Clin. Lab. 2026;72:XXX-XXX

ORIGINAL ARTICLE

Prognostic Impact of Preoperative Tumor Markers in Patients with Colorectal Carcinoma

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SUMMARY

Background: **This study aimed to evaluate the correlation between preoperative CA19-9, CEA, CA125, and AFP levels of and prognosis for patients diagnosed with colorectal carcinoma.**
Methods: **This was a retrospective study, which involved 400 CRC patients treated with radical resection between January 2022 and December 2024 and categorized into two groups: development (n = 280) and validation (n = 120). Clinicopathological data, including age, gender, operative method, tumor size, tumor location, TNM stage, CA19-9, CEA, CA125, and AFP, was assessed. The patients got checked up every three months for the first year, and then every six months afterwards.**
Results: **Univariate and multivariate analyses revealed that age (> 70 years), tumor staging, N-stage, preoperative CA125, and CA19-9 were associated with the prognosis of CRC patients. Univariate analysis revealed that tumor size (p = 0.026, HR = 1.64, 95% CI = 0.81 - 3.35) and CEA (p = 0.029, HR = 2.73, 95% CI = 0.24 - 4.42) were associated with the prognosis of CRC patients.**
Conclusions: **This study revealed the prognostic impact of the tumor markers CA125, CA19-9, and CEA in patients with nonmetastatic CRC.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250231)

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Manuscript accepted May 8, 2025

KEYWORDS

alpha-fetoprotein, colorectal cancer, carbohydrate antigen 19-9, carbohydrate antigen 125, carcinoembryonic antigen, prognosis

INTRODUCTION

On a worldwide scale, colorectal cancer (CRC) is the third most frequently identified malignancy (with about 1.9 million cases) and the second most prevalent reason for mortality (with about 0.9 million deaths around the

world) in 2020 [1]. Colorectal cancer (CRC) contributes to approximately 10% of cancer cases as well as fatalities, making it an essential part of the worldwide cancer load [2].

Biomarkers are now used extensively in CRC. Biomarkers also have the ability to alter screening and therapy procedures for a broad spectrum of patients [3].

Detecting AFP level is extremely important for the diagnosis of malignant germ cells and hepatic tumors. Malignancies in specific tissues, such as bile ducts and stomach, may result in AFP elevation [4].

Carcinoembryonic antigen (CEA) is a glycoprotein that promotes cellular adhesion and typically comes out during fetal development [5]. CEA is increasingly used as a prognostic marker. Increased preoperative CEA levels were associated with an increased risk of death compared to normal preoperative CEA levels among patients with stage I - III colon cancer [6].

CA19-9 is a monoclonal antibody that functions as an E-Selectin ligand. A rise in serum CA19-9 can occur in both malignant and benign processes [7]. There is a little proof of a link between raised CA 19-9 levels and outcome in colorectal carcinoma [8].

CA125 was discovered in gastrointestinal tumor cells [9] and used as a tumor biomarker in regular examinations of patients with gastrointestinal tumors, where it plays a critical role in tumorigenesis, tumor proliferation, and metastasis [10]. An increased preoperative CA125 level has been linked to a poor prognosis and should be considered in clinical practice [11].

The aim of this study was to evaluate the association between preoperative CEA, CA19-9, CA125, and AFP levels and prognosis of colorectal carcinoma patients.

MATERIALS AND METHODS

From January 2022 through December 2024, 400 patients with colorectal carcinoma treated with radical resection were included in the current study. The inclusion criteria were as follows: age ≥ 18 years, colorectal adenocarcinoma was confirmed by histopathological examination, no metastasis, no preoperative chemoradiotherapy, and preoperative CEA, CA19-9, CA125, and AFP levels within normal.

Ethical considerations

The study was approved by the Ethics Committee of Al Azhar University Hospital (approval no. 234/21). To protect the patients' confidentiality, every participant's name was obscured and supplanted with code numbers. Before the research was conducted, each participant provided informed consent.

We recorded the following clinical and pathological parameters: age, gender, surgical method, tumor site, and TNM staging. Measurement of tumor markers in serum as AFP, CA125, CEA, and CA19-9 was done using ELISA method, and the kits used in analysis were purchased from Sigma Aldrich. The patients got checked up every three months for the first year, then every six months afterwards.

Statistical analyses

The statistical software for social sciences, version 23.0 (IBM Corp., Armonk, NY, USA), was used to analyze the recorded data.

RESULTS

Baseline characteristics of the included patients

Based on the inclusion criteria, 400 patients were eventually enrolled, with 280 assigned to the development site group and 120 to the validation site group. Males comprised 64.6% of the development site group, while females made up 35.4%; the average age was 60.29 ± 11.57 years, with a BMI of 25.35 ± 2.97 kg/m^2. Among them, 74 (26.4%) had hypertension (HTN), 57 (20.4%) had diabetes mellitus (DM), and 108 (38.6%) were smokers. In the validation group, males accounted for 60.0%, females accounted for 40.0%, the mean age was (60.86 ± 11.17) years, and the mean BMI was (25.76 ± 1.89) kg/m^2. Among them, 33 (27.5%) had hypertension (HTN), 17 (14.2%) had diabetes mellitus (DM), and 56 (46.7%) were smokers. There was no statistically significant difference between the groups regarding age, gender, BMI, HTN, DM, and smoking, with p-values > 0.05 (Table 1).

