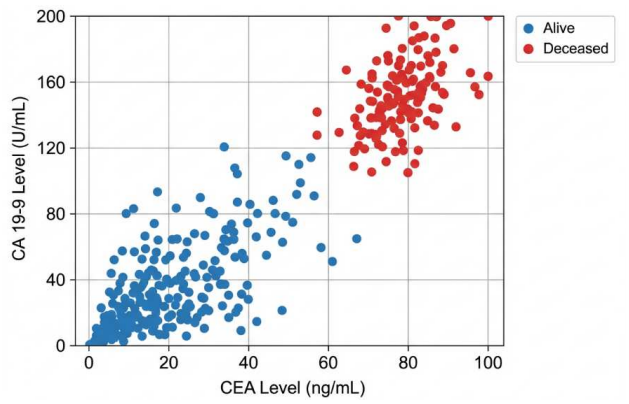

Fig. 7: Correlation scatter plot of CEA vs CA 19-9.

Table 2 indicates that the individual markers are important, but the Dual Elevation of CEA and CA 19-9 has the greatest hazard ratio (2.22 in multivariate analysis). The observed association suggests that simultaneous elevation of CEA and CA19-9 was associated with a higher estimated hazard of death than the reference biomarker category. Because of the small sample size and retrospective design, this estimate should be interpreted cautiously. In the multivariate model, age and tumor location were not statistically significant probably because of sample size.

Combined marker analysis (The "Double Hit" Effect)

Patients were classified into three biomarker-defined risk groups according to baseline CEA and CA19-9 levels. Patients with simultaneous elevation of both biomarkers (Group C) had a median overall survival of 8.4 months compared with 20.9 months in patients classified as Group A or Group B. The hazard ratio for Group C compared with Group A was 2.22 (95% CI: 1.31–3.76; p < 0.01).

Fig. 8 presents the Kaplan–Meier survival curves according to the combined CEA and CA19-9 risk groups.

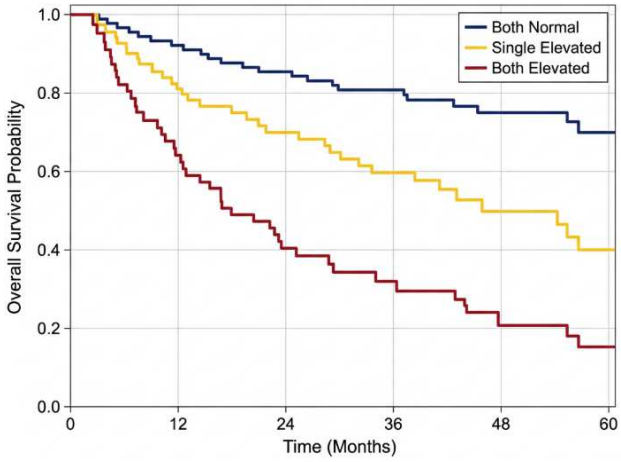

Fig. 8: Survival according to combinations of markers.

Fig. 9 illustrates the proportion of metastatic disease across the biomarker-defined risk groups.

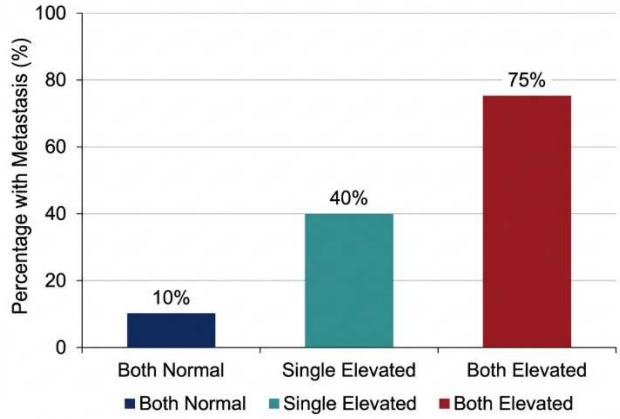

Fig. 9: Bar chart of marker group metastasis rate.

