CA 19-9 and CEA Expression in Mucinous and Non-Mucinous Colorectal Carcinoma and the Impact on Prognosis and Clinicopathological Features

Hala S. E Alaa Edin[a*], Abd AlRahman Mohammad Foda[b,c], Elsamman MK[d], Eman T. Enan[b]

[a]Pathology Department, Faculty of Medicine, South Valley University, Qena, Egypt.
[b]Anatomic Pathology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt.
[c]Department of Pathology, General Medicine Practice Program, Batterjee Medical College, Jeddah 21442, Saudi Arabia.
[d]Internal Medicine Department, Faculty of Medicine, Sohag University, Sohag, Egypt.

Abstract

Background: One of the most prevalent cancers in the world and a major contributor to cancer-related mortality is colorectal cancer (CRC). Carbohydrate antigen CA 19-9 and Carcinoembryonic antigen (CEA) are adhesion molecules that play a role in cancer cell activity, and are used to assess patients with gastrointestinal tumors.

Objectives: Evaluation of CEA and CA19-9 expression in CRC, compare the mucinous and non-mucinous CRC expression, and correlate the findings with clinicopathological data.

Patients and methods: 150 cases CRC, 75 mucinous carcinoma (MA), 19 signet ring CRC, and 75 non-mucinous carcinoma. Tissue Microarray blocks were created and stained with CA19-9 and CEA.

Results: CEA expression was significantly linked to younger age, schistosomiasis, and histologic subtype in MA (P = 0.001, 0.005, and 0.010), CA19-9 was associated with smaller tumors, and lymphovascular invasion (P = 0.013, and 0.043) in MA. In NMA tumors, the CEA positivity was higher in ordinary adenocarcinoma than in adenocarcinoma with < 50% mucinous components (p = 0.010). Co-expression of CEA and CA19-9 was significant in MA (P = 0.033). Positive CEA expression correlated with improved disease-free (P = 0.014) and overall survival (P = 0.008) in MA cases only.

Conclusion: CEA and CA19-9 are prognostic markers in CRC. CEA is associated with younger age and schistosomiasis in MA, while CA19-9 correlates with smaller tumors and less lymphovascular invasion. Co-expression of these markers is characteristic of MA. Positive CEA expression predicts better survival in MA cases.

Keywords: Colorectal Carcinoma; CA19-9; Carcinoembryonic Antigen

DOI: 10.21608/SVUIJM.2025.384427.2177

*Correspondence halasalahedin@yahoo.com

Received: 15 June,2025.
Revised: 3 July, 2025.
Accepted: 19 July, 2025.
Published: 19 July, 2025

Cite this article as Hala S. E Alaa Edin, Abd AlRahman Mohammad Foda, Elsamman MK, Eman T. Enan.(2025). CA 19-9 and CEA Expression in Mucinous and Non-Mucinous Colorectal Carcinoma and the Impact on Prognosis and Clinicopathological Features. *SVU-International Journal of Medical Sciences*. Vol.8, Issue 2, pp: 247-258.

Introduction

Colon and/or rectal cancer, also known as colorectal cancer (CRC), ranks third in terms of cancer incidence worldwide and second in terms of cancer death, with numerous complex genetic and multifactorial etiology. Their main subtypes are sporadic, hereditary, and colitis-associated CRC. However, most cases of CRC develop from conventional adenoma via the suppressor pathway, while others via the serrated pathway or germline mutations in mismatch repair genes (Lynch Syndrome) **(Hossain et al., 2022).** CRC has several histological subtypes, each determined by the major component of cancer cells. However, adenocarcinoma is the most common subtype, with other subtypes including mucinous carcinoma, signet-ring cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma **(Li et al., 2019).**

Mucinous and signet ring cells are two specific histological subtypes of CRC with variable mucinous components (Kim et al., 2019). Mucinous colorectal carcinoma is an adenocarcinoma with at least 50% of its components as an extracellular mucin secretion. Mucinous colorectal carcinoma accounts for approximately 13% of all CRC cases and exhibits unique clinicopathological characteristics. It is usually more common in females, occurs at a younger age, affects the right semicolon, and has a poor prognosis **(Huang et al., 2021)**. On the other hand, signet ring colorectal carcinoma (SRCC) is defined as a tumor in which 50% or more of the cellular components are SRCC cells. These cells are distinguished by an abundance of intracytoplasmic mucin, which pushes the nucleus eccentrically and gives the cytoplasm a pale and ample appearance **(Nam et al., 2018)**.

Regarding the histologic classification of CRC, the mucinous and non-mucinous types are thought to play the most important roles in tumor biology. The mucinous type is considered the least common and the most difficult to study and evaluate. That is why the focus is on determining the distinction between the two and incorporating it into expanding knowledge about the development and prognosis of colorectal carcinoma (Park, et al, 2015). Tumor markers are chemical substances produced in response to tumors by tumor cells or their normal counterparts. They can be used for tumor screening, diagnosis and classification, prognosis and treatment monitoring, recurrence, and metastasis **(Duffy, 2013)**.

Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 have been used to diagnose gastrointestinal tumors under certain conditions **(Sekiguchi and Matsuda, 2020)**. CEA, an immunoglobulin family member, acts as an intracellular adhesion molecule and is frequently used in immunoserologic analyses of gastrointestinal neoplasms, particularly colonic and gastric neoplasms **(Johnson and Mahadevan, 2015)**. CEA serum concentrations of up to 5 ng/ml are considered normal; however, they may be higher in patients with ulcerative colitis and liver fibrosis, and they have been linked to well-differentiated adenocarcinomas. Additionally, an increase in CEA concentration for a few months after surgery indicates recurrence **(Nicholson et al., 2015; Jelski and Mroczko, 2020)**. CA 19-9 is an e-selectin ligand that promotes cancer cell adhesion to endothelial cells. It's also called sialyl Lewis-a (sLea), a known glycolipid and an O-linked glycoprotein found on cancer cell surface. CA 19-9 is synthesized via an abnormal pathway during its normal counterpart disialyl Lewis-a synthesis. **(Ballehaninna et al., 2013; Trinchera et al., 2017)**.

Serum CA 19-9 levels are also elevated in various malignant and non-malignant diseases. Hepatocellular carcinoma, cholangiocarcinoma, gastric carcinoma, and CRC cell lines are the most common malignant conditions. The non-malignant conditions include chronic viral hepatitis B and C, autoimmune

hepatitis, primary biliary cirrhosis, alcoholic steatohepatitis, and pancreatitis **(Şeber et al., 2019; Lee et al., 2020)**. However, CA19-9 is far more important in the prognosis of pancreatic cancer patients following surgery. Patients with normalized serum levels had a higher median survival rate **(George et al., 2021)**. In an algorithmic combination, serum levels of CEA and CA19-9 may help predict the prognosis of gastric carcinoma cases **(Wu et al., 2015; Reitz et al, 2015)**.

However, few studies have investigated the serum expression of CA 19-9 and CEA in CRC but not the tissue expression. The current study investigates the immunohistochemical expression of CA19-9 and CEA in mucinous and non-mucinous CRC tissues. In addition, we hope to correlate their expression levels and the disease's prognosis and clinicopathological manifestations.

Patients and methods

Over the last three years, the surgical pathology lab at the Gastroenterology Center in Mansoura, Egypt, has revised the files of all resected CRC cases. Mucinous CRCs were selected and revised. Cases with insufficient clinical data and those made up entirely of pools of mucin with very few epithelial cells were excluded. The selection criteria were met by 75 cases of mucinous carcinoma (MA). Fifty-six of which were mucoid adenocarcinoma (MuA) (tumor with a mucinous component >50%) and 19 were signet ring cell carcinoma (SRC) (SRCC). For comparison, 75 non-mucinous adenocarcinoma (NMA) cases were randomly chosen from the same period. Forty seven of the (NMA) cases were conventional adenocarcinoma (CA), and the remaining 28 were adenocarcinoma with less than 50% mucinous components (AMC). No neoadjuvant therapy was given to any of the patients.

Informed consent has been attained from the study participants to use the tumor tissues' paraffin blocks. The study methods were implemented according to the regulations and guidelines of the Medical Research Ethics Committee, Institutional Review Board (IRB) of Faculty of Medicine, Mansoura University, Mansoura, Egypt. The study was reviewed and approved with Code No.: R.22.12.1991.

Clinical criteria and histopathological assessment

The clinicopathological records of all cases were reviewed, and the slides were re-examined. The following factors are taken into consideration: age, gender, tumor characteristics including site, number, size, shape, histopathological type, tumor grade, depth of invasion (T), microscopic edges (pushing or infiltrating), lympho-vascular or perineural invasion, lymphocytic infiltration (peri-tumoral and intra-tumoral), the density of neutrophilic infiltrate, adjacent and distant mucosa, whether or not the tumor is arising on top of adenoma, number of involved regional lymph nodes (N), distant metastasis (M), pathological TNM staging, surgical cut margins (infiltrated by the tumor or free), associated schistosomiasis and any other findings.

Construction of tissue microarray (TMA)

The modified mechanical pencil tip method **(Foda, 2013)** was used to construct three manual TMA blocks. From each case, three 0.8 mm diameter-representative cores were punched out. 4 µm-thick- sections from the TMA block were prepared for routine Hematoxylin and Eosin staining. Other sections were prepared for Immunostaining using charged slides.

Immunohistochemistry

TMA blocks were sectioned into 4µm thick sections after trimming. Deparaffinized sections were then incubated for 30 minutes in 0.3% H_2O_2 in methanol before being microwave-heated for another thirty minutes in EDTA buffer solution, pH 8.0. Then, using mouse monoclonal antibodies against anti-human CA19-9 Ab (Clone 121SLE, Cat. #760-2609, predilute ready-to-use for IHC,

Ventana) and mouse monoclonal anti-human CEA Ab (Clone CEA31, Cat. #760-4594, ready-to-use for IHC, Ventana), an indirect immunoperoxidase technique was utilized. The primary antibody was left to react for thirty minutes at room temperature. The ImmunoPure Ultra-Sensitive ABC Peroxidase (Catalog no. 32052; Thermo Scientific, UK) method was performed, with diaminobenzidine as the chromogen. The slides were examined with Olympus CX31 light microscope and photographs taken with a PC-driven digital camera (Olympus E-620).