Pathological results of the included patients

In the development group, the TNM classification results showed that 169 (60.4%) patients were in stage III, 48 (17.1%) were in stage II, 37 (13.2%) were in stage I, and 26 (9.3%) were in stage IV. In 168 (60.0%) patients, the tumor location was at the rectum, in 60 (21.4%), it was at the right colon, and in 52 (18.6%), it was at the left colon. The tumor size was < 5 in 175 (62.05%) patients and ≥ 5 in 105 (37.5%) patients. According to the N stage, 199 (71.1%) were at N2, 44 (15.7%) were at N1, and 37 (13.2%) were at N0. The operative method was laparoscopic in 179 (63.9%) patients and open in 101 (36.1%) patients, and the mean surgical time was (223.28 ± 11.27) minutes (Table 2). In the validation group, the TNM classification results showed that 70 (58.3%) patients were in stage III, 26 (21.7%) were in stage II, 18 (15.6%) were in stage I, and 6 (5.0%) were in stage IV. In 75 (62.5%) patients, the tumor location was at the rectum, in 22 (18.3%), it was at the right colon, and in 23 (19.2%), it was at the left colon. The tumor size was < 5 in 78 (65.0%) patients and ≥ 5 in 42 (35.0%) patients. According to the N stage, 82 (68.3%) were at N2, 18 (15.0%) were at N1, and 20 (16.7%) were at N0. The operative method was laparoscopic in 78 (65.0%) patients and open in 42 (35.0%) patients, and the mean surgical time was (224.23 ± 13.10) minutes (Table 2).

There was no statistically significant difference between the study groups regarding tumor location, tumor size

Table 1. Comparison between development group and validation group according to baseline data.

Baseline data	Total (n = 400)	Development group (n = 280)	Validation group (n = 120)	Test value	p-value	Sig.
Age (years)						
Mean ± SD	60.46 ± 11.44	60.29 ± 11.57	60.86 ± 11.17	0.210	0.647	NS
Range	38 - 85	38 - 85	40 - 80			
Gender						
Females	147 (36.8%)	99 (35.4%)	48 (40.0%)	0.779	0.377	NS
Males	253 (63.3%)	181 (64.6%)	72 (60.0%)			
BMI (kg/m^2)						
Mean ± SD	25.48 ± 2.69	25.35 ± 2.97	25.76 ± 1.89	1.971	0.161	NS
Range	20.36 - 34.31	20.36 - 34.21	21.23 - 34.31			
HTN						
No	293 (73.3%)	206 (73.6%)	87 (72.5%)	0.049	0.824	NS
Yes	107 (26.8%)	74 (26.4%)	33 (27.5%)			
DM						
No	326 (81.5%)	223 (79.6%)	103 (85.8%)	2.135	0.144	NS
Yes	74 (18.5%)	57 (20.4%)	17 (14.2%)			
Smoking						
No	236 (59.0%)	172 (61.4%)	64 (53.3%)	2.276	0.131	NS
Yes	164 (41.0%)	108 (38.6%)	56 (46.7%)			

To analyze data, we used the independent sample *t*-test for mean ± SD, the chi-squared test for numbers (%), or the Fisher's exact test as needed.
Non-significant (NS), significant (S), and highly significant (HS).

Table 2. Comparison between development group and validation group according to pathological results.

Pathological results	Total (n = 400)	Development group (n = 280)	Validation group (n = 120)	Test value	p-value	Sig.
Tumor location						
Left colon	75 (18.8%)	52 (18.6%)	23 (19.2%)	0.495	0.781	NS
Rectum	243 (60.8%)	168 (60.0%)	75 (62.5%)			
Right colon	82 (20.5%)	60 (21.4%)	22 (18.3%)			
Tumor size (cm)						
< 5	253 (63.3%)	175 (62.5%)	78 (65.0%)	0.226	0.635	NS
≥ 5	147 (36.8%)	105 (37.5%)	42 (35.0%)			
TNM stage						
I	55 (13.8%)	37 (13.2%)	18 (15.0%)	3.110	0.375	NS
II	74 (18.5%)	48 (17.1%)	26 (21.7%)			
III	239 (59.8%)	169 (60.4%)	70 (58.3%)			
IV	32 (8.0%)	26 (9.3%)	6 (5.0%)			
N-stage						
N0	57 (14.3%)	37 (13.2%)	20 (16.7%)	0.820	0.664	NS
N1	62 (15.5%)	44 (15.7%)	18 (15.0%)			
N2	281 (70.3%)	199 (71.1%)	82 (68.3%)			
Operative method						
Laparoscopic	257 (64.3%)	179 (63.9%)	78 (65.0%)	0.042	0.838	NS
Open	143 (35.8%)	101 (36.1%)	42 (35.0%)			
Surgical time (minutes)						
Mean ± SD	223.57 ± 11.84	223.28 ± 11.27	224.23 ± 13.10	0.534	0.466	NS
Range	180.6 - 278.2	197.9 - 278.2	180.6 - 251.8			

Table 3. Comparison between development group and validation group according to preoperative tumor markers.