Impact of tumor localization on survival

Median overall survival differed according to tumor location.

Table 2: Univariate and multivariate cox regression analysis for overall survival.

Variable	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age > 65	1.45 (0.82-2.56)	0.19	1.32 (0.75-2.31)	0.33
Elevated CEA	1.88 (1.12-3.15)	0.02*	1.75 (1.05-2.92)	0.03*
Elevated CA 19-9	1.92 (1.15-3.22)	0.01*	1.81 (1.08-3.04)	0.02*
Dual elevation	2.45 (1.45-4.12)	<0.01*	2.22 (1.31-3.76)	<0.01*
Distal location	0.65 (0.38-1.12)	0.12	0.72 (0.41-1.25)	0.24

Table 3: Survival parameters by tumor location.

Location	Median OS (Months)	1-Year survival (%)	2-Year survival (%)
Cervical	12.0	40%	15%
Thoracic	16.0	55%	28%
Distal/GEJ	22.0	72%	45%

Patients with distal/gastroesophageal junction tumors had a median overall survival of 22.0 months. In contrast, patients with thoracic tumors had a median overall survival of 16.0 months and patients with cervical tumors had a median overall survival of 12.0 months. Distal/gastroesophageal junction tumors demonstrated the longest observed overall survival within the study cohort.

Fig. 10 presents Kaplan–Meier survival curves according to tumor location.

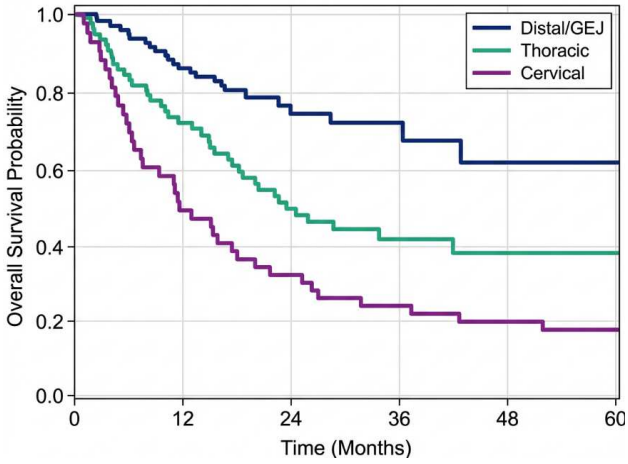

Fig. 10: Survival curves based on tumor location.

Fig. 11 presents a visual representation of the anatomical distribution of tumor locations within the study cohort. Color intensity reflects the relative frequency of tumors observed in each anatomical region.

Table 3 summarizes survival outcomes according to tumor location. The two-year survival rate was 45% for patients with distal/gastroesophageal junction tumors, 28% for patients with thoracic tumors and 15% for patients with cervical tumors.

