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Serum CEA Level in Predicting Liver Metastases of Colorectal Cancer Among Young Adult Patients

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Abstract

Introduction: Incidence and mortality of CRC are currently increasing in those under 50 years. The study aims to determine the predictive value of serum CEA levels as the liver metastases predictor of colorectal cancer (CRC) in young adults.
Methods: A cross-sectional study was conducted using secondary data (patient medical records) from 2015–to 2021. Patients aged <50 years who were diagnosed histopathologically with primary colorectal cancer at dr. Cipto Mangunkusumo General Hospital (CMGH) were recruited. We excluded patients with a history of other malignancies, who had undergone operative management for colorectal cancer, and preexisting liver disease. The outcome of this study is the cut-off of the CEA value obtained by the ROC curve and the sensitivity and specificity of the CEA value in predicting CR liver metastases.
Results: Out of 181 subjects enrolled, a total of 43.6% were female. Fifty-nine subjects (32.6%) had liver metastases. The CEA level of the metastases group was 208.1 (2.1–12503.2) ng/mL; this was much higher than the non-metastases group, which was 6.27 (0.8– 1099.4) ng/mL (p <0.001). The AUC value was at 0.904, and the CEA level cut-off was 38.765 ng/mL (Youden's Index = 1.718). The sensitivity and specificity were 91.53% (91.5 CI, 81.32%– 97.19%) and 80.3% (72.16%– 86.97%), respectively. The odds ratio of young colorectal cancer patients having liver metastases was 44.10 (95% CI, 15.92–122.20).
Conclusion: CEA level ≥38.765 ng/mL has good sensitivity and specificity in predicting liver metastases among young adults with CRC.

Key words: carcinoembryonic antigen; colorectal cancer; prognostic study; young adult

Introduction

Colorectal cancer (CRC) is a malignancy of the colon and rectum that almost always begins with polyps.[1] Colorectal cancer is the third most common cancer in Indonesia, following breast and cervical cancer.[2] Colorectal cancer survival rates for stages I, IIA, IIB, IIIA, IIIB, IIIC, and IV are 92%, 87%, 65%, 90%, 72%, 53%, and 12%.[2] Based on Jeo's (2020) study, the five-year survival rate for colorectal cancer in CMGH was 43%.[3] Factors that influence the five-year survival of colorectal cancer patients are metastases, degree of pathological differentiation, tumor location, obstruction, and the type of treatment.[4,5] Incidence and mortality of CRC are currently decreasing in patients aged over 50 years but increasing in those under 50 years. Most cases of colorectal cancer at young age occur sporadically and are associated with environmental and behavioral backgrounds, although the exact etiology remains uncertain. Colorectal cancer often metastasizes to bone, lung, brain, and liver, with hepatic metastases occurring in 80%.[6] Appropriate staging will significantly influence the choice of treatment.

According to the National Guidelines for Colorectal Cancer Medical Services in Indonesia, the diagnosis of colorectal cancer starts by looking at clinical signs and symptoms, digital rectal examination, and supporting examinations such as endoscopy, double-contrast barium enema, and CT colonography. Another supporting examination that can be used is ultrasound, but the results are very dependent on the operator's assessment.[7] A more objective but practical method in predicting liver metastases need to be elaborated.

Carcinoembryonic antigen (CEA) is one of the oldest tumor markers. Increased CEA levels are associated with cancers of the gastrointestinal, breast, respiratory and genitourinary systems.[8] Studies from Alam et al. 2020 concluded that preoperative CEA levels >12 ng/mL can provide an excellent predictive value for liver metastases with an accuracy rate of 85.3%.[9] The minor cut-off was proposed by the study of Lalosevic et al. 2017 where CEA levels of 3.5 ng/mL are referred to as a marker of liver metastases.[10] Different cut-off values are determined by the number of study subjects and population characteristics. So far, there is no research on the cut-off of CEA values in the young age group, and there is a trend of increasing CRC incidence in young adults. Therefore, determining the CEA cut-off value as an indicator of liver metastases in CRC in young adult patients is required.