Preoperative tumor markers	Total (n = 400)	Development group (n = 280)	Validation group (n = 120)	Test value	p-value	Sig.
AFP (ng/mL)						
< 18	110 (27.5%)	76 (27.1%)	34 (28.3%)	0.060	0.807	NS
≥ 1.8	290 (72.5%)	204 (72.9%)	86 (71.7%)			
CA125						
< 13.4	276 (69.0%)	191 (68.2%)	85 (70.8%)	0.161	0.688	NS
≥ 13.4	124 (31.0%)	89 (31.8%)	35 (29.2%)			
CA19-9						
< 10.1	269 (67.3%)	187 (66.8%)	82 (68.3%)	0.035	0.852	NS
≥ 10.1	131 (32.7%)	93 (33.2%)	38 (31.7%)			
CEA						
< 2.9	277 (69.3%)	194 (69.3%)	83 (69.2%)	0.001	0.981	NS
≥ 2.9	123 (30.8%)	86 (30.7%)	37 (30.8%)			

Table 4. Univariate and multivariate analyses of Cox proportional hazards of OS in the development group compared to the validation group.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age > 70 years	1.70 (1.04 - 2.80)	0.034 *	1.64 (0.65 - 2.92)	0.041 *
Gender (male/female)	2.04 (0.98 - 4.21)	0.374	--	--
Obese	2.01 (1.04 - 3.89)	0.162	--	--
HTN	1.79 (0.91 - 4.01)	0.251	--	--
DM	1.46 (0.68 - 3.13)	0.677	--	--
Smoker	1.53 (0.89 - 2.62)	0.552	--	--
Colorectal location	1.87 (0.86 - 4.06)	0.152	--	--
Tumor size (≥ 5 cm/< 5 cm)	1.64 (0.81 - 3.35)	0.026 *	--	--
Tumor stage (IV/III/II/I)	2.70 (0.41 - 5.18)	0.016 *	1.82 (1.10 - 4.33)	0.018 *
N-stage (2/1/0)	2.44 (0.13 - 3.08)	0.021 *	1.42 (0.63 - 3.19)	0.019 *
Operative method	1.37 (0.97 - 3.21)	0.031 *	--	--
AFP (≥ 1.8/< 1.8)	1.82 (0.49 - 5.46)	0.540	--	--
CA125 (≥ 13.4/< 13.4)	3.57 (1.04 - 4.47)	0.043 *	2.53 (0.14 - 3.21)	0.049 *
CA19-9 (≥ 10.1/< 10.1)	4.94 (2.86 - 6.33)	0.027 *	3.68 (2.11 - 4.75)	0.027 *
CEA (≥ 2.9/< 2.9)	2.73 (0.24 - 4.42)	0.029 *	--	--

HR - Hazard ratio, CI - confidence interval. * - Statistically significant (p < 0.05).

(cm), TNM stage, N-stage, operative method, and surgical time (minute), with p-values > 0.05.

Table 3 shows that preoperative AFP was elevated (≥ 1.8) in 204 (72.9%) patients in the development group and in 86 (71.7%) patients in the validation group, with no statistically significant difference between both groups (p = 0.807). Preoperative CA125 was elevated (≥ 13.4) in 89 (31.8%) patients in the de-