Evaluation of IHC

For each case, the CEA and CA19-9 expressions were assessed semi-quantitatively. As previously described, immunoreactivity was considered positive for each core if 10% or more of the tumor was stained with moderate or greater intensity **(Loy et al., 2013)**. The loss of tissue core during processing or an unrecognizable tumor in the core causes the case to be excluded from the analysis. The TMAs were scored independently, and any discrepancies were re-examined to reach a consensus score for each core.

Statistical analysis

SPSS 24.0 for Windows was used to analyze the data (SPSS Inc, IBM, Chicago, Illinois). The $\chi 2$ (Chi-square) test was performed to compare the clinical and histopathological criteria between the MA and NMA groups and to determine the significance of CEA and CA 19-9 expression in relation to these criteria within each group. The Kaplan-Meier test was used for analyzing survival data. The log-rank test was used for comparing the survival curves. Cox proportional hazard models were used for multivariate analysis. For all tests, a 2-tailed $P \leq 0.05$ was considered statistically significant.

Results

The study included 150 CRC cases; 93 men and 57 women aged between 20 to 80 years (mean, 52.7 years). (**Table. 1, 2)** summarize the clinical and histopathological characteristics of the MA and NMA cases and the expression of CEA and CA19-9.

MA was significant in younger patients ($P = 0.017$) with greater invasion depth ($P = 0.008$), higher LN metastasis frequency ($P = 0.008$), and fewer peri-tumoral and intra-tumoral neutrophils ($P < 0.001$) than NMA. There were insignificant variatin between the MA and NMA groups for the remaining factors. Furthermore, NMA showed a non-significant difference in CEA and CA-19 expression compared to MA ($p = 0.054$) (**Table. 3**) (**Fig.1**).

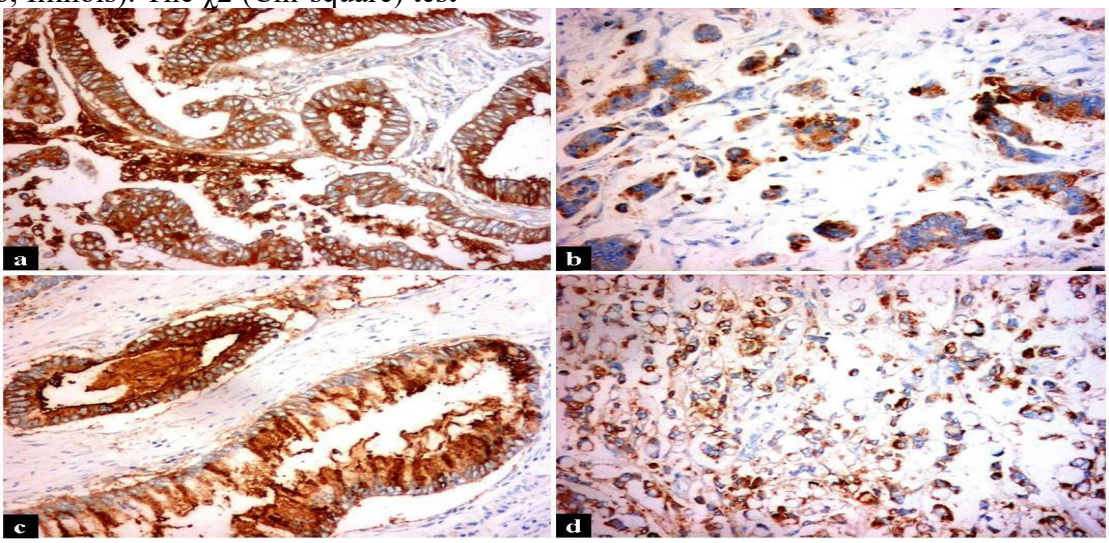

Fig. 1. (a) Strong CEA staining in a case of conventional adenocarcinoma (b) Moderate CEA staining in a case of mucinous adenocarcinoma (c) Strong CA19-9 staining in a

case of conventional adenocarcinoma (d) Moderate CA19-9 staining in a case of signet ring cell carcinoma (x200).

The relationship between CEA expression and clinicopathological and histological features of NMA and MA is depicted in (**Table.1**). CEA expressions in MA and age at presentation differed significantly (p = 0.001). CEA was found to be more prevalent in patients under the age of 50. Similarly, there was a significant (p = 0.005) association between schistosomiasis infestation and CEA expression in MA cases. However, CEA positivity was found in all schistosomiasis cases. Furthermore, there was a significant difference (p = 0.010) in CEA expression and the histologic subtype of the NMA tumor. The CEA positivity was higher in ordinary adenocarcinoma than in adenocarcinoma with < 50% mucinous components (**Table.1**).