Methods

The study was conducted cross-sectionally to investigate the prospective of preoperative CEA as a predictive factor for colorectal cancer metastases in young adults. Data obtained from the medical record unit at dr. Cipto Mangunkusumo General Hospital (CMGH), Jakarta, from January 2015 to September 2021. The inclusion criteria in the study were 1) histopathologically diagnosed primary colorectal cancer, 2) aged between 18–50 years old, 3) the metastatic status of colorectal cancer, which is known intraoperatively, and 4) CEA level was measured and recorded in the medical record. We excluded patients with a history of other malignancies, patients who had undergone operative management for their colorectal cancer, and patients who had a primary malignancy of the liver or other liver disease (hepatitis, cirrhosis of the liver, or fatty liver). CEA serum level used was those before the patient underwent treatment and were categorized into two classes (dichotomous) according to the cut-off to assess liver metastases in colorectal cancer patients. This CEA value was compared to the status

of liver metastases, which were obtained from radiological examination (abdominal CT-scan) and intraoperative findings. In addition, other variables (metastatic hepatic status, smoking status, comorbid disease, stage, gender, age, and nutritional status) were descriptively presented. Normality distribution of CEA levels which was numeric, were analyzed to the categorical hepatic metastasis status. An unpaired comparative test of two parametric variables (unpaired T-test) was performed, and the Mann-Whitney test was used when the data were not normally distributed. In contrast, a chi-square test or Fisher's exact test was used for categorical data. The p-value, which shows a significance was 0.05.

The cut-off point was determined using the Youden index, obtained using the receiver operating characteristic (ROC) curve, looking for the highest sensitivity and specificity. The committee of ethics approved the study.

Results

In this study, a total of 181 subjects enrolled comprised 79 (43.60%) females and 102 (56.40%) males with a median age of 39 (18-49) years. The median weight and height of the subjects were 52 (29-102) kg and 160 (143-180) cm, respectively. Seventeen (9.40%) subjects reported having comorbidities, with the proportions of each comorbidity described in Table 1.

Table 1. Subject's characteristics

	n	Proportion
Gender		
– Female	79	43.60%
– Male	102	56.40%
Comorbidity		
– No	164	90.60%
– Yes	17	9.40%
Asthma bronchial		
– No	176	97.20%
– Yes	5	2.80%
Hypertension		
– No	171	94.50%
– Yes	10	5.50%
Diabetes Mellitus		
– No	180	99.40%
– Yes	1	0.60%
Smoking		
– No	139	76.80%
– Yes	42	23.20%
Tumor		
T		
– T1	1	0.60%
– T2	20	11.00%
– T3	67	37.00%
– T4	93	51.40%
N		
– N0	56	30.90%
– N1	87	48.10%
– N2	38	21.00%
M		
– M0	92	50.80%
– M1	89	49.20%
Liver metastases		
– No	122	67.40%
– Yes	59	32.60%

Tumor sizes in most subjects were T3 (51.40%) and 20 (11.00%) subjects with T1. Metastasis in <4 regional lymph nodes was found in 87 (48.10%) subjects (N1). Metastases in more than three lymph nodes were reported in 38 (21.00%) subjects. Distant metastases were found in 89 (49.20%) subjects (Table 2.)

Table 2. Subjects' characteristics based on liver metastases

	Groups		p-value
	Non-metastases (n = 122)	Metastases (n = 59)	
Age [median (min–max)]	39.5 (18–49)	39 (18–49)	0.489
Weight [median (min-max)]	54 (33–102)	47 (29–74)	0.171
Height [median (min-max)]	160 (145–177)	160 (143–180)	0.382
Gender			0.472
– Female [n (%)]	51 (41.80)	28 (47.50)	
– Male [n (%)]	71 (58.20)	31 (52.50)	
Comorbidity [n (%)]	13 (10.70)	4 (6.80)	0.402
Asthma bronchial [n (%)]	4 (3.30)	1 (1.70)	1.000
Hypertension [n (%)]	8 (6.60)	2 (3.40)	0.502
Diabetes mellitus [n (%)]	0 (0.00)	1 (1.70)	0.326
Smoking [n (%)]	33 (27.00)	9 (15.30)	0.078
T			0.010
– T1 [n (%)]	1 (0.80)	0 (0.00)	
– T2 [n (%)]	18 (14.80)	2 (3.40)	
– T3 [n (%)]	50 (41.00)	17 (28.80)	
– T4 [n (%)]	53 (43.40)	40 (67.80)	
N			0.110
– N0 [n (%)]	48 (39.30)	8 (13.60)	
– N1 [n (%)]	56 (45.90)	31 (52.50)	
– N2 [n (%)]	18 (14.80)	20 (33.90)	

The median age of subjects without metastases was 39.5 (18-49) years, while in the metastases group was 39 (18-49) years and showed a difference with a p-value of 0.489. The weight and height variables show a difference between the metastases and non-metastases groups with a p-value of 0.171 and 0.382, respectively. The males were predominant in the two groups. i.e., 31 subjects (52.50%) in the metastases group and 71 subjects (58.20%) in non-metastases group.