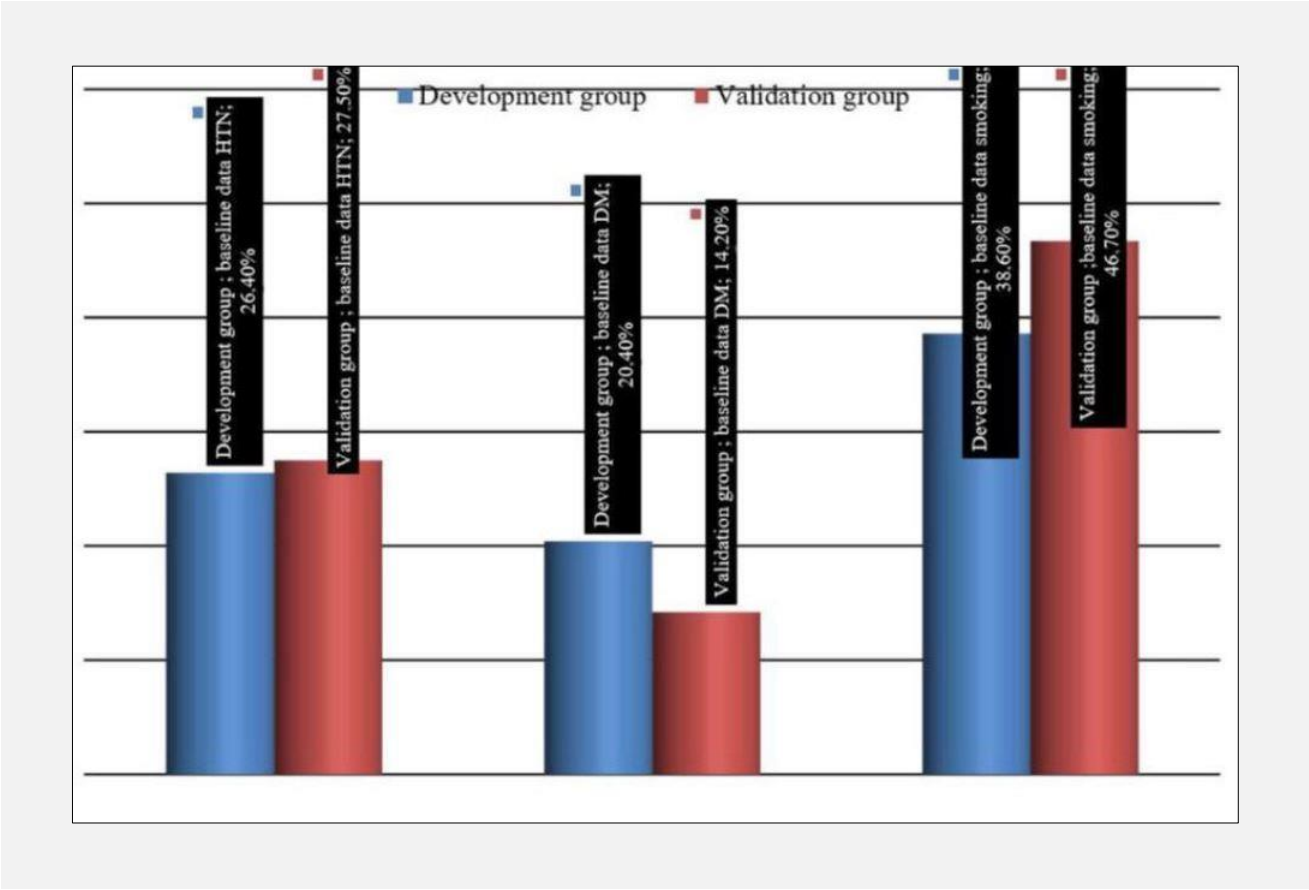

Figure 1. Comparison between development group and validation group according to baseline data.

velopment group and in 35 (29.2%) patients in the validation group, with no statistically significant difference between both groups (p = 0.688). Preoperative CA19-9 was elevated (≥ 10.1) in 93 (33.2%) patients in the development group and in 38 (31.7%) patients in the validation group, with no statistically significant difference between both groups (p = 0.852). Preoperative CEA was elevated (≥ 2.9) in 86 (30.7%) patients in the development group and in 37 (30.8%) patients in the validation group, with no statistically significant difference between both groups (p = 0.981).

Univariate analysis revealed that the following parameters showed statistically significant difference: age (> 70 years) (p = 0.034, HR = 1.70, 95% CI = 1.04 - 2.80), tumor size (p = 0.026, HR = 1.64, 95% CI = 0.81 - 3.35), tumor staging (p = 0.016, HR = 2.70, 95% CI = 0.41 - 5.18), N-stage (p = 0.021, HR = 2.44, 95% CI = 0.13 - 3.08), operative method (p = 0.031, HR = 1.37, 95% CI = 0.97 - 3.21), and preoperative CA125 (p = 0.043, HR = 3.57, 95% CI = 1.04 - 4.47) (Table 4). Multivariate analysis showed that age (> 70 years) (p = 0.041, HR = 1.64, 95% CI = 0.65 - 2.92), tumor staging (p = 0.018, HR = 1.82, 95% CI = 1.10 - 4.33), N-stage (p = 0.019, HR = 1.42, 95% CI = 0.63 - 3.19), preoperative CA125 (p = 0.049, HR = 2.53, 95% CI = 0.14 - 3.21), and CA19-9 (p = 0.027, HR = 3.68, 95% CI = 2.11 - 4.75) were associated with the prognosis of patients (Table 4).

The overall survival curve of AFP levels regarding improvement (Figure 4) showed the AFP < 18 vs. AFP ≥ 18. The bad prognostic prediction for CRC through overall survival with HR (95% CI) was 1.82 (0.49 - 5.46); therefore, these results indicate that AFP was not a prognostic biomarker in CRC, with a p-value > 0.05.

The overall survival curve of CA125 levels regarding improvement (Figure 5) showed the CA125 < 13.4 vs. CA125 ≥ 13.4. The good prognostic prediction for CRC through overall survival with hazard ratio (95% CI) was 2.53 (0.14 - 3.21); therefore, these results indicate CA125 as a good prognostic biomarker in CRC, with p-value = 0.049.

