IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 1 | Jan – Feb 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i1.22

Correlation Between C-Reactive Protein (CRP) Level and Chemotherapy Response in Colorectal Cancer Patients Based on Carcinoembryonic Antigen (CEA) Levels in Post Definitive Operative and Adjuvant Chemotherapy Three Series at Prof. Dr. I.G.N.G Ngoerah Denpasar Hospital

Anak Agung Ngurah Bayu Putra[1*], Made Agus Dwianthara Sueta[2], and Tjokorda Gde Bagus Mahadewa[3]

[1]Department of General Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

[2]Division of Digestive Surgery, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

[3]Division of Neurosurgery, Department of Surgery, Faculty of Medicine, Udayana University, Prof. Dr. IGNG Ngoerah General Hospital, Denpasar, Indonesia (80113)

E-mail: aangurahbayuputra@gmail.com; agus_sueta@yahoo.com; tjokmahadewa@unud.ac.id

*Corresponding author details: Anak Agung Ngurah Bayu Putra; aangurahbayuputra@gmail.com

ABSTRACT

Background: Colorectal cancer is the third leading cause of cancer-related deaths worldwide. Surgical therapy is the primary modality for early-stage cancer with curative goals; chemotherapy is the direct option in advanced cancer with palliative goals; radiotherapy is one of the primary therapy modalities for rectal cancer. The markers for chemotherapy response include CRP and CEA. Elevated CRP and CEA levels in CRC patients are associated with poor chemotherapy response. ***Objective:*** to determine the relationship between C-reactive protein (CRP) levels and chemotherapy response measured by Carcinoembryonic Antigen (CEA) levels in colorectal cancer patients at Prof. Dr. IGNG Ngoerah Hospital. ***Method:*** analytic observational study with a retrospective cohort study design. The sample in this study used the total consecutive sampling method. The analysis was carried out with the help of SPSS, including descriptive statistical tests, chi-square tests, and correlation tests with Spearman-Rho. ***Results:*** 58 patients were divided into 2 groups of 29 each for the group with high CRP levels (≥5 mg/dl) and low CRP levels (<5 mg/dl). The male subjects with the most age <60 years and stage III. Most duration of illness < 2 years. The relationship between CRP levels and chemotherapy response was based on CEA, RR 3.2 [95% CI 1.1-9.6; p 0.030], and the value of the positive correlation coefficient with strong strength is r = 0.722. ***Conclusion:*** high CRP levels are significantly associated with a strong correlation to worse chemotherapy response in colorectal cancer patients characterized by a high risk of increasing CEA levels 3.7 times after three series of FOLFIRI adjuvant chemotherapy.

Keywords: colorectal cancer; C-reactive protein (CRP); carcinoembryonic antigen (CEA); adjuvant chemotherapy; definitive surgery

INTRODUCTION

Colorectal cancer (CRC) is a malignant tumor that arises from the epithelial tissue of the colon, consisting of the colon and/or rectum, part of the large intestine in the digestive system called the gastrointestinal tract [1]. According to Global Burden Cancer (GLOBOCAN) data, there are 1.93 million newly diagnosed colorectal cancer cases, and according to World Health Organization (WHO) data, there are 0.94 million colorectal cancers that cause death in 2020 worldwide [2].

Colorectal cancer is the third leading cause of cancer-related deaths worldwide, with an estimated 515,637 deaths among men and 419,536 deaths among women in 2020 [3]

According to the American Cancer Society in the same year, there were 104,610 new cases of colon cancer and 43,340 cases of rectal cancer diagnosed in the United States.

Although the majority of colorectal cancers occur in adults aged ≥50 years, 17,930 (12%) cases were diagnosed in individuals <50 years. There are an estimated 53,200 deaths from colorectal cancer, including 3,640 deaths in men and women under the age of 50 [4]. In 2018 colorectal cancer ranked 5th (8.6%) and 3rd (9.2%) cause of death in Indonesia[5]. The prevalence of colorectal cancer in Bali, especially at Prof. Dr. I.G.N.G Ngoerah Hospital in the period 2010 - 2014 based on research conducted by Yogi et.al reported a total of 64 cases in 2010, 71 cases in 2011, 96 cases in 2012, 77 cases in 2013 and in 2014 there were 127 cases. Based on these findings, it was found that the prevalence of colorectal cancer cases in Bali based on data at Prof. Dr. I.G.N.G Ngoerah Hospital has increased [6]. While in 2017 at Prof. Dr. I.G.N.G Ngoerah Hospital, 44 cases were found with the youngest age being 23 years old and the oldest age being 80 years old [7].

In the early stages of cancer growth, people who have colorectal cancer generally have no symptoms. Symptoms generally start to appear in advanced stages of cancer, which is a contributing factor to delayed diagnosis. A digital rectal examination in patients with anorectal symptoms and a colonoscopy are the most recommended methods. A fecal occult blood test can be performed as an initial screening. This test has high sensibility based on the Guaiac test or immunologic tests [8,9].

