

Prognostic value of increased postoperative carcinoembryonic antigen in patients with early intestinal anastomosis leakage who underwent right hemicolectomy surgery

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B – Data Collection
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ABSTRACT:

Introduction: Anastomotic leak after colorectal surgery is a serious complication that causes significant postoperative morbidity and mortality.

Aim: This study aimed to investigate the predictive value of increased postoperative carcinoembryonic antigen (CEA) in early intestinal anastomosis leakage in patients who underwent right hemicolectomy surgery.

Material and methods: In this prospective study, 535 patients who underwent right colon cancer surgery with stapled anastomosis were enrolled. A subset of 315 patients was included in the study after meeting the inclusion criteria. Preoperatively, their serum CEA levels were measured, and on postoperative days 3 and 6, the levels were measured again.

Results: Early AL occurred in 18 patients (5.71%). The mean \pm SD age of patients was 65.06 ± 11.69 years. Increased CEA level was associated with increased odds of intestinal AL among the patients after three and six days of surgery (OR after three days = 1.3; 95%CI = 1.1–1.5, OR after six days = 1.7 95%CI = 1.14–2.5). The mean CEA level significantly increased among patients with anastomose leakage (P-value < 0.001).

Conclusion: The results showed that increasing CEA levels can be used as one of the non-invasive markers in detecting early AL in patients with right colon cancer surgery.

KEYWORDS:

anastomosis leakage, carcino-embryogenic antigen, colon cancer

ABBREVIATIONS

AL – Anastomotic Leakage
ASA – American Society of Anesthesiologists
BMI – Body Mass Index
CEA – carcinoembryonic antigen
CI – confidence interval
CRP – C-reactive protein
CT – computed tomography
MMP – matrix metalloproteinases
NSAID – nonsteroidal anti-inflammatory drugs
OR – odds ratio
TNF – tumor necrosis factor

INTRODUCTION

Today, about a quarter of deaths occur due to cancer in countries that follow western lifestyles [1]. Colorectal cancer is the third most prevalent and deadly cancer globally, affecting about one million people a year, and half a million die from its complications [2]. This cancer is known as one of the most important leading causes of death in different parts of the world, such as the United States, Europe, and Asia [3]. Statistics show that the prevalence

of colorectal cancer is the fifth and third most common malignancy among men and women, respectively [4]. According to the Cancer Department of Centers for Disease Control in Iran in 2005, the number of cases of colorectal cancer was 4.056, accounting for 7.3% of all cancers [5].

Anastomotic Leakage (AL) is still one of the most severe complications of colon cancer surgery, with an incidence of 2.8 to 8.4% [6]. Its mortality rate is reported around 6% to 22% [7] and is associated with low quality of life [8]. AL's risk factors include male sex, smoking, obesity, alcohol consumption, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids before surgery, prolonged surgery, preoperative blood transfusion, and infection [9]. A meta-analysis based on studies from 1980 to 2015 showed that AL had been associated with neoadjuvant treatment [10].

The time of AL is crucial due to the severity and management of its complications. Early AL usually occurs between days five to eight after surgery [11]. In contrast, late AL is generally defined as an anastomotic leak occurring one month after surgery [12]. In general, early AL is associated with severe generalized peritonitis, which leads to further mortality and recurrent laparotomy [13]. Late AL is associated with an increased risk of pelvic abscesses [12]. Elevated levels of cytokines, especially tumor necrosis factor (TNF) and interleukin-6,

Tab. I. Descriptive features of patients with/without occurrence of AL.

	AL+	AL-
Sex	Female	225 (75.8)
	Male	9 (50)
Age	64.89 ± 11.63	67.83 ± 12.72
Median (Q1–Q3)	66 (33–100)	70.5 (62.75–73)
(Min–Max)	33–100	43–100
CEA before surgery	9.97 (9.4)	10.83 (5.81)
Median (Q1–Q3)	5.72 (2.9–19.6)	6.55 (617.52)
(Min–Max)	(0.8–33)	(3.6–18.6)
CEA day 3	4.33 ± 6.43	19.2 ± 12.51
Median (Q1–Q3)	1.71 (1.2–4)	19.05 (7–31)
(Min–Max)	(0.4–28)	(6.96–32)
CEA day 6	4.11 ± 5.79	27.4 ± 13.32
Median (Q1–Q3)	1.7 (1.1–3.8)	27.6 (0)
(Min–Max)	(0.5–25.5)	(9–45)

Tab. II. The association of CEA level and other risk factors in patients in logistic regression analyses.