The overall survival curve of CA19-9 levels regarding improvement (Figure 6) showed the CA19-9 < 10.1 vs. CA19-9 ≥ 10. The good prognostic prediction for CRC through overall survival with hazard ratio (95% CI) was 3.68 (2.11 - 4.75); therefore, these results indicate CA19-9 as a good prognostic biomarker in CRC, with p-value = 0.027.

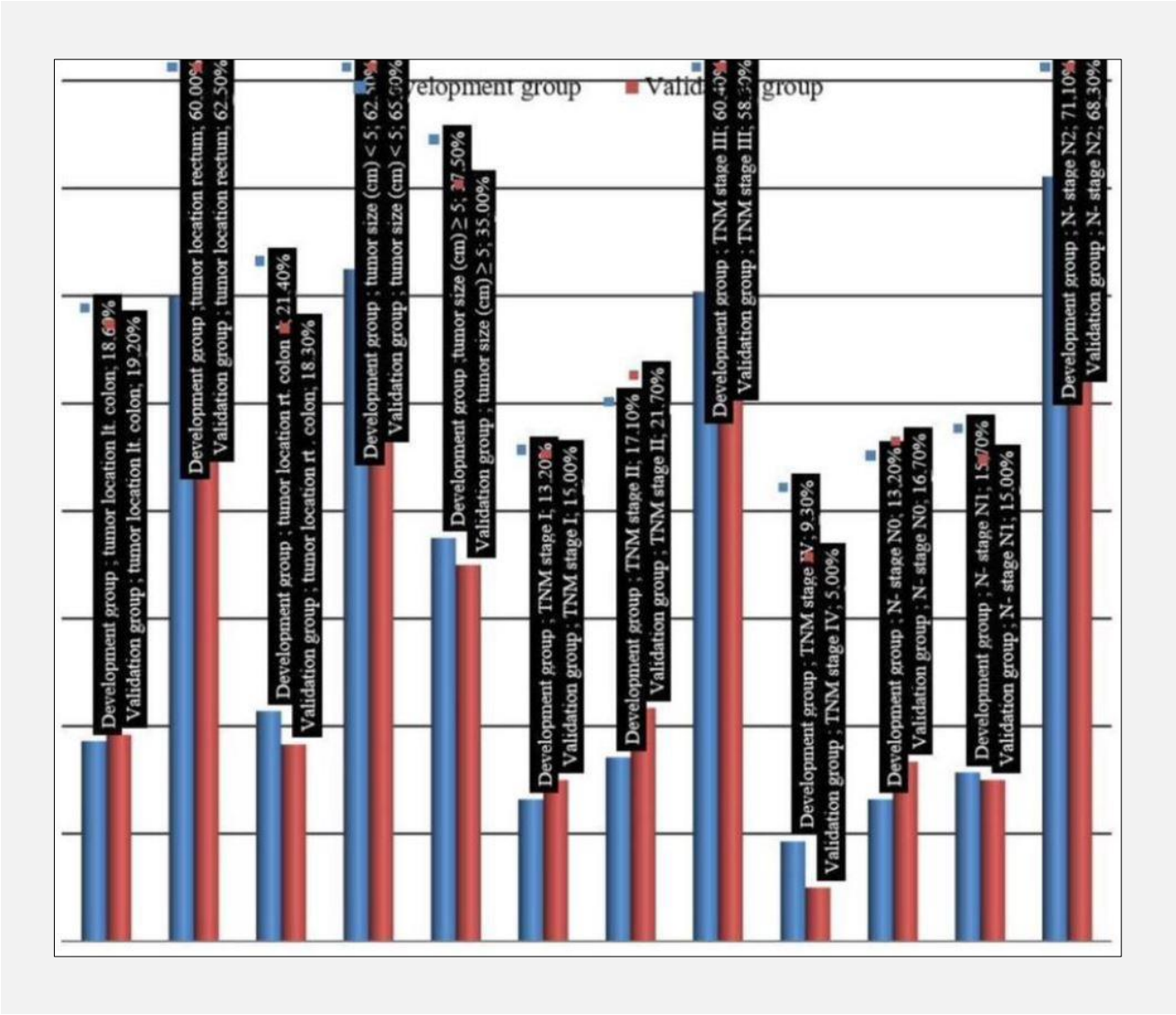

Figure 2. Comparison between development group and validation group according to tumor location, tumor size (cm), TNM stage, and N-stage.

The overall survival curve of CEA levels regarding improvement (Figure 7) showed the CEA < 2.9 vs. CEA ≥ 2.9. The good prognostic prediction for CRC through overall survival with hazard ratio (95% CI) was 2.73 (0.24 - 4.42); therefore, these results indicate CEA as a good prognostic biomarker in CRC, with p-value = 0.029.

DISCUSSION

A tumor marker is a compound generated by either the tumor or the host in response to a malignancy. Tumor markers have been extensively used in the monitoring of gastrointestinal cancers [12,13]. As a result, there is a pressing requirement for finding beneficial biomarkers capable of predicting the prognosis of CRC in clinical practice in order to improve CRC prevention, screening, and treatment [14].