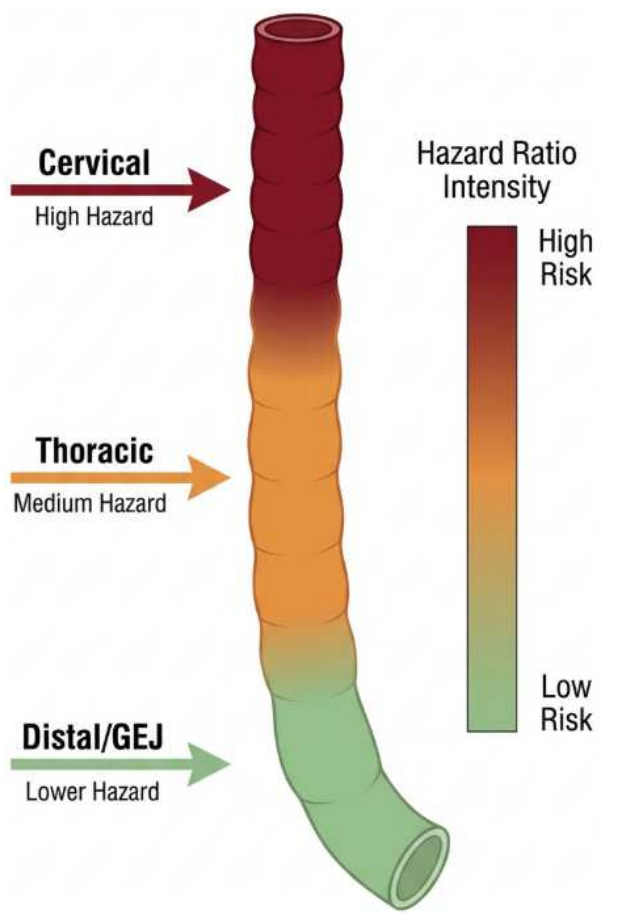

Fig. 11: Anatomical heatmap illustrating the distribution of tumor locations within the study cohort. Color intensity represents the relative frequency of tumors observed in each anatomical region and is based solely on the distribution of the 38 study patients. The Fig. is intended as a descriptive visualization and does not represent a statistically weighted risk model.

Comparative efficacy of chemotherapy regimens

Four chemotherapy regimen groups were evaluated within the study cohort.

Table 4: Chemotherapy regimen details and outcomes.

Regimen	Patients (n)	Median OS (Months)	Grade 3/4 toxicity (%)
MDCF	15	20.5	45%
FOLFOX/FLOT	10	17.2	30%
FOLFIRI/XELIRI	8	14.8	25%
Cisplatin/Etoposide	5	9.5	40%

Table 5: Characteristics of long-term survivors (>36 Months).

Patient ID	Age/Sex	Location	CEA / CA 19-9	Regimen	Status
P-04	58/M	Distal	Normal / Normal	MDCF -> Surg	Alive
P-12	62/F	GEJ	Normal / Normal	FLOT -> Surg	Alive
P-23	55/M	Distal	Elev / Normal	MDCF -> Surg	Alive
P-31	66/M	Thoracic	Normal / Normal	ChemoRad	Alive

The MDCF regimen was administered to 15 patients (39.5%) and was associated with the longest median overall survival of 20.5 months. Median overall survival was 17.2 months for patients treated with FOLFOX/FLOT, 14.8 months for patients treated with FOLFIRI/XELIRI and 9.5 months for patients treated with Cisplatin/Etoposide.

Fig. 12 presents Kaplan–Meier survival curves according to chemotherapy regimen. Differences in overall survival were observed among the four treatment groups.

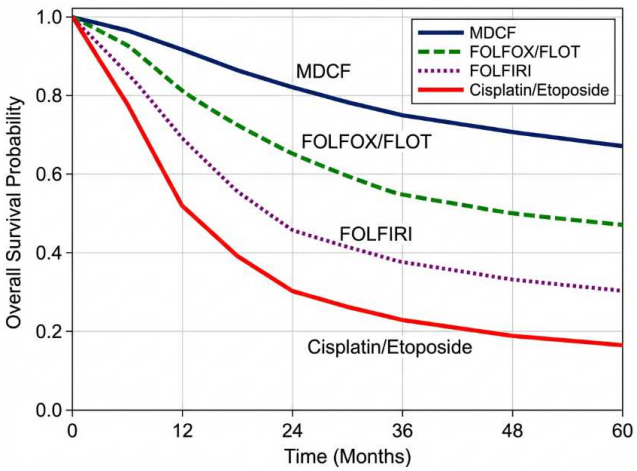

Fig. 12: Survival curves by chemotherapy regimen.

Fig. 13 illustrates treatment response rates across the four chemotherapy regimen groups, including partial response, stable disease, and progressive disease.

Table 4 summarizes the treatment outcomes for each chemotherapy regimen. The MDCF regimen demonstrated a median overall survival of 20.5 months with a grade 3–4 toxicity rate of 45%, whereas the Cisplatin/Etoposide regimen demonstrated a median overall survival of 9.5 months with a grade 3–4 toxicity rate of 40%.