	UNIVARIATE LOGISTIC REGRESSION		MULTIPLE LOGISTIC REGRESSION	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Sex	Female	1		
	Male	3.12 (1.2–8.2)	0.02	2.99 (1.12–7.97)
Age	1.02 (0.98–1.07)	0.29		
CEA before surgery	1.01 (0.96–1.06)	0.7		
CEA day 3	1.15 (1.1–1.2)	<0.001	1.3 (1.1–1.5)	0.002
CEA day 6	1.21 (1.14–1.3)	<0.001	1.7 (1.14–2.5)	0.01

matrix metalloproteinases (MMP), C-reactive protein (CRP), and lactate one day after surgery are associated with an increased risk of AL. However, none of these markers effectively predicted AL and were not used as conventional markers [14].

Carcinoembryonic antigen (CEA) is a glycoprotein found in embryonic endodermal epithelium and is overproduced by cancer cells in the gastrointestinal tract. CEA levels may increase plasma and intestinal contents in patients with colorectal cancer [15]. Also, Serum CEA levels may increase in patients with colorectal cancer before surgery (more than five ng/mL) [15]. CEA serum levels are also a sensitive indicator of cancer recurrence. Therefore, the marker is a choice in tracking patients after surgery [16]. In another study, Bekrovich et al. found that a significant increase in CEA (above 1000 ng/mL) in the abdominal drain after surgery may indicate the early AL. However, no significant increase in CEA levels was observed in patients with the late anastomotic leak [17].

AIM

Therefore, this study was conducted to investigate the predictive value of intestinal AL and increased postoperative CEA in patients with right colon cancer surgery.

MATERIALS AND METHODS

The study was performed under the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and was approved by the Ethics Committee of Urmia University of Medical Sciences with code: IR.UMSU.REC.1398.297. All patients provided written informed consent before being included in the study.

This research was conducted among 535 patients who underwent right colon cancer surgery (right hemicolectomy) with stapled anastomosis between February 2018 and September 2020 at the surgical ward of Imam Khomeini hospital, Urmia university of medical sciences, Iran. A subset of 315 patients was included in the study after meeting the inclusion criteria. The inclusion criteria were age over 18 years, BMI between 20–30 kg/m², the patient undergoing right colon stapled anastomosis surgery, having a normal level of albumin, and free margin in pathological findings. Exclusion criteria were having a history of chemotherapy or radiotherapy, anemia, diverting stoma, history of smoking, history of drug or alcohol consumption, history of corticosteroid or NSAIDs (non-steroidal anti-inflammatory drugs) use, long time of surgery, preoperative blood transfusion, urgent surgery, high ASA grade, different anastomosis technique, metastasis, high CEA level before operation and infection. The patients were divided into two groups: one group without anastomotic leakage and another group with clinical anastomotic leakage. The study looked at early AL, which occurred during the first ten days after colorectal surgery. Blood for serum CEA analysis was sampled one day prior and three and six days after the surgical procedure. The samples were kept cool at 4°C until analyzed, and CEA levels were measured using BM Chemiluminescence ELISA Substrate assay (Roche Diagnostic Systems, Nutley, NJ). The patients' clinical data were documented, including postoperative anastomotic leaks and minor complications such as wound infections, paralytic ileus, blood transfusions.

Of 315 patients who underwent right colon anastomosis, 31 with symptoms, such as fever, tachycardia, tachypnea, leukocytosis, and acidosis, were suspected of having AL. After performing CT with IV and oral contrast to quantify the risk of anastomotic leak in the suspected patients, 18 of them were found to have this complication. Furthermore, by surgery, the leak in these 18 patients was confirmed with certainty.