CEA, CA19-9, CA125, and AFP are critical for planning therapy as they are strongly linked to the prognosis of CRC patients [15]. Elevated postoperative tumor markers indicate a poor prognosis in CRC, regardless of whether the preoperative markers are normal [16,17]. This study was set out to investigate the association between the prognosis of patients with colorectal cancer and preoperative levels of CEA, CA19-9, CA125, and AFP. This study included 280 patients in the development site group and 120 in the validation site group, with the majority of patients being males and with an average age of 60 years. There was no statistically significant difference between both groups regarding age,

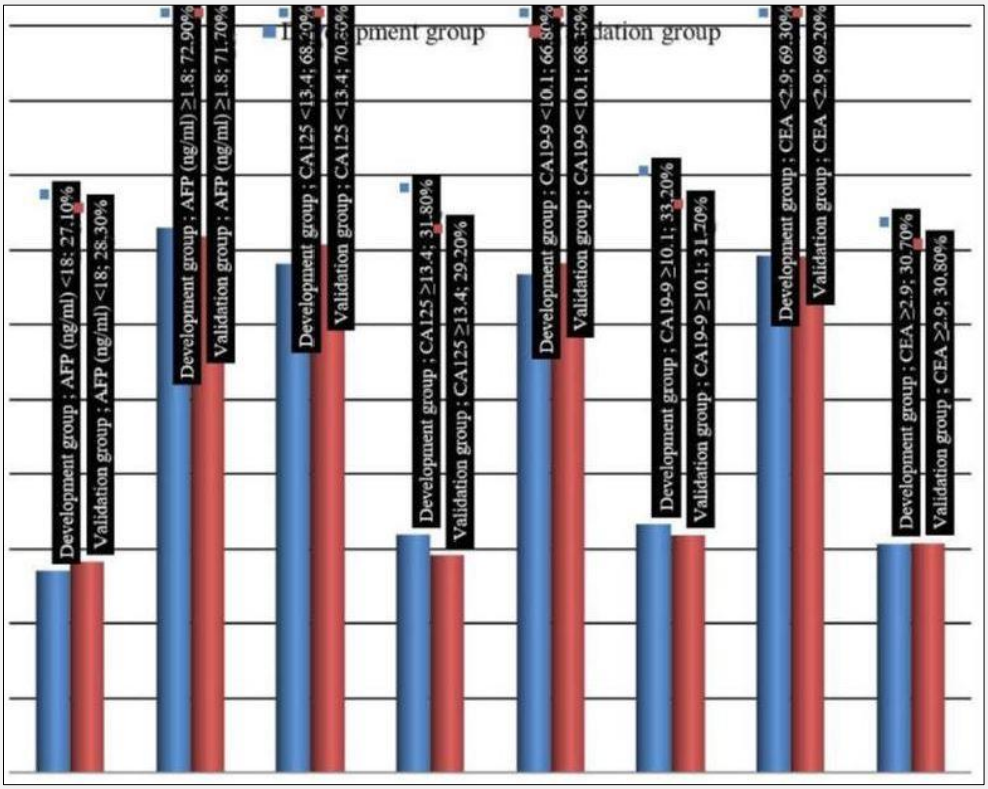

Figure 3. Comparison between development group and validation group regarding preoperative tumor markers.

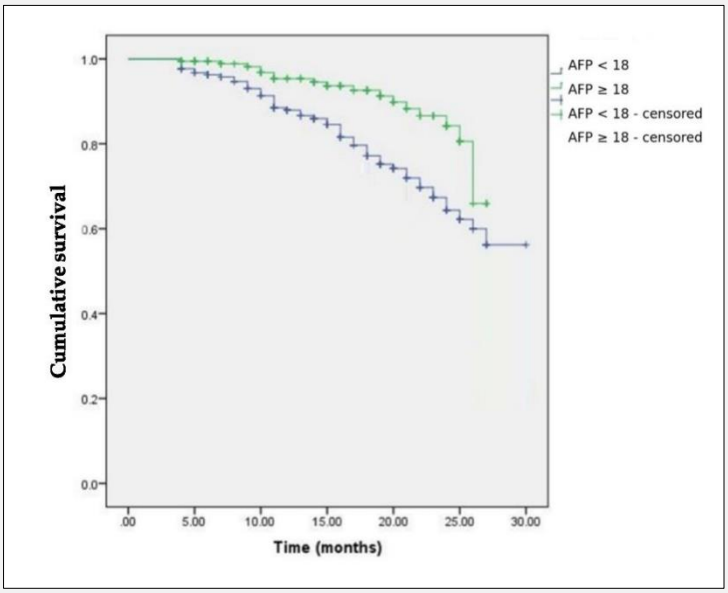

Figure 4. Overall survival curves by AFP (ng/mL) levels according to improvement.