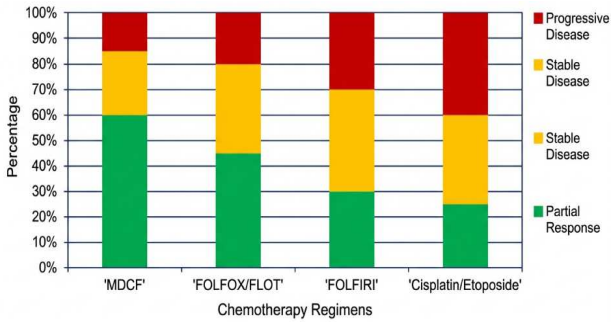

Fig. 13: Response rate bar chart by regimen.

Interaction between biomarkers and treatment response

An exploratory comparison was performed to evaluate treatment outcomes across biomarker-defined subgroups and chemotherapy regimens. Because of the limited sample size, formal statistical interaction testing was not performed. Differences in treatment outcomes were observed across biomarker-defined groups and chemotherapy regimens; however, these observations should be regarded as exploratory.

Fig. 14 illustrates treatment outcomes according to baseline CEA status and chemotherapy regimen.

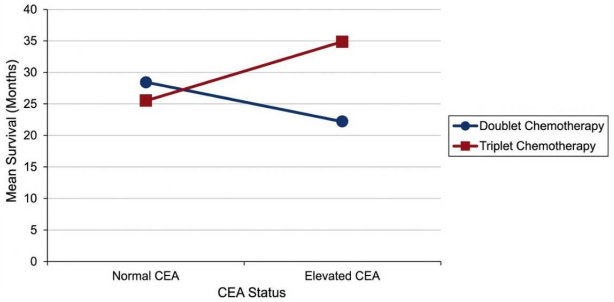

Fig. 14: Interaction plot of CEA and chemotherapy.

Fig. 15 presents the subgroup analysis according to patient characteristics and chemotherapy regimen. Hazard ratios and corresponding 95% confidence intervals are presented for each subgroup.

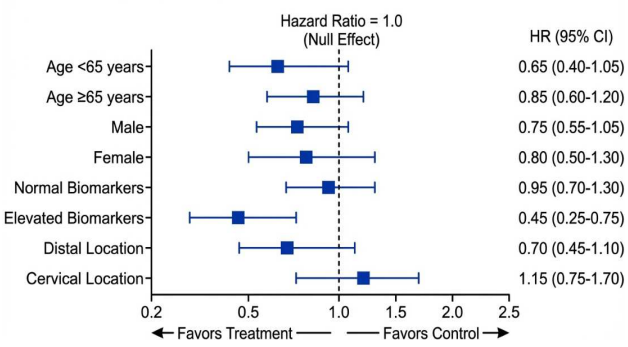

Fig. 15: Forest plot of subgroup analysis.

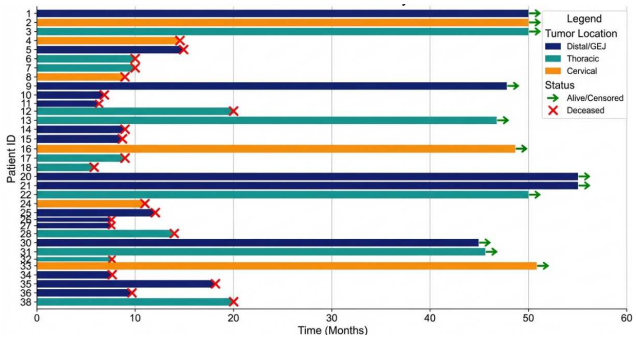

Fig. 16: Swimmer plot of individual patient timelines.

Long-term survivors and outliers

Four patients survived longer than 36 months. These patients had distal or gastroesophageal junction tumors and normal baseline CA19-9 levels. Three patients underwent MDCF-based induction chemotherapy followed by curative-intent surgery. Six patients died within six months of diagnosis and all had simultaneous elevation of both baseline biomarkers together with poor performance status.