Tumor staging and prognosis are based on the American Joint Committee on Cancer (AJCC/UICC) TNM system, which also determines which patients receive additional chemotherapy after surgery. However, patients within the same TNM stage may show different recurrence and survival rates. For example, it was found that 20-25% of patients with cancer without lymph node (KGB) metastasis or distant metastasis still had recurrence (Galon et al., 2018). This clearly shows that the TNM system alone is not sufficient and additional information is needed to improve prediction and outcomes [10].

Once a diagnosis of CRC is made, the selection of appropriate management is necessary to improve the patient's condition. Surgical therapy is the main modality for early-stage cancer with curative purposes. Meanwhile, chemotherapy is divided into 3 types, namely neoadjuvant, adjuvant, and therapeutic/palliative chemotherapy. Neoadjuvant chemotherapy is the use of precursor drugs to shrink the size of the primary cancer so that additional treatments are more effective. This is different from adjuvant chemotherapy which is done after surgery or radiation with the aim of killing any remaining cancer cells. Palliative chemotherapy is a treatment designed to relieve symptoms and prolong survival. Radiotherapy is generally performed on rectal cancer types [11].

Some of the widely used colorectal cancer treatment regimens are the FOLFOX and FOLFIRI regimens. The FOLFOX regimen consists of folinic acid (FOL), fluorouracil (F), and oxaliplatin (OX). This regimen has been the standard adjuvant therapy for stage III colon cancer patients since 2004. Oxaliplatin works by intracellular hydrolysis which inhibits cell death DNA replication, and since oxaliplatin is known to cause neurotoxicity, a reduction in therapy cycles has been made. The FOLFIRI regimen consists of folinic acid (FOL), fluorouracil (F), and irinotecan (IRI). This regimen is used for the treatment of advanced and metastatic colorectal cancer. Irinotecan works by inhibiting the function of the topoisomerase I enzyme which results in the disruption of DNA replication [12].

Chemotherapy in CRC can be influenced by several factors such as age, location of metastases, and the presence of inflammatory factors [13]. There are several signs of systemic inflammation in colorectal cancer patients that are acute in nature, most notably C-reactive protein (CRP) [10]. The potential of CRP as a marker to predict survival, chemotherapy response, and tumor progression in patients with CRC has been widely evaluated. Recently, markers of systemic inflammation have been reported to correlate with survival in patients with different types of cancer [14–16]. CRP is secreted by hepatocytes in the acute phase after proinflammatory stimulus, especially IL-6, IL-1, and tumor necrosis factor-α (TNF-α). IL-6 induces CRP from MMP-9 via Cox-2-dependent and Cox-2-independent mechanisms, which are directly linked to the pathogenesis of chronic inflammatory diseases and cancer [8,17].

Several previous studies have shown an association between the expression of inflammatory markers such as CRP and chemotherapy response in colorectal cancer. Partl et al's 2020 study found that increased pre-treatment CRP levels in patients with locally advanced rectal cancer were associated with a worse prognosis, especially in patients who received neo-adjuvant radiochemotherapy [11]. Another study evaluating the inflammatory marker CRP on chemotherapy response showed that patients with low CRP levels tended to have a better chemotherapy response rate than the high CRP group (36.0% vs. 11.8%, p=0.085). In addition, there was a significantly higher disease control rate in the low CRP group than in the high post-chemotherapy CRP group (81.4% vs. 47.1%, p=0.005). Evaluation of prognosis based on CRP levels showed that the overall survival rate was significantly worse in the group of patients with high CRP levels (p<0.0001). Similarly, progression-free survival rate was found to be significantly worse in post-chemotherapy patients with high CRP levels (p=0.0402). Both pre-chemotherapy and post-chemotherapy CRP levels have been shown to correlate with survival and chemotherapy response [18].

Tumor markers CEA, absolute lymphocyte count, platelet count, NLR, and fibrinogen can also be used as pre-CRT (chemoradiotherapy) biomarkers to predict oncological outcomes in CRC patients treated with CRT followed by total mesolectal excision (TME). A study showed that elevated pre-CRT levels of CRP, NLR, and CEA in CRC patients treated with preoperative CRT were predictors of worse OS Multivariate analysis revealed that elevated CRP and

ypN-positive (pathologic TNM stage III) were significant independent prognostic factors associated with poor OS, while elevated pre-CRT CRP and CEA levels also predicted early recurrence [19].

Therefore, elevated CRP and CEA levels in CRC patients are associated with poor chemotherapy response [10,20]. Thus, this study aims to determine the relationship between CRP and CEA levels with post-adjuvant chemotherapy response in three series of CRC patients at Prof. Dr. I.G.N.G Ngoerah Hospital.