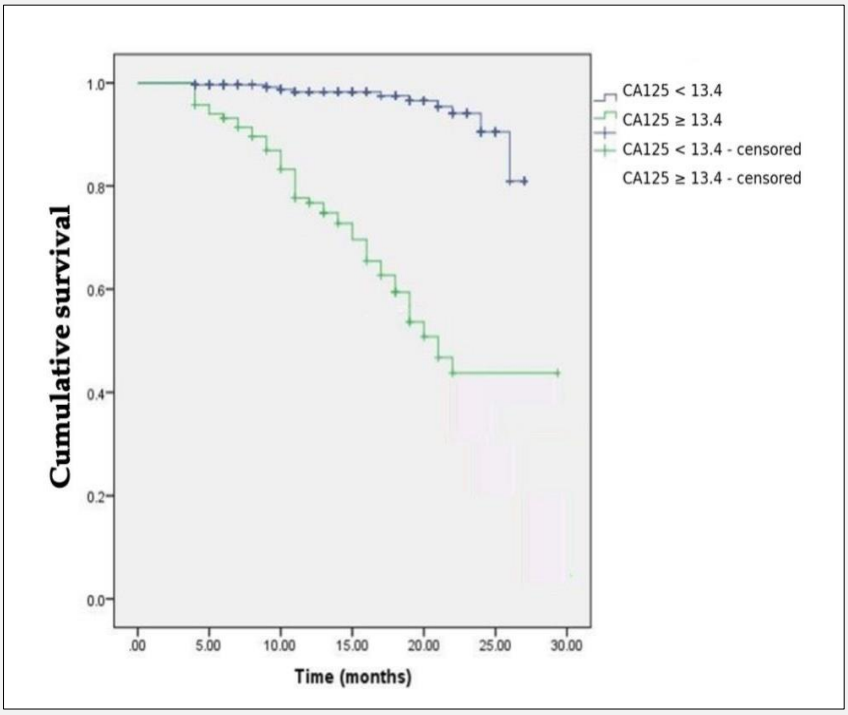

Figure 5. Overall survival curves by CA125 levels according to improvement.

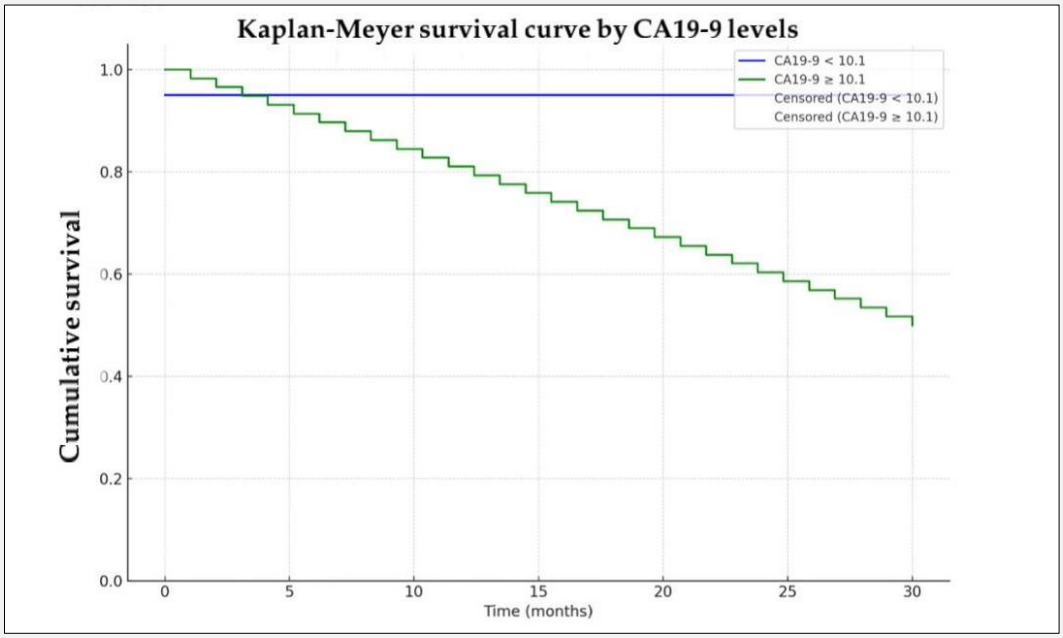

Figure 6. Overall survival curve by CA19-9 levels according to improvement.