Fig. 16 illustrates the clinical course and survival duration of individual patients included in the study cohort.

Table 5 summarizes the clinical characteristics of patients who survived longer than 36 months, including age, sex, tumor location, biomarker status, treatment regimen and survival status.

Fig. 17 presents an exploratory biomarker-guided clinical decision framework derived from the observed associations between baseline CEA, CA19-9, tumor location, chemotherapy regimen and overall survival in the present study.

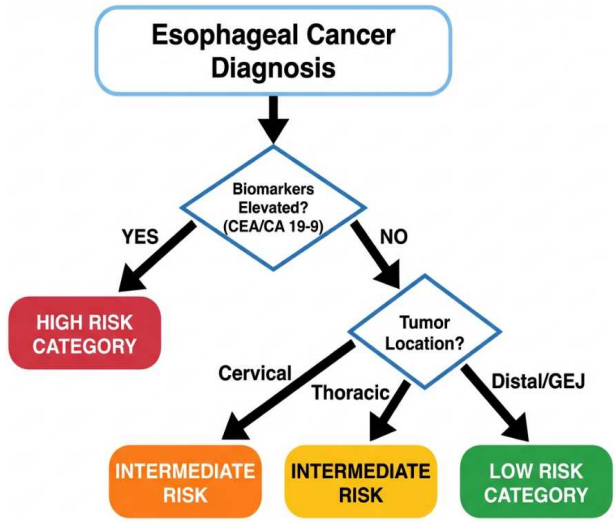

Fig. 17: Exploratory biomarker-guided clinical decision framework derived from the observed associations between baseline CEA, CA19-9, tumor location, chemotherapy regimen and overall survival in the present retrospective cohort. This framework is intended only to summarize the study findings and should not be interpreted as a validated clinical prediction model. Prospective external validation is required before clinical implementation.

Table 6 compares the outcomes observed in this real-world cohort with selected findings from previously published randomized controlled trials. The reduced survival in our cohort (approximately 30 vs 57/58) is indicative of the so-called efficacy-effectiveness gap that is characteristic of real-world studies in which patients are older and have more comorbidities. These differences illustrate the potential efficacy-effectiveness gap between selected clinical-trial populations and patients treated in routine clinical practice.

Compared with the FLOT4 and CROSS randomized controlled trials, lower survival outcomes were observed in the present real-world cohort. This difference is likely attributable to the broader clinical population encountered in routine practice, including older patients, greater comorbidity burden, heterogeneous disease characteristics and variations in treatment delivery that are generally minimized in randomized clinical trials.

Overall, these findings support the potential role of biomarker-guided precision medicine using serum CEA and CA19-9 for biological risk stratification in patients with esophageal adenocarcinoma. Because of the exploratory nature of the study, these observations require prospective validation before clinical implementation (Andre *et al*., 2024).

Table 6: Comparison of study findings with key historical trials.

Metric	Current study (Real-World)	FLOT4 trial (RCT)	CROSS trial (RCT)
Median Age	63.5	62.0	60.0
Distal/GEJ %	47.3%	56% (Gastric/GEJ)	24% (Adeno)
3-Year Survival	~30%	57%	58%
Key Finding	Biomarker synergy	Triplet efficacy	ChemoRad efficacy

DISCUSSION

This study evaluated the prognostic associations of baseline serum CEA and CA19-9 levels and explored their potential utility for biological risk stratification among patients with esophageal adenocarcinoma receiving systemic chemotherapy in routine clinical practice. The results suggest that combining routinely available serum biomarkers with clinical outcomes may provide a practical framework for biomarker-guided precision medicine and biological risk stratification in patients with esophageal adenocarcinoma (Andre *et al*., 2024; Ilson *et al* 2023). At the same time, this work expands the role of tumor markers from the prognostic context to the assessment of their potential application in choosing chemotherapy and its intensity (Tokunaga *et al*., 2015).