This study is an analytic observational study with a cross-sectional design. This study assesses the relationship of C-reactive protein (CRP) levels to the chemotherapy response of colorectal cancer (CRC) patients assessed based on Carcinoembryonic Antigen (CEA) levels in patients who have received three series of FOLFIRI adjuvant chemotherapy.

The study was conducted at the Department of Surgery and Medical Records Installation of Prof. Dr. I.G.N.G Ngoerah Hospital Denpasar. The study will be conducted in February-December 2022. Inclusion criteria: CRC patients based on histopathological examination; Patients age ≥40 years; Patients who have undergone definitive surgical procedures such as ultra-low resection, low anterior resection, right/left hemicolectomy, and Hartman procedure; Patients who received 3 series of FOLFIRI chemotherapy; Patients already have CRP and CEA examination data. Exclusion criteria: Patients experiencing loss to follow-up; Incomplete patient medical record data; Patients who did not undergo definitive surgery; Patients who did not receive chemotherapy; and Patients who did not receive FOLFIRI chemotherapy.

The sample in this study used the total consecutive sampling method, namely all patients suffering from CRC who fit the inclusion criteria.

Data analysis using the Windows SPSS 24.0 (Statistical Package for Social Science) program with the following stages: Descriptive statistical analysis, chi-square test, and spearam rho test.

RESULTS

Data characteristics obtained by gender were not significantly different in the two groups, the group with high CRP found 16 men (55.2%) and 13 women (44.8%) while the group with low CRP found 15 men (51.7%) and 14 women (48.3%). Age did not differ in the two groups with a mean ± SD of 52.9 ± 7.2 years in the high CRP group and 58.1 ± 8.8 years in the low CRP group with the most age < 60 years 25 people (86.2%) in the high CRP group and 18 people (62.1%) in the low CRP group. The type of surgery performed most in the high CRP group was with Hartman Procedure 12 people (41.4%) while in the low CRP group the most surgery with Hemicolectomy 9 people (31.1%). The stage of cancer in both groups was the same, namely at stage III, with 26 people in the high CRP group (89.6%) and 24 people in the low CRP group (82.8%). The length of disease was mostly < 2 years in both groups, in the high CRP group 24 people (82.8%), and low CRP 17 people (82.8%) (Table 1).

TABLE 1: Characterization of study subjects (n=58).

Characteristics	CRP levels		P-value
	High (n-29) (%)	Low (n=29) (%)	
Gender			
Male	16 (55,2)	15 (51,7)	0,599
Female	13 (44,8)	14 (48,3)	
Age (years) mean±SD	52,9±7,2	58,1±8,8	0,116
< 60 years	25 (86,2)	18 (62,1)	
60-69 years	3 (10,3)	7 (2,4)	0,103
≥ 70 years	1 (3,4)	4 (13,8)	
Operation Type			
Ultra-Low Resection	3 (10,3)	7 (24,1)	
Low Anterior Resection	4 (13,8)	6 (20,7)	0,120
Hemicolectomy D/S	10 (34,5)	9 (31,1)	
Hartman Procedure	12 (41,4)	7 (24,1)	
Cancer Stage			
II	3 (10,1)	5 (17,2)	0,446
III	26 (89,9)	24 (82,8)	
Duration of Disease			
< 2 years	24 (82,8)	17 (82,8)	0,043*
2-4 years	5 (17,2)	12 (17,2)	
Age at menopause (mean ± SD) years	50,24	50,38	0,820

Characteristics	CRP levels		P-value
	High (n= 29) (%)	Low (n= 29) (%)	
Nutritional status (mean±SDS) kg/m²	21,69	21,70	0,789
Less	1 (3,4)	2 (6,9)	
Normal	27 (93,1)	25 (86,2)	0,689
Obesity	1 (3,4)	2 (6,9)	
CRP (Median (Min-Max)) * mg/dL	7,8 (1-10,9)	3,5 (1,2-4,8)	<0,001*
CEA (Median (Min-Max)) * µg/L	16,2 (3,7-78,5)	4,7 (1,8-10,9)	0,002*

*Significant; SD: Standard Deviation.

The age of menopause in both groups did not have a significant difference with the results in high and low CRP levels at the age of 50 years. Gixi status was found to be not significantly different in the two groups with the results of undernutrition in the high CRP group only 1 person (3.4%) while in the low CRP group 2 people (6.9%), the most normal nutrition in the high CRP group was 27 people (93.1%) and low CRP as many as 25 (86.2%).

The value of CRP levels (Median (Min-Max)) was obtained in the high CRP group 7.8 (1-10.9) mg/L and in the low CRP group 3.5 (1.2-4.8) mg/L. The value of CEA levels (Median (Min-Max)) in the high CRP group was 16.2 (3.7-78.5) µg/L and in the low CRP group was 4.7 (1.8-10.9) µg/L.