Table 1. Relation of CEA expression with clinic-pathological and histological parameters within NMA and MA groups

Variable	NMA		MA	
	CEA Negative (N=15)	CEA Positive (N=56)	CEA Negative (N=26)	CEA Positive (N=47)
	No. (%)	No. (%)	No. (%)	No. (%)
Age (y)				
- < 50	07 (46.7%)	18 (32.1%)	04 (15.4%)	26 (55.3%)
- ≥ 50	08 (53.3%)	38 (67.9%)	22 (84.6%)	21 (44.7%)
P Value	0.296		**0.001***	
Gender				
- Male	09 (60.0%)	36 (64.3%)	16 (61.5%)	27 (57.4%)
- female	06 (40.0%)	20 (35.7%)	10 (38.5%)	20 (42.6%)
P Value	0.760		0.734	
Gross picture				
- Fungating	11 (73.3%)	21 (37.5%)	11 (42.3%)	14 (29.8%)
- Ulcerating	03 (20.0%)	15 (26.8%)	07 (26.9%)	20 (42.5%)
- Annular	01 (06.7%)	20 (35.7%)	08 (30.8%)	13 (27.7%)
P Value	**0.031***		0.381	
Multiplicity				
- Negative	13 (86.7%)	49 (87.5%)	24 (92.3%)	44 (93.6%)
- Positive	02 (13.3%)	07 (12.5%)	02 (07.7%)	03 (06.4%)
P Value	0.931		0.832	
Size				
- < 06cm	07 (46.7%)	36 (64.2%)	14 (53.8%)	22 (46.8%)
- > 06cm	08 (53.3%)	20 (35.8%)	12 (46.2%)	25 (53.2%)
P Value	0.215		0.360	
Histologic subtype				
- Ordinary adenocarcinoma	05 (33.3%)	39 (69.6%)		
- With mucinous component <50%	10 (66.7%)	17 (30.4%)		
- Mucoid adenocarcinoma			19 (73.1%)	35 (74.5%)
- Signet ring adenocarcinoma			07 (26.9%)	12 (25.5%)
P Value	**0.010***		0.897	
Lymphovascular emboli				
-Negative	07 (46.7%)	20 (35.8%)	11 (42.3%)	12 (25.5%)
-Positive	08 (53.3%)	36 (64.2%)	15 (57.7%)	35 (74.5%)
P Value	0.438		0.140	

Associated schistosomiasis -Negative -Positive	15(100.0%) 0 (0%)	46 (82.1%) 10 (17.9%)	26 (100.0%) 0 (0%)	35 (74.5%) 12 (25.5%)
P Value	0.077		**0.005***	
Peri- and intra-tumoral lymphocytic and neutrophilic infiltration -Negative -Positive	15 (100%) 0 (0%)	52 (92.8%) 04 (07.2%)	24 (92.3%) 02 (07.7%)	47 (100%) 0 (0%)
P Value	0.287		0.124	

* P ≤ 0.05 is significant. NMA: Non-mucinous adenocarcinoma, MA: Mucinous adenocarcinoma, CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

There was a significant (p = 0.013) correlation between tumor size and CA19-9 expression in MA cases. CA19-9 was more abundant in tumors less than 6 cm in size. CA19-9 expression was also significantly (p = 0.043) associated with lymphovascular invasion of the cancer. The more CEA expression there was, the more lymphovascular emboli were found. However, no significant relationship was discovered between CA19-9 expression and clinicopathological or histological parameters in NMA cases, as shown in (**Table.2**).

Table 2. Relation of CA19-9 expression with clinic-pathological and histological parameters within NMA and MA groups

Variable	NMA		MA	
	CA-19-9 Negative (N=47)	**CA-19-9 Positive (N=23)**	**CA-19-9 Negative (N=39)**	**CA-19-9 Positive (N=32)**
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**
Age (y) - < 40 - ≥ 40	06 (12.8%) 41 (87.2%)	03 (13.0%) 20 (87.0%)	11 (28.2%) 28 (71.8%)	11(34.4%) 21 (65.6%)
P Value	0.974		0.576	
Gender - Male - female	32 (68.1%) 15 (31.9%)	11 (47.8%) 12 (52.3%)	25 (64.1%) 14 (35.9%)	17 (53.1%) 15 (46.9%)
P Value	0.122		0.467	
Gross picture - Fungating - Ulcerating - Annular	22 (46.8%) 11 (23.4%) 14 (29.8%)	10 (43.5%) 06 (26.1%) 07 (30.4%)	13 (33.3%) 14 (35.9%) 12 (30.8%)	10 (31.3%) 13 (40.6%) 09 (28.1%)
P Value	0.958		0.919	
Multiplicity - Negative - Positive	39 (83.0%) 8 (17.0%)	22 (95.6%) 01 (4.4%)	37 (94.8%) 02 (5.2%)	29 (90.6%) 03 (9.4%)
P Value	0.254		0.652	
Size - < 06cm - > 06cm	27 (57.4%) 20 (42.6%)	15 (65.2%) 08 (34.8%)	14 (35.9%) 25 (64.1%)	21 (65.6%) 11 (34.4%)
P Value	0.533		**0.013***	