In this cohort, simultaneous elevation of CEA and CA19-9 was associated with shorter overall survival and therefore identified a subgroup with an unfavorable prognostic profile. Patients demonstrating a concomitant rise of biomarkers showed much lower survival rate and poorer results from chemotherapy. The hazard ratio for concomitant elevation of CEA and CA19-9 was higher than the one for each marker alone.

Nevertheless, previous studies have reported inconsistent findings regarding the prognostic significance of CEA and CA19-9 in esophageal cancer. While several investigations demonstrated an association between elevated biomarker levels and adverse survival outcomes, others reported only modest prognostic value after adjustment for established clinicopathological variables or failed to demonstrate independent significance. These discrepancies may reflect differences in study populations, tumor stage, histological subtype, biomarker cut-off values, treatment strategies and sample size. Therefore, the present findings should be interpreted as supportive evidence that requires confirmation in larger prospective studies.

From a pharmacotherapeutic perspective, treatment selection in esophageal cancer depends on multiple clinicopathological and patient-related factors. Although tumor stage contributes substantially to treatment planning, patients with similar stages may experience different responses to systemic therapy. In the present cohort, baseline CEA and CA19-9 levels were explored as potential complementary markers of biological risk; however, their ability to predict benefit from a specific chemotherapy regimen cannot be established from this retrospective analysis.

The association between elevated biomarker levels and poorer treatment outcomes may reflect greater tumor burden or more aggressive tumor biology rather than a direct effect of the biomarkers on chemotherapy resistance. It is known that elevated CEA level reflects increased tumor volume and enhanced cellular adhesion, metastatic capacity and chemo resistance. Also, increased CA19-9 may be indicative of an aggressive adenocarcinoma phenotype characterized by the increased invasion and metastatic ability. Thus, the combination of these factors can result in increased biological aggressiveness and a lower response to conventional treatment regimens. It should also be recognized that CEA and CA19-9 are non-specific serum biomarkers. Elevated concentrations may occur in several benign conditions, including chronic liver disease, pancreatitis, inflammatory disorders and cigarette smoking. Consequently, these biomarkers should always be interpreted alongside clinical findings, imaging results and pathological assessment rather than being used in isolation for treatment decisions.

One relevant finding in pharmaceutical sciences concerns the differential efficacy of chemotherapy regimens across biomarker-defined subgroups of esophageal cancer patients (Al-Batran *et al*., 2019). Patients classified in the high-risk biomarker group showed different treatment outcomes across chemotherapy regimens; however, these observations cannot be interpreted as evidence that high-risk patients derive greater benefit from intensive triplet regimens because treatment allocation was not randomized and residual confounding is possible. Low-risk patients, on the contrary, achieved desirable results without maximum treatment intensiveness.

The presented findings support the notion of biomarker-driven treatment intensification. In modern oncology, one of the key challenges relates to a proper balance between drug efficacy and toxicity (Andre *et al*., 2024; Kasi and Grothey, 2022). In particular, intensive therapy protocols (e.g., MDCF and FLOT regimens) increase the risk of developing toxicities but are associated with enhanced disease control. Prospective identification of biomarkers that reliably predict treatment benefit could potentially

support treatment individualization, but such predictive utility cannot be established from the present retrospective cohort.

The biomarker-based framework evaluated in this study should therefore be regarded as an exploratory approach to risk stratification rather than as a validated tool for precision pharmacotherapy. With biomarker-driven risk stratification, a clinician could determine whether a patient falls into low-, intermediate-, or high-risk groups (Lordick *et al*., 2022). Hence, personalized treatment could be administered based on biological risk, which is an important aspect of the contemporary approach to pharmacotherapy focused on maximizing benefits while minimizing the risk of adverse events.

Another observation in this cohort was the longer overall survival observed among patients with distal and gastroesophageal junction tumors compared with those with cervical and thoracic tumors. The reasons for this outcome may relate to a biological similarity of the distal type with gastric adenocarcinoma. Also, improvements in multimodal treatment strategies allow for curative intent in cases of gastroesophageal junction tumors.