The results of the analysis of the relationship between CRP levels and adjuvant chemotherapy response in CRC patients based on CEA levels are presented in Table 2.

TABLE 2: Chi-Square Analysis.

CRP levels	CEA levels		RR	95% IK	P-value
	High (≥5 µg/L) (n= 34) (%)	Low (<5 µg/L) (n=24) (%)			
High (≥5 mg/L)	21 (61,7)	8 (33,3)	3,231	1,081-9,656	0,030
Low (< 5 mg/L)	13 (38,3)	16 (66,7)			

The results of Table 5.2 show that high CRP levels ≥5 mg/L have an RR of 3.2 [IK 95% 1.1-9.6; p 0.030] on adjuvant chemotherapy response in CRC patients based on CEA levels, which means that high CRP ≥5 mg/L has a risk factor for an increase in CEA levels ≥5 µg/L 3.2 times compared to low CRP levels <5 mg/dL with a range of 1.1-9.6 times which is statistically significant (p=0.030).

Correlation analysis using the Spearman Rho test between CRP levels and CEA levels results are shown in Table 3 and the scatter plot in Figure 1.

TABLE 3: Correlation test of CRP levels with CEA levels.

Variables	CEA levels	
CRP levels	Correlation (r)	0,722
	P-value	<0,001*
	Number (n)	58

*Significant when p<0.05; correlation analysis with Spearman Rho test.

In Table 3, the positive correlation coefficient value with strong strength is r = 0.722. This means that there is a strong positive relationship between CRP levels and CEA levels. The greater the CRP level, the higher the CEA level.

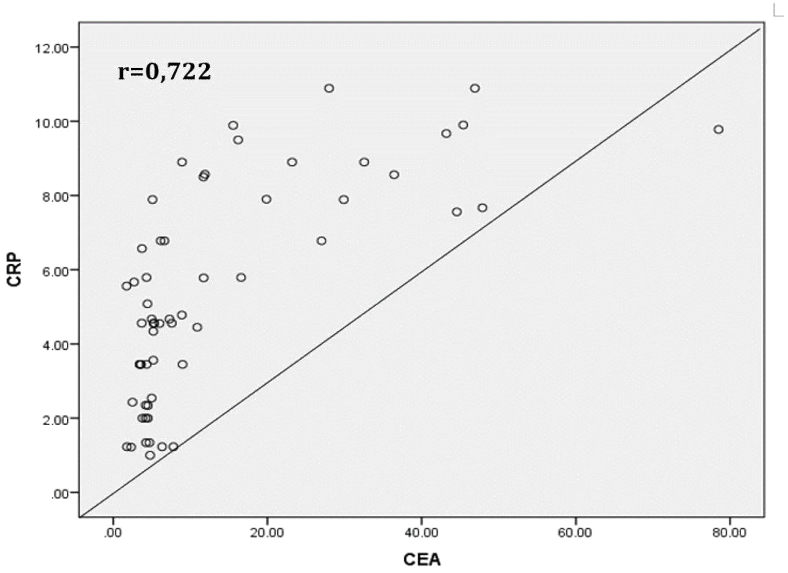

FIGURE 1: Scatter plot of CRP levels with CEA levels.

DISCUSSION

The results of this study obtained the number of subjects involved as many as 58 patients with a division of 2 groups of 29 people each for the high CRP level group and low CRP levels. The results of gender were found to be not significantly different in the two groups, the group with high CRP was found to be 16 men (55.2%) and 13 women (44.8%) while the group with low CRP was 15 men (51.7%) and 14 women (48.3%). The results of gender were also not found to be associated with CEA levels.

Colorectal cancer affects most men and is the third leading cause of cancer-related deaths worldwide, with an estimated 515,637 deaths among men and 419,536 deaths among women in 2020 [3]. The results of this study are the same as those of [21] where there were 44 (55.7%) more men, [22] men 41 (58.6%), and in Fauzia (2018) men 23 (69.7%), and data from previous research at Prof. Dr. I.G.N.G Ngoerah Hospital CRC patients in 2016-2017 were also dominated by men 73 (53.3%) [23].

Hormonal factors are said to be less influential although external use of estrogen and progestin has a protective effect against colorectal cancer. Many studies suggest that the risk of colorectal cancer is increased in people with obesity, a high-fat diet (fat is associated with the development of bacterial flora that degrades bile salts into potentially carcinogenic N-nitroso components), high calories, and lack of fiber, consuming a lot of red meat, (meat cooked at high temperatures triggers the production of heterocyclic amino and polycyclic aromatic hydrocarbons, which are carcinogenic ingredients), consuming less fruit, rarely exercising, and smoking [24].

The prevalence of CRC in Indonesia is 8.6% of all cancers with a male prevalence of 19.1 per 100,000 and in women 15.6 per 100,000 population with most cases experienced by individuals with advanced age [25].