Histologic subtype - Ordinary adenocarcinoma - with mucoid activity < 50% - Mucoid adenocarcinoma - Signet ring adenocarcinoma	29 (61.7%) 18 (38.3%)	14 (60.9%) 09 (39.1%)	31(79.5%) 08 (20.5%)	21 (65.6%) 11 (34.4%)
P Value	0.946		P=0.189	
Lymphovascular emboli -Negative -Positive	17 (36.2%) 30 (63.8%)	10 (43.5%) 13 (56.5%)	16 (41.0%) 23 (59.0%)	06 (18.8%) 26 (81.3%)
P Value	0.555		**0.043***	
Associated schistosomiasis -Negative -Positive	42 (89.4%) 05 (10.6%)	18 (43.5%) 05 (56.5%)	32 (82%) 07 (18%)	27 (84.4%) 05 (15.6%)
P Value	0.279		1.000	
Peri- and intra-tumoral lymphocytic and neutrophilic infiltration -Negative -Positive	44 (93.6%) 03 (06.4%)	22 (95.7%) 01 (04.3%)	39 (100.0%) 0	30 (93.8%) 02 (06.3%)
P Value	0.730		0.113	

* P ≤ 0.05 is significant.NMA: Non-mucinous adenocarcinoma, MA: Mucinous adenocarcinoma, CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen.

Table 3. CEA and CA19-9 expression in NMA and MA

Markers	NMA	MA	P value
	No. (%)	No. (%)	
CEA expression -Negative -Positive	15 (21.1%) 56 (78.9%)	26 (35.6%) 47 (64.4%)	**0.054**
CA19-9 expression -Negative -Positive	47 (67.1%) 23 (32.9%)	39 (54.9%) 32 (45.1%)	0.137

* P ≤ 0.05 is significant. NMA: Non-mucinous adenocarcinoma, MA: Mucinous adenocarcinoma, CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen.

CA-19-9 and CEA co-expression were significant (p = 0.033) in MA. Unlike NMA, most cases showed co-expression of both markers (**Table.4**).

Table 4. Interrelation between CEA and CA19-9 expression in NMA and MA cases

Tumor	Marker	CEA expression		P=value
		Negative	Positive	
NMA	**CA-19-9 expression** Negative Positive	12 (80.0%) 03 (20.0%)	34 (63.0%) 20 (37.0%)	0.216
MA	**CA-19-9 expression** Negative Positive	18 (72.0%) 07 (28.0%)	21 (45.7%) 25 (54.3%)	**0.033***

* P ≤ 0.05 is significant. NMA: Non-mucinous adenocarcinoma, MA: Mucinous adenocarcinoma, CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

CEA and CA19-9 expression associations with DFS and OS within the NMA and MA groups were also studied (**Table.5**). Positive CEA expression was associated with significantly better DFS (p = 0.014) and OS (p=0.008) only in MA cases (**Fig.2**).

Table 5. Relation of CEA and CA19-9 expression with DFS and OS within NMA and MA groups

Expression of		3 yr DFS	Median DFS (months)	P value	5 years OS	Median OS (months)	P value
CEA in NMA	Negative	46.7%	40.6	0.39	53.3%	11.658	0.383
	Positive	50.0%	43.3		53.6%	12.784	
CEA in MA	Negative	26.9%	11.2	**0.014***	26.9%	15.0	**0.008***
	Positive	40.4%	25.6		44.7%	31.5	
CA19-9 in NMA	Negative	59.6%	11.2	0.062	59.6%	47.1	0.068
	Positive	34.8%	25.6		39.1%	28.9	
CA19-9 in MA	Negative	38.5%	18.5	0.83	41.0%	29.2	0.060
	Positive	34.4%	16.4		34.4%	19.6	

* P ≤ 0.05 is significant. NMA: Non-mucinous adenocarcinoma, MA: Mucinous adenocarcinoma, CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen. EGFR: Epidermal growth factor receptor, DFS: Disease-free survival, OS: Overall survival

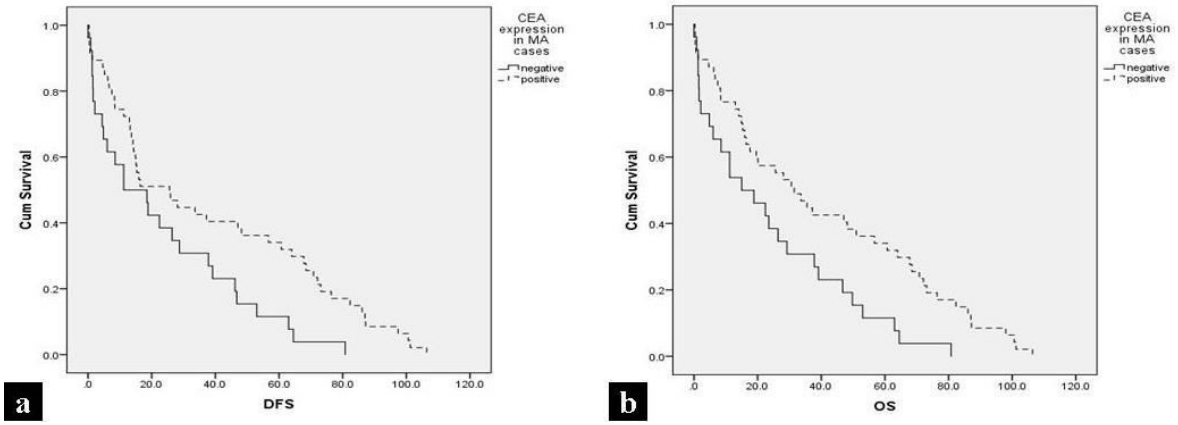

Fig. 2. Relation of CEA expression to disease-free (DFS) (a) and overall survival (OS) (b) in mucinous colorectal carcinoma patients.