A total of 40 subjects (67.80%) in the metastases group first presented with T4, whiles in the non-metastases group, T4 was found in 53 subjects (43.40%). Most of the subjects in the metastases group (52.50%) and non-metastases (45.90%) reported having an N2 lymph node involvement. However, the difference between these groups was 0.110.

Serum CEA and the occurrence of liver metastases

The median serum CEA levels in the non-metastases group were 6.27 (0.8–1099.4), much lower than in the metastases group, i.e., 208.1 (2.1–12503.2) U/mL. The Mann-Whitney test's inferential analysis showed a significant difference in the median CEA value between groups ($p < 0.001$). The receiver operating characteristic analysis to assess the area under the curve (AUC) was 0.904, and the cut-off based on the Youden index was 38.765 U/mL (Youden's index = 1.718). Therefore, the AUC value of 0.904 was considered excellent (Figure 1).

The further evaluation of the predictive value of CEA levels with a cut-off of 38.765 U/mL noted the sensitivity and specificity of serum CEA values of 91.53% (95% CI, 81.32%–97.19%) and 80.3% (95% CI, 72.16%– 86.97%), respectively.

Finally, the investigation was addressed to quantify the association between CEA levels of 38.765 U/mL with the incidence of liver metastases in colorectal cancer subjects. The cut-off was a significant difference between the non-metastases and metastases groups with the odds ratio of 44.10 (95% CI, 15.92-122.20)(Table 3 and 4).

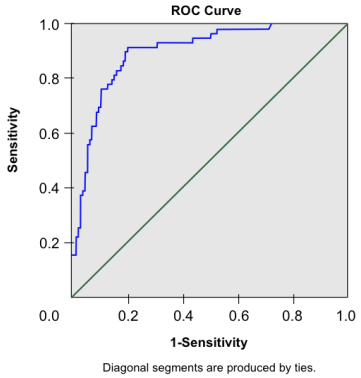

Figure 1. AUC-ROC curve presenting the sensitivity and specificity of serum CEA level in predicting liver metastases

Table 3. AUC of serum CEA level in predicting liver metastases

Area under curve	SE	95% CI	p-value
0,904	0,024	0,858–0,950	<0,001

*SE = standard error

Table 4. Prognostic value of serum CEA level ≥38.765 U/mL in predicting liver metastases

Parameter	Value	95% CI
Sensitivity	91.53%	81.32%–97.19%
Specificity	80.33%	72.16%–86.97%
Positive predictive value	69.23%	60.92%–76.46%
Negative predictive value	95.15%	89.40%–97.85%
Positive likelihood ratio	4.65	3.22–6.71
Negative likelihood ratio	0.11	0.05–0.25

Discussion

CEA is a classic tumor marker for colorectal cancer and has been used to monitor colorectal cancer recurrence and as a predictive measure.[11] In this study, we compared the level of CEA serum in those subjects with liver metastases and those with no metastases and found that the CEA serum of subjects with metastases was higher than those with no metastases, i.e., 208.1 (2.1–12503.2) U/mL vs. 6.27 (0.8– 1099.4) U/mL. This finding is like the Su et al. (2012) study, which found that patients with single or multiple metastases show higher CEA levels than the non-metastases group. Patients with local lymph node metastases also showed higher CEA levels than those with no lymph node involvement.[11] Studies by Aggarwal et al. (2013) in India contradict our findings. This multicenter study found no significant association between CEA levels and the incidence of liver metastases. However, such a study used a relatively low CEA level (>10 ng/mL) and did not describe why using such a level.[12]

We found that tumor size was associated with liver metastases, where 67.8% of subjects with liver metastases were those with T4 and 43.4% of subjects with non-metastases with T4. A study has proven an association between high CEA levels and stage T. The result is that patients with stage T4 were significantly higher than patients with increased CEA levels.[13]

Although the CEA test is available in many hospitals, its role in patients with colorectal cancer remains not well defined.[12] Preoperative CEA levels are an excellent predictive parameter for patient survival. After resection of the primary tumor, increased CEA levels have also been used to evaluate the possibility of recurrence.[14] CEA has not been shown to predict antitumor response for patients with metastatic disease undergoing chemotherapy. Despite the lack of clear consensus on monitoring CEA in mCRC patients, CEA levels are widely used to monitor response to chemotherapy.[15]

In this study, we evaluated the role of CEA levels as a predictor of liver metastases in colorectal cancer patients. We found that the accuracy of CEA levels was assessed using the ROC, and the area under the curve (AUC) was 0.904 (95% CI, 0.858–0.950). The finding indicates that CEA levels are an excellent marker in predicting the incidence of liver metastases in colorectal cancer in young adults.