The results of this study showed that age was not different in the two groups with a mean ± SD of 52.9 ± 7.2 years in the high CRP group and 58.1 ± 8.8 years in the low CRP group with the most age < 60 years 25 people (86.2%) in the high CRP group and 18 people (62.1%) in the low CRP group. Age was found to have no effect on CRP and CEA levels.

The results of this study are the same as the research (Fernanda and Wisnaningsih, 2018) in 70 sample patients, the most age results were obtained in> 50 years [22]. The results of this study are also in accordance with the results of this study Sitorus, 2010 [21] where the most age was also at the age of 40-60 years 47 patients (59.49%) and Fauza's research (2018) also stated that the most age was <60 years as many as 22 (66.7%) [26].

The results are different from Pestana, 2016 where CRC is a disease that is often found in the elderly, occurring more frequently in the sixth and seventh decades of life, although an increase in incidence in younger individuals has been observed in recent decades. Previous research conducted by Myers where in his research Myers used a sample of 180 patients under the age of 50 years [27].

The type of surgery performed most in the high CRP group was with Hartman Procedure 12 people (41.4%) while in the low CRP group the most surgery with Hemicolectomy 9 people (31.1%). The Hartman procedure was found to have an incidence of morbidity of 23%-69% and mortality of 1%-28%. [28]. Hemicolectomy has an incidence of complications of 42.8%-83.3% which include infection, sepsis, abscess, anastomosis leakage, and obstruction, with morbidity of 12.5-28.1%, and mortality of 13% [29].

The incidence of CRC is complex because it has a high mortality rate.

The high mortality rate is influenced by prognostic factors of CRC patients, clinicians use clinical indicators including clinical stage, histopathological grade, and tumor location (Sutrisna, 2018). According to the American Society of Clinical Oncology (ASCO) recommendations in 2006, Carcinoembryonic Antigen (CEA) is checked before surgery to assist in staging or action plans as well as in monitoring therapy response during active treatment. The prognostic of the patient is good if it comes at an early stage so that therapy can be carried out curatively. Unfortunately, most patients in Indonesia present at an advanced stage, resulting in low life expectancy, regardless of the therapy given. Patients come to the hospital often in an advanced stage due to unclear initial symptoms and do not know or consider the importance of early symptoms that occur [30]. The results showed that the stage of cancer in both groups was the same, namely at stage III, the most people, were 26 people in the high CRP group (89.6%) and 24 people in the low CRP group (82.8%). Stage in this study was not significantly associated with CRP levels or CEA levels. The results of this study are different from Koike et al., (2008) who found that CRP ≥ 5 mg/dl is associated with a higher stage. High CRP levels found in stages I and II would be predictive of early disease recurrence, even when the CEA test was found to be a modest value <6 µg/L. High CRP levels were significantly associated with higher stage and incidence of metastasis p<0.001 [31].

The length of disease was mostly < 2 years in both groups, in the high CRP group 24 people (82.8%), and low CRP 17 people (82.8%). The 3-year survival of CRC patients is only 55% without adjuvant chemotherapy and will increase to 90% with adjuvant chemotherapy [32]. Disease duration is not associated with CEA and CRP levels.

The ASCO Tumor Marker Expert Panel recommends postoperative CEA screening every 3 months for stages II and III for 3 years. CEA is the only biomarker that should be routinely measured in patients with CRC [33,34]. Postoperative CEA is important because it is an independent prognostic factor for disease-free survival (DFS) of colorectal cancer. At a CEA relevance score of 5 ng/ml, the sensitivity of CEA is 37% for diagnosing colorectal cancer, 37% for patients with Dukes stage B, 66.6% for patients with stage C, and 75% for patients with stage D. The specificity of CEA for colorectal cancer at 5 ng/ml is 76.98% and at 10 ng/ml is 86% [35].

The value of CRP levels (Median (Min-Max)) was obtained in the high CRP group 7.8 (1-10.9) mg/L and in the low CRP group 3.5 (1.2-4.8) mg/L. The value of CEA levels (Median (Min-Max)) in the high CRP group was 16.2 (3.7-78.5) µg/L and in the low CRP group was 4.7 (1.8-10.9) µg/L. The cut-off limit value of CEA was 5 µg/L with a sensitivity of 79.3% and a specificity of 82.8%.

Research results [36] The results of CRP levels (Median (Min-Max)) in CRC were 11.3 (0-152.4) while CEA levels were 4.2 (0-4488.9) µg/L. In stage III, the CRP level was found to be 6.2 (2.3-60.8) higher than the CRP level in stage II which was 4.0 (1.6-191.5) while the CEA level was found to have the same median between stages II and III, in stage II 2.8 (0-116.3) while stage III 2.2 (0.5-366.6). Patients who are still alive within 3 years have CRP levels with a Median (Min-Max) of 8.3 (0-152.4) while those who died are 75.3 (2-147.6), while the CEA results are obtained in those who are still alive with a Median (Min-Max) of 2.2 (0.2-366.6) while those who died with a result of 3.1 (0.6-1982). The limit of increasing CRP levels was found to be 9.7 mg/dL with a sensitivity of 82.1%, while the CEA limit with a cut-off point of 5 µg/L had a sensitivity of 79.4%. [36].