Discussion

CRC is a common health issue worldwide today, and it is regarded as the third-listed common malignancy and the second in mortality rates. CRC is more common in developed countries and is becoming more prevalent in middle- and low-income countries **(Xi and Xu, 2021)**. The 5-year survival rate of CRC varies with gender, and different factors, such as the diagnosed cancer stage and the quality of the provided public health services, have been attributed to this variation **(Cardoso et al., 2022)**. As a result, it is widely accepted that earlier detection of CRC improves patient outcomes. As a result, the emphasis has shifted to developing a better tool for earlier diagnosis, and tumor markers' role and benefit have come into play **(Jelski and Mroczko, 2020)**.

CEA was the first marker identified as elevated in CRC and is a reliable predictor of postoperative CRC prognosis **(Zhang et al., 2020)**. Furthermore, increased CA 19-9 expression was considered a risk factor for extrahepatic metastasis in colorectal carcinoma patients with liver metastasis. CEA indicates early detection of hepatic metastasis in CRC patients **(Lee et al., 2020)**. It was reported that the levels of CEA and CA 19-9 expressed in signet ring CRC were 100% and were equal to the percentage of

expression in normal colonic tissue **(Lakemeyer et al., 2021)**. This contradicts the current study, which states that only 34.4% of the patients had high CA 19-9 expression.

In contrast, another study reported that the high serum levels of CEA and CA 19-9 were not correlated with mucus production (meaning there is no difference between mucinous and non-mucinous adenocarcinoma), tumor stage, abnormal liver function, and T level **(Marks et al., 2015)**. The current study reports a higher expression of CEA antigen in NMA than in MA, with a higher expression in ordinary adenocarcinoma compared to mucinous adenocarcinoma. It was also noted that a higher expression of CEA antigen with annular pattern of growth and a higher expression of CA 19-9 in smaller cancer (less than 6 cm). Furthermore, Naicker et. Al **(Naicker et al., 2021)** reported the same finding regarding the depth of invasion, but they found non-significant difference considering the size of the tumor and the expression of CA 19-9.

Our results showed that most CRC patients with positive CEA expression were under the age < 50 years. This contrasts with other findings **(Feng et al., 2017; Lakemeye et al., 2021)** reported that most cases of colorectal carcinoma with elevated CA 19-9 and CEA were found in patients ≥ 65 years. Moreover, this work indicated that cases with higher levels of CEA expression, either histologically or in the serum, had an increased incidence of lymphatic spread, as previously reported by other studies **(Bray et al., 2022; Wu and Gu, 2020)**. Furthermore, several studies **(Shin et al., 2019; Lee et al, 2020)** linked higher serum CA 19-9 levels to a higher lymphovascular invasion prevalence of colorectal carcinoma into surrounding tissue, consistent with our findings.

Kim et al., 2019 found a link between high CEA expression levels and elevated levels of lymphocytes and neutrophils in colorectal carcinoma. Conversely, the current study showed no relation between CEA expression levels and concentrated on peritumoral and intratumoral lymphocytes and neutrophils infiltration. Our findings also revealed a strong link between schistosomiasis and susceptibility to CRC and its complications. In addition, we discovered that all patients with CRC and schistosomiasis had high levels of CEA expression. However, similar findings have been reported in previous studies **(Abdalkareem and Yin, 2019; Wang et al., 2020)**. Higher CA 19-9 levels were also linked to an increased chance of recurrence and a lower 5-year recurrence-free survival **(Coppola et al., 2022)**.

Furthermore, high CEA and CA 19-9 levels were linked to a poor prognosis and decreased survival in CRC, as well as pancreatic and gall bladder cancer **(Hata et al., 2022; Ermiah et al., 2022; 40. Sachan et al., 2020)**. However, combined CA 19-9 and CEA could be used as markers to identify advanced CRC stages **(Lakemeyer, et al., 2021)**. This finding is consistent with the current study, which discovered that the combination is more prevalent in mucinous colorectal carcinoma. Other researchers, on the other hand, reported that CEA and CA 19-9 are each non-specific serum biomarkers elevated in association with various malignant and non-malignant conditions **(Kankanala and Mukkamalla, 2023; Kim et al., 2020)**. As a result, their combination could be helpful in cancer screening, diagnosis, and prognosis.

Conclusion

CEA and CA 19-9 expression are essential prognostic tools in CRC. CEA expression was associated with NMA, being younger with schistosomiasis. Smaller tumors with less lymphovascular invasion usually accompany CA 19-9 expression. CEA and CA 19-9 were co-expressed and had a significant relationship in MA but not in NMA. Better DFS and OS were only significantly associated with positive CEA expression in MA cases.

Acknowledgment: The authors would like to thank all the academic and technical staff who provided administrative and technical support.
Funding: No external funding sources are relevant to this submission.
Competing interests: The authors declare that they have no conflict of interest.
Availability of data and material: The dataset generated in the current study is available from the corresponding author upon request.
Ethical Approval: The study was reviewed and approved by the members of the Medical Research Ethics Committee, Institutional Review Board (IRB), Faculty of Medicine, Mansura University, Mansura, Egypt, with Code No.: R.22.12.1991.