Statistical analysis

Mean ± SD (Standard deviation) was calculated for continuous variables, and frequencies were measured for qualitative variables. The univariate logistic regression test was used to assess the association between CEA level, sex, age, and occurrence of early AL. We fitted a multiple logistic regression model for adjusting the gender. One-way ANOVA test was used to adjust the gender effect in this association. Willcoxon Signed Rank Test was used to analyze the mean difference between CEA at three and six days after surgery among the patients with AL. P-value < 0.05 was considered significant. SPSS statistical software version 17 was used for data analysis.

RESULTS

This study encompasses 315 patients who underwent right colon cancer surgery with stapled anastomosis. Tab. I. shows the descriptive characteristics of patients in two groups with and without AL. Half of the patients with AL were male, and the other half were female. Among patients without AL, 24.2% were male. The mean and median age of patients with AL was higher than of patients without AL.

The mean \pm SD age of patients was 65.06 ± 11.69 years. Early AL occurred in 18 patients (5.71%). The number of male and female patients with early AL was the same. The age of patients with early AL was higher than of patients without early AL, but it is not statistically significant (67.83 ± 12.72 , 64.89 ± 11.63 ; $P = 0.3$) (Tab. I.). Male patients had higher odds of AL occurrence than female patients (OR = 3.12, 95%CI = 1.2–8.2) (Tab. II.).

Before surgery, there was no significant difference in CEA levels between the group with intestinal AL compared to the group without intestinal AL. Also, it is not statistically significant (10.83 ± 5.81 vs. 9.97 ± 9.37 , P -value = 0.7) (Tab. I.). The odds of intestinal AL among the patients depending on preoperative CEA levels were similar (OR = 1.01, 95%CI = 0.96–1.06) (Tab. II.).

Three days after surgery, the CEA level was higher in patients with intestinal AL than in patients without intestinal AL. Increased CEA level was associated with increased odds of intestinal AL among the patients after three days of surgery (OR adjusted for sex = 1.3, 95% CI = 1.1–1.5). After six days of surgery, the CEA level was higher in the group with intestinal AL vs. patients without intestinal AL. Higher CEA level after six days of surgery increased odds of intestinal AL among studied patients (OR adjusted for sex = 1.7, 95%CI = 1.14–2.5). This association was stronger at six days of surgery (Tab. II.).

The association of CEA level and occurrence of AL between sex categories of patients was shown in Tab. III. On day three of surgery, the mean CEA level was significantly high among female patients with early AL (31.34 ± 0.5 vs. 3.32 ± 5.13 ; P -value < 0.001). On day three of surgery, the mean CEA level was similar among male patients with early AL and without AL (7.02 ± 0.06 vs. 7.50 ± 8.72 ; P -value = 0.1). The mean CEA level on day six of surgery was significantly high among patients with early AL irrespective of their sex (39.67 ± 4.1 vs. 3.05 ± 4.05 ; P -value < 0.001 in females and 15.14 ± 4.7 vs. 7.4 ± 8.54 ; P -value = 0.01 in males).

Tab. IV. shows the CEA levels among patients with anastomose leakage. The mean CEA level had a significant increasing trend among the patients with early AL (Mean \pm SD of CEA level before, on day three and day 6 of surgery were 10.83 ± 5.81 , 19.2 ± 12.51 and 27.4 ± 13.32 (CEA levels ng/mL, respectively; P -value < 0.001).

DISCUSSION

Anastomotic leak is difficult to predict which may be due to many variables related to both systemic and local factors. Elevated postoperative serum CEA levels in the colon may be linked to an increased incidence of distant metastases in colon cancer patients and a higher incidence of local recurrence in rectal cancer patients [18]. Based on the data presented in the current study, early AL was associated with an increased CEA level after surgery that was statistically

Tab. III. The association of CEA level and occurrence of anastomose leakage.

		AL-	AL+	P-VALUE
		MEAN \pm SD		
CEA day 3	Male	7.50 \pm 8.72	7.02 \pm 0.06	0.1
	Female	3.32 \pm 5.13	31.34 \pm 0.5	<0.001
	Total	4.33 \pm 6.43	19.2 \pm 12.51	<0.001
CEA day 6	Male	7.4 \pm 8.54	15.14 \pm 4.7	0.01
	Female	3.05 \pm 4.05	39.67 \pm 4.1	<0.001
	Total	4.11 \pm 5.8	27.4 \pm 13.32	<0.001

Tab. IV. Comparison of CEA level among patients with anastomose leakage.