Serum CRP levels above 140 mg/L have a sensitivity of 80%, specificity of 81%, and a positive predictive value of 85.7% in predicting postoperative complications of CRC. [37]. The results of Koike's research, 2008 mentioned that CRP levels ≥5 mg/dl can be used as a predictor of worse in patients with CRC. In the study of Nikiteas et al., 2005 serum CRP levels in CRC patients were obtained (median value: 6.79 mg/L, range 0.3-182 mg/L), the limit of pre-operative CRP ≥7 mg/dl increase can be an indicator of potential tumor malignancy and a predictor of poor prognosis in CRC patients.

Elevated CEA showed an increased potential for recurrence with an HR of 7.91 (CI 95% 3.43-18.24,). In univariate analysis adjusted for baseline characteristics, elevated CEA was associated with disease free-survival (DFS) (HR 7.23, CI95% 3.85-13.58 with a 10-year DFS rate of 6% in elevated CEA vs 63% in normal CEA). In multivariate analysis, it was found that elevated CEA was associated with poor DFS (HR 8.63, CI 95% 3.82-19.50) and overall survival (OS) (HR 10.17, CI 95% 4.35-23.79). Elevated pre-treatment CEA (>9 µg/mL) was associated with poor response to long-term chemoradiotherapy compared with CEA <3 ng/mL. Decreased CEA after neoadjuvant chemoradiotherapy has prognostic significance in CRC, with CEA 5 ng/mL correlating with improved clinical and pathologic response and better overall survival and DFS [38,39].

In the results of bivariate analysis, it was found that high CRP levels ≥5 mg/L had an association with the chemotherapy response of CRC patients based on the increase in CEA levels ≥5 µg by 3.2 times [IK 95% 1.1-9.6; p 0.030]. The results of this study are not different from those conducted by Koike et al., (2008) who found that high CRP levels ≥5 mg/L can be used as a significant predictor (p<0.01) of a worse chemotherapy response in colorectal cancer patients, and the results of multivariate tests also found that CRP is an independent factor in post-chemotherapy, chemoradiotherapy and postoperative prognostics [32]. The average survival after undergoing curative resection of the tumor in the presence of CRP ≥5 mg/L with CRP <5 mg/L results were found to be 14 months with 40 months; p=0.0002. CRP levels ≥5 mg/L and CEA levels ≥6 µg/L preoperatively were found to be the same as predictors of poor survival with p values in CRP 0.01 and CEA 0.03.

Whereas in the study of Nikiteas (2005) [40] showed that CRP ≥7 mg/L before surgery can be used as a worse prognostic marker even though there is no increase in CEA levels. This increase in CRP concentration reflects acute phase protein synthesis during tumor progression. In the study by Groblewska et al.'s (2008), it was found that CRP ≥9.7 mg/dL was a predictor of chemotherapy response with p < 0.001 by 82.1%, while in this study, the effect of CRP was 66.9%, this result was lower because the subjects in the study were limited to stages II and III, while Groblewska's study was conducted at all stages. The value of CRP levels was found to increase in stage IV, namely with a median (min-max 16.9 (2-147.6))[36].

In a study conducted by Hermunen 2020, an increase in CRP ≥5 mg/L had a sensitivity of 20% to predict recurrence (CI95% 12-30%), specificity of 96% (CI95% 89-99%), and PPV of 77% (CI95% 44-93%). Elevated CRP was also associated with DFS (HR 2.53; CI 95% 1.10-5.81), but was not associated with OS as with CEA (HR 2.49; CI 95% 0.95-6.51) [41].

The correlation between CRP levels and CEA levels obtained a positive correlation coefficient value with a strong strength of r = 0.722, this result is not different from the research conducted by Yu, 2021 [42] with the results of a strong correlation of p = 0.745, research by Li 2019 [43] with the results of a strong correlation p = 0.760 and research by Dabbous et al., (2019) also proved a strong correlation of 0.733. While a very strong correlation was found in the research of Kwon et al., (2010) with the results of p = 0.824 [44]. The strong correlation is due to the same marker of malignancy response in CRC. CRP and CEA levels respond to postoperative chemotherapy. Increased levels of CRP and CEA in CRC patients are associated with poor chemotherapy response this is because both markers respond to the effects of chemotherapy, the results show that the higher the value of both levels, the worse the survival in CRC patients [10,20].