Informed consent was obtained from all the study participants to use the tumor tissues' paraffin blocks.
Authors' contribution: All authors have read and approved the manuscript. The authors declare that all data were generated in-house, and no paper mill was used.

Research conception and design: AAMF, ETE and HSEA; experiments: AAMF, ETE and HSEA; statistical analysis of the data: AAMF, ETE and HSEA; interpretation of the data: AAMF, ETE and HSEA; writing of the manuscript: All authors; work revision and final approval: AAMF, ETE and HSEA.
Conflict of interest: The authors could declare No conflict of interest.
References

- **Abdalkareem EA, Yin KB. (2019).** A Current Perspective of Schistosomiasis in Association with Colorectal Carcinogenesis. The Open Infectious Diseases Journal, 11:7–12.
- **Ballehaninna UK, Ronald S, Chamberlain RS. (2012)**. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence-based appraisal. Journal of Gastrointestinal Oncology, 3(2): 105–119.
- **Bray AW, Duan R, Malalur P, Drusbosky L, Gourdin T, Hill E, et al. (2022)**. Elevated serum CEA is associated with liver metastasis and distinctive circulating tumor DNA alterations in patients with castration resistant prostate cancer. The Prostate, 82: 1264–1272.
- **Cardoso R, Guo F, Heisser T, De Schutter H, Van Damme N, Nilbert MC, et al. (2022)**. Overall and stage-specific survival of patients with screen-detected colorectal cancer in European countries: A population-based study in 9 countries. The Lancet Regional Health – Europe, 21: 100458.
- **Coppola A, La Vaccara V, Farolfi T, Fiore M, Cammarata R, Ramella S, et al. (2022)**. Role of CA 19.9 in the Management of Resectable Pancreatic Cancer: State of the Art and Future Perspectives. Biomedicines, 10: 2091.
- **Duffy MJ. (2013)**. Tumor Markers in Clinical Practice: A Review Focusing on Common Solid Cancers. Medical Principles and Practice, 22: 4–11.
- **Ermiah E, Eddfair M, Abdulrahman O, Elfagieh M, Jebriel A, Al-Sharif M, et al. (2022).** Prognostic value of serum CEA and CA19-9 levels in pancreatic ductal adenocarcinoma. Molecular Clinical Oncology 17: 126.
- **Feng F, Tian Y, Xu G, Liu Z, Liu S, Zheng G, et al. (2017)**. Diagnostic and prognostic value of CEA, CA19–9, AFP and CA125 for early gastric cancer. BioMed Central Cancer, 17: 737.
- **Foda AA. (2013)**. No-cost manual method for preparation of tissue microarrays having high quality comparable to semiautomated methods. Applied Immunohistochemistry & Molecular Morphology, 21(3): 271–274.
- **George B, Kent M, Surinach A, Lamarre N, Cockrum P. (2021)**. The Association of Real-World CA 19-9 Level Monitoring Patterns and Clinical Outcomes Among Patients With

Metastatic Pancreatic Ductal Adenocarcinoma. Frontiers in Oncology, 11: 754687.

- **Hata T, Chiba K, Mizuma M, Masuda K, Ohtsuka H, Nakagawa K. (2022)**. Levels of tumor markers CEA/CA 19–9 in serum and peritoneal lavage predict postoperative recurrence in patients with pancreatic cancer. Annals of Gastroenterological Surgery, 6: 862–872.
- **Hossain MS, Karuniawati H, Jairoun AA, Urbi Z, Ooi DJ, John A, et al. (2022).** Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers, 14(7): 1732.
- **Huang A, Yang Y, Shi JY, Li YK, Xu JX, Cheng Y, et al. (2021)**. Mucinous adenocarcinoma: A unique clinicopathological subtype in colorectal cancer. World Journal of Gastrointestinal Surgery, 13(12): 1567–1583.
- **Jelski W, Mroczko B. (2020).** Biochemical Markers of Colorectal Cancer – Present and Future. Cancer Management and Research, 12: 4789–4797.
- **Johnson B, Mahadevan D. (2015)**. Emerging Role and Targeting of Carcinoembryonic Antigen-related Cell Adhesion Molecule 6 (CEACAM6) in Human Malignancies. Clinical Cancer Drugs, 2(2): 100–111.
- **Kankanala VL, Mukkamalla SKR. (2023).** Carcinoembryonic Antigen. In: StatPearls \[Internet]. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK578172/
- **Kim H, Jung HI, Kwon SH, Bae SH, Kim HC, Baek MJ, et al. (2019)**. Preoperative neutrophil-lymphocyte ratio and CEA is associated with poor prognosis in patients with synchronous colorectal cancer liver metastasis. Annals of Surgical Treatment and Research, 96(4): 191–200.
- **Kim H, Kim B-H, Lee D, Shin E. (2019)**. Genomic alterations in signet ring and mucinous patterned colorectal carcinoma. Pathology – Research and Practice, 215(10): 152566.
- **Kim S, Park BK, Seo JH, Choi J, Choi JW, Lee CK**, **et al. (2020).** Carbohydrate antigen 19-9 elevation without evidence of malignant or pancreatobiliary diseases. Scientific Reports 10, 8820.
- **Lakemeyer L, Sander S, Wittau M, Henne-Bruns D, Kornmann M, Lemke J. (2021)**. Diagnostic and Prognostic Value of CEA and CA19-9 in Colorectal Cancer. Diseases, 9(1): 21.
- **Lee T, Teng TZJ, Shelat VG. (2020)**. Carbohydrate antigen 19-9 – tumor marker: Past, present, and future. World Journal of Gastrointestinal Surgery, 12(12): 468–490.
- **Li C, Zheng H, Jia H, Huang D, Gu W, Cai S, et al. (2019)**. Prognosis of three histological subtypes of colorectal adenocarcinoma: A retrospective analysis of 8005 Chinese patients. Cancer Medicine, 8(7): 3411–3419.
- **Loy TS, Sharp SC, Andershock CJ, Craig SB. (1993).** Distribution of CA 19-9 in adenocarcinomas and transitional cell carcinomas. An immunohistochemical study of 527 cases. American Journal of Clinical Pathology, 99(6): 726–728.
- **Marks EI, Brennan M, El-Deiry WS. (2015).** Correlation of CEA but not CA 19-9 as serum biomarkers of disease activity in a case of metastatic rectal adenocarcinoma. Cancer Biology & Therapy, 16(8): 1136–1139.
- **Naicker YD, Moolla Z, Madiba T. (2021)**. The role of carcinoembryonic antigen as an assessment tool for predicting disease severity among patients with colorectal cancer in resource-poor setting of Kwazulu-