In the study, the cut-off at CEA levels of 38.765 U/mL with the odds ratio of the group with liver metastases was 44.10 (95% CI, 15.92–122.20), and 91.53% of subjects in the metastases group showed CEA serum of 38.765 U/mL where <20% of subjects in the non-metastases group show CEA serum of 38.765 U/mL. The large discrepancy leads to a CEA level of 38.765 U/mL as a significant predictive factor for liver metastases.

CEA level of 38.765 U/mL has an excellent predictive value in predicting colorectal cancer liver metastases with a sensitivity of 91.53% (95% CI, 81.32%– 97.19%). The high sensitivity indicates that patients with a CEA value of <38.765 U/mL are less likely to have liver metastases. The specificity was 80.33% (95% CI, 72.16%–86.97%), which means a patient with a CEA of 38.765 U/mL, so it is unlikely that the patient will not develop liver metastases. Nature et al. (2020) reported that CEA levels >12ng/mL might provide an excellent predictive value for liver metastases with an accuracy of 85.2%.[9] In his study, Lalosevic et al. (2017) showed that the CEA level of 3.5 ng/mL may be a marker of liver metastases. However, the predictive value of such a CEA level was not elaborated.[10] His study also did not enroll the young age as the subjects. The variety of findings regarding serum CEA levels in each study depends on the patient's comorbidities. CEA values may be increased in pancreatitis, peptic ulcer, inflammatory bowel disease (IBD), biliary tract disorders, hypothyroidism, and liver disease.[16,17] Chung et al. (2019) added that false-positive results in CEA tests are possibly caused by lung cancer, colon polyps, diabetes, smoking, and chronic obstructive pulmonary diseases (COPD).[18] However, it has been proven that CEA levels showed an excellent value in predicting the incidence of liver metastases in colorectal cancer patients.

Since Gold et al. (1965) first described and characterized CEA in 1965,[19] CEA has become one of the most widely recognized tumor markers for gastrointestinal diseases, especially colorectal cancer. The association between CEA levels and tumor volume has also been reported.[20] It was found that increased serum CEA levels detected before surgery may indicate a more significant tumor burden. In the present study, preoperative serum CEA levels were significantly associated with tumor size expressed in the T category but not with the N. These findings are consistent with other studies and confirm that increased serum CEA levels are independent predictive factors for five years of disease-free survival, particularly for stage IIA and IIIB.[21]

As the CEA has an outstanding predictive value on the incidence of liver metastases in colorectal cancer, CEA is considered an accurate screening test. Unfortunately, although surgical resection offers the best chance of survival in patients with colorectal cancer with or without liver metastases, merely a minority were subjected to be resected following the diagnosis.[22] Ongoing research in this area aims to increase the number of those eligible for resection, improve indications and a contraindication to laparotomy, and improve overall survival. In addition, with information on the presence of liver metastases, it is hoped that the choice of proper treatment may be better adjusted between resection or chemotherapy.

Over the past three decades, the five-year survival rate for colorectal cancer patients with liver metastases has almost doubled, from 30% to 60%. Further, specific treatment of colorectal cancer patients with liver metastases may offer patients new hopes. Thus, detecting liver metastases, which require different treatment from patients without liver metastases, affects patient survival.

In this study, we have found an association between CEA levels and the incidence of liver metastases in colorectal cancer patients. However, some limitations of the study should be underlined. Firstly, the study was retrospective, with data collected from medical records. Therefore, the measuring instruments could not be homogenized, thus leading to the risk of measuring bias. In addition, some comorbid factors were not analyzed in this study referred to another limitation. Finally, the limited information in medical records leads to insufficient adequate data.

Conclusions

CEA levels were associated with the incidence of liver metastases in young adults' colorectal cancer ($p < 0.001$) with the cut-off 38.765 U/mL of predicting value. Specificity, sensitivity, positive predictive value, negative predictive value, and area under the curve (AUC) of CEA were 91.53% (95% CI, 81.32%–97.19%), 80.33% (95% CI, 72.16%–86.97%), 69.23 % (95% CI, 60.92%–76.46%), 95.15% (95% CI, 89.40%–97.85%), and 0.904 (95% CI, 0.858–0.950), respectively.

Disclosure

Authors declare no conflict of interest

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