In Indonesia, the FOLFERI regimen given in 4 series is the most frequently used option as first-line therapy for CRC patients. In this study, only 3 series were given because according to the evaluation of several patients, the most patients were obtained in the 3rd series. After giving the 3rd series there will be an increase in DFS and OS of stage III patients obtained with DFS 66% and OS 73% with laboratory results obtained can reduce the levels of inflammatory markers, one of which is CRP and also CEA markers, the decrease that occurs is statistically significant with the results of RR 1.76 (IK 95% 0.6-5.6 p=0.002) for CRP and the difference in the decrease in CEA levels with 2.3 (IK95% 0.7-7.8, p=0.013) (Pectasides et al, 2015). In a study conducted by Ishizuka, 2013, CRP levels decreased significantly in 108 patients with colorectal cancer (p = 0.18), the results showed this decrease occurred in 63 patients with the initial CRC results of all patients > 1 mg/dL. Patients after the 3rd series of FOLFOX chemotherapy in 236 patients with stage III CRC found a decrease in CEA levels ≤2 ng/ml (OR 2.891 p 0.0233) (Huang et al, 2020).

CONCLUSION

From the results and discussion in this study, it can be concluded that high CRP levels are significantly associated with worse chemotherapy response with a strong positive correlation in colorectal cancer patients characterized by a high risk of increasing CEA levels 3.7 times after three series of FOLFIRI adjuvant chemotherapy.

ACKNOWLEDGMENTS

The authors would like to thank the Department of Surgery, Prof. Dr. IGNG Ngoerah Hospital, for the support of the authors in this work.

DECLARATIONS

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee.

REFERENCES

[1] Sayuti M& N. Kanker Kolorektal. Jurnal Averrous 2019;5:76–88.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209–49. https://doi.org/10.3322/caac.21660.

[3] Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol 2021;14:101174. https://doi.org/10.1016/j.tranon.2021.101174.

[4] American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. Atlanta: American Cancer Society 2020.

[5] Candrawati O, Utomo BEBH, Sofi'i lmam. Correlation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and carcinoembrionic antigen level in colorectal cancer. Jurnal Kedokteran Dan Kesehatan Indonesia 2018;9:82–8. https://doi.org/10.20885/jkki.vol9.iss2.art4.

[6] Yogi D. Profil Penderita Kanker Kolorektal RSUP Sanglah Denpasar Periode 2010-2014. Universitas Udayana: Denpasar Indonesia 2015.

[7] Pranata AANS, Dewi NNA, Surudarma IW, Sumadi IWJ. Karakteristik Pasien Kanker Kolorektal di Rumah Sakit Umum Pusat Sanglah Tahun 2017. Jurnal Medika Udayana 2021;10:53–7.

[8] Astin M, Griffin T, Neal RD, Rose P, Hamilton W. The diagnostic value of symptoms for colorectal cancer in primary care: a systematic review. British Journal of General Practice 2011;61:e231–43. https://doi.org/10.3399/bjgp11X572427.

[9] Granados-Romero JJ, Valderrama-Treviño AI, Contreras-Flores EH, Barrera-Mera B, Herrera Enríquez M, Uriarte-Ruíz K, et al. Colorectal cancer: a review. Int J Res Med Sci 2017;5:4667. https://doi.org/10.18203/2320-6012.ijrms20174914.

[10] Turvey SE, Broide DH. Innate immunity. Journal of Allergy and Clinical Immunology 2010;125:S24–32. https://doi.org/10.1016/j.jaci.2009.07.016.

[11] Partl R, Lukasiak K, Thurner EM, Renner W, Stranzl-Lawatsch H, Langsenlehner T. The elevated pre-treatment C-reactive protein predicts poor prognosis in patients with locally advanced rectal cancer treated with neo-adjuvant radiochemotherapy. Diagnostics 2020;10:1–16. https://doi.org/10.3390/diagnostics10100780.

[12] Neugut AI, Lin A, Raab GT, Hillyer GC, Keller D, O'Neil DS, et al. FOLFOX and FOLFIRI Use in Stage IV Colon Cancer: Analysis of SEER-Medicare Data. Clin Colorectal Cancer 2019;18:133–40. https://doi.org/10.1016/j.clcc.2019.01.005.

[13] Labianca R, Pancera G, Luporini G. Factors influencing response rates for advanced colorectal cancer chemotherapy. Annals of Oncology 1996;7:901–6. https://doi.org/10.1093/oxfordjournals.annonc.a010791.

[14] Kishiki T, Masaki T, Matsuoka H, Kobayashi T, Suzuki Y, Abe N, et al. Modified Glasgow prognostic score in patients with incurable stage IV colorectal cancer. Am J Surg 2013;206:234–40. https://doi.org/10.1016/j.amjsurg.2012.07.051.

[15] Chua W, Charles KA, Baracos VE, Clarke SJ. Neutrophil/lymphocyte ratio predicts chemotherapy outcomes in patients with advanced colorectal cancer. Br J Cancer 2011;104:1288–95. https://doi.org/10.1038/bjc.2011.100.