Natal, South Africa. Pan African Medical Journal, 39: 185.

- **Nam JY, Oh BY, Hong HK, Bae JS, Kim TW, Ha SY, et al. (2018).** Molecular Characterization of Colorectal Signet-Ring Cell Carcinoma Using Whole-Exome and RNA Sequencing. Translational Oncology, 11(4): 836–844.
- **Nicholson BD, Shinkins B, Pathiraja I, Roberts NW, James TJ, Mallett S, et al**. **(2015).** Blood CEA levels for detecting recurrent colorectal cancer. Cochrane Database of Systematic Reviews, (12): CD011134.
- **Park JS, Huh JW, Park YA, Cho YB, Yun SH, Kim HC, et al. (2015)**. Prognostic comparison between mucinous and non-mucinous adenocarcinoma in colorectal cancer. Medicine (Baltimore), 94(15): e658.
- **Reitz D, Gerger A, Seidel J, Kornprat P, Samonigg H, Stotz M, et al. (2015)**. Combination of tumour markers CEA and CA19-9 improves the prognostic prediction in patients with pancreatic cancer. Journal of Clinical Pathology, 68: 427–433.
- **Sachan A, Saluja SS, Nekarakanti PK, Nimisha, Mahajan B, Nag H, et al. (2020)**. Raised CA19–9 and CEA have prognostic relevance in gallbladder carcinoma. BioMed Central Cancer, 20: 826.
- **Sekiguchi M, Matsuda T. (2020)**. Limited usefulness of serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for gastrointestinal and whole-body cancer screening. Scientific Reports, 10(1): 18202.
- **Şeber S, Güzel S, Yılmaz A, Kara SP, Yetişyiğit T. (2019)**. Causes of Elevated Levels of Serum CA 19.9 in Patients without Prior Diagnosis of Malignant Disease. Southern Clinics of Istanbul Eurasia, 30(3): 198–203.
- **Shin JK, Kim HC, Lee WY, Yun SH, Cho YB, Huh JW, et al. (2019)**. High preoperative serum CA 19-9 levels can predict poor oncologic outcomes in colorectal cancer patients on propensity score analysis. Annals of Surgical Treatment and Research, 96(3): 107–115.
- **Trinchera M, Aronica A, Dall'Olio F. (2017)**. Selectin Ligands Sialyl-Lewis a and Sialyl-Lewis x in Gastrointestinal Cancers. Biology, 6(1): 16.
- **Wang Z, Du Z, Liu Y, Wang W, Liang M, Zhang A, et al. (2020)**. Comparison of the clinicopathological features and prognoses of patients with schistosomal and nonschistosomal colorectal cancer. Oncology Letters, 19(3): 2375–2383.
- **Wu L, Huang P, Wang F, Li D, Xie E, Zhang Y, et al. (2015)**. Relationship between serum CA19-9 and CEA levels and prognosis of pancreatic cancer. Annals of Translational Medicine, 3(21): 328.
- **Wu S, Gu W. (2020**). Association of T Stage and Serum CEA Levels in Determining Survival of Rectal Cancer. Frontiers in Medicine, 6: 270.
- **Xi Y, Xu P. (2021)**. Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology, 14(10): 101174.
- **Zhang C, Zheng W, Lv Y, Shan L, Xu D, Pan Y, et al. (2020)**. Postoperative carcinoembryonic antigen (CEA) levels predict outcomes after resection of colorectal cancer in patients with normal preoperative CEA levels. Translational Cancer Research, 9(1): 111–118.