The interplay between tumor localization and biomarker impact emphasizes the importance of biological factors in making appropriate treatment decisions in esophageal cancer patients. Anatomical features may not always serve as a sufficient basis for choosing a particular treatment protocol. On the contrary, a multidimensional assessment of biological, anatomical and pharmacological characteristics should contribute to a more personalized and effective treatment strategy.

A major strength of this study was the use of real-world clinical data from patients treated in routine oncology practice. Randomized trials still represent the primary method to assess the efficacy of a treatment but fail to take into account the differences between participants included in trials and the general population (Catenacci *et al*., 2020). Real-world data usually involve older patients with comorbidities, lower performance status and diverse treatment regimens.

The findings provide exploratory evidence regarding the potential role of readily available serum biomarkers in biological risk stratification, particularly in clinical settings where comprehensive molecular profiling may not be routinely accessible. Although comprehensive genomic profiling is increasingly incorporated into routine oncology practice, access to advanced molecular testing remains limited in many healthcare systems because of cost and infrastructure requirements. Consequently, inexpensive serum biomarkers such as CEA and CA19-9 remain attractive adjuncts for biological risk stratification. Recent reviews have emphasized that conventional serum biomarkers continue to provide clinically meaningful prognostic information when integrated with molecular biomarkers and modern precision oncology strategies (Matsumoto *et al*., 2026; Biomarker-targeted therapies for advanced-stage esophageal cancer, 2026).

The proposed biomarker-based framework should be regarded as an exploratory summary of observed associations rather than a treatment algorithm or validated clinical decision tool. Because chemotherapy regimens were selected according to routine clinical practice rather than randomized allocation, comparisons between treatment groups are susceptible to treatment-selection bias and should not be interpreted as evidence of comparative treatment efficacy. Prospective clinical studies are required before this framework can be applied in routine practice (Liu *et al*., 2024).

Despite the advantages, the study is limited by several aspects. First, the use of retrospective data collection may introduce selection bias and confounders. Second, the relatively small sample size makes it less powerful for subgroup analysis, and effect estimates may lack precision. Third, treatment assignment was done according to routine clinical practices, so treatment selection bias is possible. Variations in chemotherapy doses, support therapies and treatment adaptations may affect outcomes.

A limitation worth mentioning is the absence of more recent molecular biomarkers, such as HER2 status, PD-L1 expression, microsatellite instability and circulating tumor DNA. The integration of these parameters, along with traditional biomarkers, can improve prediction, and researchers are encouraged to examine this option. Additionally, serial measurement of biomarkers throughout the course of treatment can provide more valuable information for treatment prediction than a single baseline test (Ilson *et al* 2023; Heitzer *et al*., 2022; Ignatiadis *et al*., 2021).

Future research should focus on prospective, multicenter validation of the proposed biomarker-guided prognostic model in larger and more diverse patient populations. Future investigations should also evaluate the integration of serum biomarkers with molecular profiling, artificial intelligence-assisted prognostic models, liquid biopsy technologies and digital pathology to improve individualized treatment strategies and clinical decision-making in patients with esophageal adenocarcinoma (Bian *et al*., 2026; Yang *et al*., 2026; Chakrabarti *et al*., 2023).

In conclusion, this paper supports the hypothesis that the combination of serum CA19-9 and carcinoembryonic antigens contains useful biological information that could be utilized in addition to standard prognostic evaluations.

A correlation between biomarker-defined biological risks and patterns of chemotherapy response provides an opportunity to build clinically meaningful, biomarker-driven treatment guidance.

Limitations and future prospects

Several limitations should be considered when interpreting these findings. First, the retrospective design is susceptible to selection bias, information bias and residual confounding and does not permit causal inference. Second, the small sample size of 38 patients limits statistical power, particularly for subgroup analyses and multivariable Cox regression, and increases the risk of overfitting and imprecise effect estimates. Third, treatment assignment was based on routine clinical practice rather than randomization, creating the possibility of treatment-selection bias and confounding by indication. Fourth, the study was conducted at a single institution, which may limit the generalizability of the findings. Finally, the proposed biomarker-based framework was not subjected to internal or external validation and should therefore be considered exploratory and hypothesis-generating.