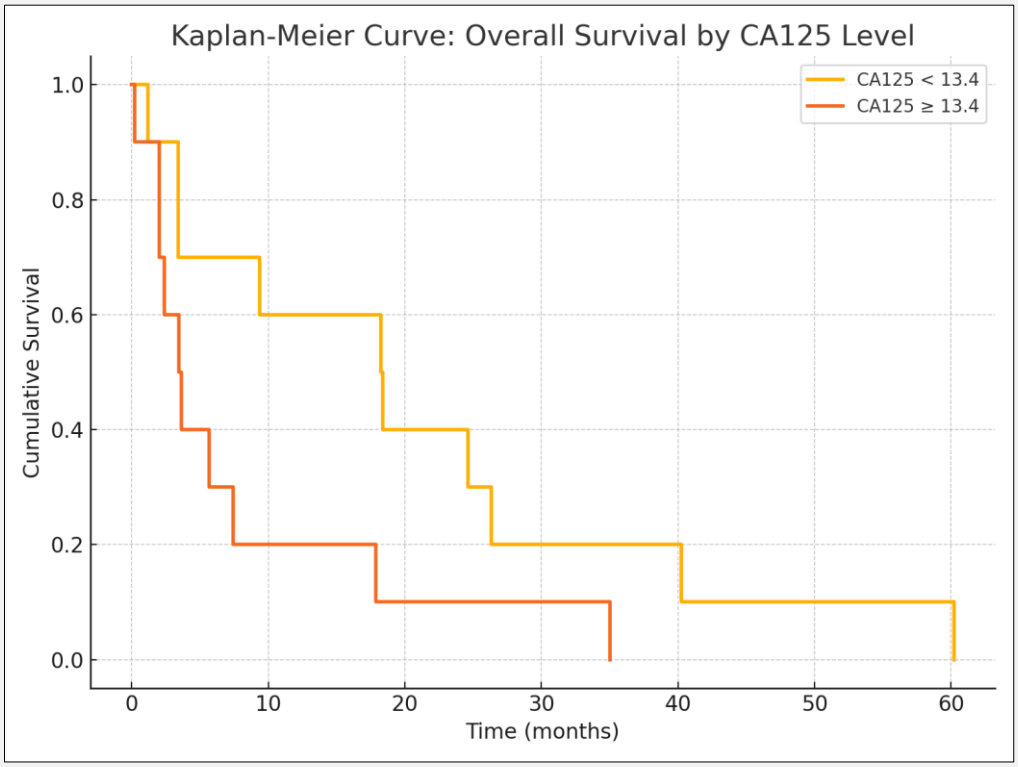

Figure 7. Overall survival curves by CEA levels according to improvement.

gender, BMI, HTN, DM, and smoking, with p-values > 0.05. These findings are in agreement with a past study that reported that males accounted for more than half of the studied samples in development and validation groups, with no statistically significant difference between both groups regarding BMI and chronic diseases (smoking, drinking, HTN, DM, and chronic heart disease) [18].

The current study's results demonstrated no statistically significant differences between the development and validation groups in terms of tumor site, tumor size (cm), TNM stage, N-stage, operating procedure, and surgical time (min), with p-values p > 0.05. Ren et al. discovered no statistically significant differences between the two groups in terms of tumor location, size, TNM and N-staging, surgery method, and time [19]. Our study's univariate and multivariate analyses demonstrated that age (> 70 years), tumor staging, N-stage, preoperative CA125, and CA19-9 were all linked with CRC patients' prognosis. Univariate analysis demonstrated that tumor size (p = 0.026, HR = 1.64, 95% CI = 0.81 - 3.35) and CEA (p = 0.029, HR = 2.73, 95% CI = 0.24 - 4.42) were linked with CRC patients' prognosis. These findings were congruent with those of Ren et al., who reported that pre-surgical CA 19-9 and CA 125 within normal values are significant independent prognostic parameters for colorectal carcinoma patients. So, the overall levels of pre-surgical serum CA 19-9 and CA 125 are a valuable indication of cancer prognosis in spite of tumor stage [19].

Various studies have shown the significant impact of CA19-9 [20,21] in colorectal carcinoma patients with normal pre-surgical CEA levels [6,22].

In a previous study, preoperative serum CA19-9 outperformed CEA as a predictive factor in multivariate analysis of gastric cancer [23]. The recommendations also recommended CEA as an excellent predictor of OS [24]. Previous studies demonstrated that impact of post-surgical CEA levels is positively correlated with pre-surgical CEA values [25,26].

High blood CEA and CA19-9 levels have been confirmed as independent prognostic variables in multivariate analysis and were recently found to be strongly connected with shorter OS and disease-free survival (DFS) in patients with gastric cancer, according to Zhu et al. [27]. Additionally, studies have indicated that measuring preoperative serum CEA and CA19-9 levels can enhance CRC patients' prognosis and diagnosis [7].

The effect of age on colorectal carcinoma prognosis was still in debate [28,29]. Zhao et al. reported that colorectal carcinoma prognosis was poor in young patients [30]. However, Yang et al. observed that young patients' prognosis was different from old patients' prognosis [31]. Another research revealed that young patients showed better prognosis [29].

Malaysians' colorectal cancer survival rates and related prognostic factors were documented in a prior study. After adjusting for age, gender, and ethnicity, Cox regression analysis revealed that staging at diagnosis, primary tumor size, lymph node involvement, and treatment approaches were independent survival predictors [32].

According to our research, high-risk patients who may require more monitoring or medical attention can be identified with the use of normal preoperative serum levels of CA125, CA19-9, and CEA. In conclusion, our research demonstrated how the tumor markers CA125, CA19-9, and CEA affect prognosis in patients with non-metastatic colorectal cancer.

Acknowledgment:
The authors would like to thank the Deanship of Graduate Studies and Scientific Research, Taif University, for funding this work.

Source of Funds:
The Deanship of Graduate Studies and Scientific Research, Taif University.

Declaration of Interest:
The authors declare no conflict of interest.

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