	CEA BEFORE SURGERY	CEA DAY 3	CEA DAY 6	P-VALUE*
Mean \pm SD	10.83 \pm 5.81	19.2 \pm 12.51	27.4 \pm 13.32	
(Min–Max)	(3.6–18.6)	(6.96–32)	(9–45)	<0.001
Median (Q1–Q3)	6.55(6–17.52)	19.05 (7–31)	27.6 (17.2–38)	

* Friedman Test

significant. CEA levels in patients with intestinal AL increased on the third and sixth days after surgery compared to the day before surgery. An increasing trend for CEA levels was observed among patients with AL independent of age and gender of patients. In this study, the gender distribution of patients with AL was different than of patients without AL, and we adjusted this effect in the analysis phase. After the adjustment, CEA levels were increased in patients with early AL as compared to patients without AL.

The association between CEA elevation and the inflammatory process indicates AL [19]. The higher the level of inflammation, the more likely the leak. Because CEA is an inflammatory factor, it indicates inflammation [20]. Enterocytes and mucosal colonic cells may be substantially separated from the damaged anastomosis during an early anastomotic leak [21]. We believe these cells can fracture and leak their plasma locally, resulting in elevated CEA levels in drain fluids.

CEA has remained the most frequently analyzed tumor marker since its discovery in 1965 [22]. High serum CEA has been demonstrated to be related to several malignancies, including those of colorectal, pancreas, and lung types [23]. Previous studies have shown that preoperatively increased serum CEA is associated with a poor prognosis [24]. In addition, most studies evaluating postoperative CEA levels demonstrate it to be an independent predicting factor after surgical resection for colorectal cancer [25–27]. According to Ma et al., patients who continue to have elevated postoperative serum CEA may require more intensive follow-up and treatment, even in stage I or II diseases for which adjuvant chemotherapy is conventionally considered unnecessary or controversial [28]. Consistent with these studies, our results demonstrated that increased serum CEA after surgery was a significant prognostic factor of postoperative early AL. However, some contradictory studies reported that the preoperative CEA level is a predictor for AL [29, 30].

Contrary to our observation, Sun et al. also found that preoperative CEA level could affect the postoperative outcome of colorectal cancer [31]. Also, Gara et al. found preoperative CEA to predict

recurrence in colorectal cancer [32]. In line with our study, Kanellos et al. showed that high CEA levels were associated with liver metastasis and local recurrence [33]. In another study, bile CEA levels greater than five ng/mL were associated with an increased risk of liver metastases in patients with positive lymph nodes [34].

Higher levels of peritoneal cytokines, TNF α , IL-6 matrix metalloproteinases, C-reactive protein, and lactate in the postoperative days were linked to an increased risk of AL [21]. Anyway, none of these markers was sufficient to predict AL. Therefore, they do not act as typical markers. At one to two days after surgery, intestinal anastomosis is relatively weak. It depends on the ability of the existing collagen to hold the surgical sutures until the new collagen is synthesized [14].

Furthermore, in agreement with the results of this study, Berkovic et al. [17] conducted a study on 535 patients who underwent right colon cancer surgery in 2016, in which early AL was observed in three patients (2.8%). Their study showed an early leak of anastomosis, an increase in CEA level in patients' abdominal drainage, and a significant relationship between the outcomes. In a study by Gyoung Noh et al. [35], preoperative CEA was 8.8 ± 2.26 ng/mL in patients with AL but 8.9 ± 2.36 ng/mL in patients without

anastomosis leakage. It was determined that there was no significant difference between patients with and without anastomosis leakage, which is different from the present study results. The CEA levels were measured only preoperatively, but the increase in CEA was measured before and after surgery in our study.

CONCLUSION

This study concluded that increased postoperative serum CEA levels could be used as one of non-invasive markers in detecting early intestinal anastomosis leakage in patients with right colon cancer surgery. In this study, predicting postoperative AL was performed by non-invasive methods. Further research that includes more patients for confirming postoperative AL is needed to strengthen our findings.

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