Heterogeneity among chemotherapy regimens represents an additional limitation. Because treatment was delivered under routine clinical conditions, variations in dose intensity, treatment intervals, dose modifications and supportive care may have influenced clinical outcomes. Although we grouped regimens in general (e.g., MDCF, FOLFOX), variations within the regimen by dose intensity may confound the outcome. The study period from 2016 to 2021 also encompassed changes in the systemic treatment landscape, including increasing use of immune checkpoint inhibitors. Because treatment-era effects and immunotherapy exposure were not consistently captured as separate analytical variables, temporal changes in treatment practice may have contributed to outcome differences. The absence of specific genetic sequencing data (ex. HER2 status, PD-L1 expression) also makes it hard to combine these results with contemporary molecular-based classifications.

In spite of these shortcomings, the study provides the future research with multiple opportunities. Future studies should prospectively evaluate a combined CEA and CA19-9 risk score in larger, multicenter cohorts to determine reproducible biomarker thresholds and clinically meaningful risk categories. Through such a study, definitive cut-off values and risk categories can be established. Future studies should also evaluate longitudinal changes in CEA and CA19-9 during treatment. Dynamic biomarker assessment (marker kinetics) may provide additional prognostic and predictive information beyond baseline measurements and could improve treatment monitoring and individualized therapeutic decision-making. Also, combining such serum protein markers with next-generation liquid biopsy methods, including circulating tumor DNA (ctDNA), may yield a new, building-block-like prognostic model, which integrates the cost-effectiveness of protein markers with the sensitivity of genomic analysis. Finally, prospective randomized studies comparing chemotherapy strategies within biomarker-defined risk groups are required to determine whether biomarker-guided treatment selection improves clinical outcomes. The interaction observed in the present retrospective analysis should therefore be considered hypothesis-generating until confirmed in appropriately designed prospective studies.

CONCLUSION

This retrospective cohort study found that combined baseline serum CEA and CA19-9 elevation was associated with shorter overall survival among patients with esophageal adenocarcinoma receiving systemic chemotherapy. Simultaneous elevation of both biomarkers identified a subgroup with an unfavorable prognostic profile. However, the observed associations should not be interpreted as evidence that CEA and CA19-9 can independently guide chemotherapy selection, because treatment allocation was non-randomized and the study included only 38 patients from a single institution. The proposed biomarker-based framework should therefore be considered exploratory and hypothesis-generating. Prospective multicenter studies with larger patient populations, standardized treatment assessment and independent validation are required to determine whether combined CEA and CA19-9 assessment has clinically useful prognostic or predictive value.

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Author's contributions

Orcun Can: Conceptualized and designed the study; developed the study methodology; supervised the research; collected, analyzed and interpreted the data; drafted the manuscript and approved the final version of the manuscript; Abdullah Sakin: Contributed to study design, clinical data acquisition, data interpretation and critical revision of the manuscript for important intellectual and scientific content. He also supervised the clinical aspects of the study and approved the final version of the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the study. This statement is consistent with the ICMJE authorship recommendations. Artificial intelligence tools

were not used to generate, analyze or interpret the study data. Any language-editing assistance was limited to improving grammar, clarity and readability, and the authors take full responsibility for the accuracy, integrity and scientific content of the manuscript.

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Data availability statement
All data generated or analysed during this study are included in this published article and its supplementary information files.

Ethical approval
This retrospective study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Medipol University Non-Interventional Clinical Research Ethics Committee, Istanbul, Turkey (Approval No. E-10840098-772.02-2021/356). All patient data were anonymized prior to analysis and confidentiality was maintained throughout the study in accordance with institutional and national ethical guidelines. Written informed consent was obtained from all participants before inclusion in the study. This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare that they have no competing interests.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787915780.pdf

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