[16] M. Z, I.D. X, A. L, T. S, C. K, A. D, et al. Predictors of survival in stage IV metastatic colorectal cancer. Anticancer Res 2010;30:653–60.

[17] Chung YC, Chang YF. Serum interleukin-6 levels reflect the disease status of colorectal cancer. J Surg Oncol 2003;83:222–6. https://doi.org/10.1002/jso.10269.

[18] Shibutani M, Maeda K, Nagahara H, Ohtani H, Sakurai K, Yamazoe S, et al. Significance of markers of systemic inflammation for predicting survival and chemotherapeutic outcomes and monitoring tumor progression in patients with unresectable metastatic colorectal cancer. Anticancer Res 2015;35:5037–46.

[19] Toiyama Y, Inoue Y, Saigusa S, Kawamura M, Kawamoto A, Okugawa Y, et al. C-reactive protein as predictor of recurrence in patients with rectal cancer undergoing chemoradiotherapy followed by surgery. Anticancer Res 2013;33:5065–74.

[20] Nakayama G, Tanaka C, Kodera Y. Current Options for the Diagnosis, Staging and Therapeutic Management of Colorectal Cancer. Gastrointest Tumors 2014;1:25–32. https://doi.org/10.1159/000354995.

[21] Sitorus N. Determinan Ketahanan Hidup Lima Tahun Penderita Kanker Kolorektal di Rumah Sakit Kanker Dharmais Jakarta 2010;10.

[22] Fernanda JW, Wisnaningsih ER. MENGGUNAKAN JARINGAN SARAF TIRUAN (ARTIFICIAL NEURAL NETWORK) 2018; 6:46–51.

[23] Agung A, Mirah S, Agus M, Sueta D, Adnyana MS. Hubungan antara obesitas dan insiden kanker kolorektal di RSUP Sanglah tahun 2016-2017 2019;10:297–300. https://doi.org/10.15562/ism.v10i2.278.

[24] Dianty RM, Nur IM, Widyanti. Karakteristik Pasien Kanker Kolorektal di Bagian Patologi Anatomi Rumah Sakit Al-Islam Bandung Januari 2012-Desember 2017. Prosiding Pendidikan Dokter 2018;4:131–40.

[25] Kemenkes RI. Laporan nasional riskesdas 2018. Jakarta: Kemenkes RI 2018:154–66.

[26] Fauza D, Muhar AM, Siregar ES. Hubungan Antara Platelet-to-Lymphocyte Ratio (PLR) Pretreatment dan Neuthrophil-to-Lymphocyte Ratio (NLR) Pretreatment dengan Prognosis Kanker Kolon pada Seluruh Pasien Poli Bedah Digestif RSUP H. Adam Malik Medan. (Tesis Magister) Medan: Universitas Sumatera Utara 2018:1–89.

[27] Myers EA. Colorectal cancer in patients under 50 years of age: A retrospective analysis of two institutions' experience. World J Gastroenterol 2013;19:5651. https://doi.org/10.3748/wjg.v19.i34.5651.

[28] Vasilescu A, Târcoveanu E, Chirurgie CI, T I, Bu V. Opera Ţ Ia Hartmann – Opera Ţ Ie De Salvare 2010;6:201–11.

[29] Tabola R, Mantese G, Cirocchi R, Gemini A, Grassi V, Boselli C, et al. Postoperative mortality and morbidity in older patients undergoing emergency right hemicolectomy for colon cancer. Aging Clin Exp Res 2017;29:121–6. https://doi.org/10.1007/s40520-016-0643-1.

[30] Kemenkes RI. Panduan Penatalaksanaan Kanker kolorektal. Kementerian Kesehatan Republik Indonesia 2016:76.

[31] Łukaszewicz-zając M, Mroczko B. Circulating biomarkers of colorectal cancer (Crc)—their utility in diagnosis and prognosis. J Clin Med 2021;10. https://doi.org/10.3390/jcm10112391.

[32] Koike Y, Miki C, Okugawa Y, Yokoe T, Toiyama Y, Tanaka K, et al. Preoperative C-reactive protein as a prognostic and therapeutic marker for colorectal cancer. J Surg Oncol 2008;98:540–4. https://doi.org/10.1002/jso.21154.

[33] Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny N, Macdonald JS, et al. ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer. Journal of Clinical Oncology 2006;24:5313–27. https://doi.org/10.1200/jco.2006.08.2644.

[34] Duffy MJ, van Dalen A, Haglund C, Hansson L, Holinski-Feder E, Klapdor R, et al. Tumour markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines for clinical use. Eur J Cancer 2007;43:1348–60. https://doi.org/10.1016/j.ejca.2007.03.021.

[35] American Cancer Society. Colorectal Cancer Facts and Figures 2017-2019. Atlanta: American Cancer Society; 2017.

[36] Groblewska M, Mroczko B, Wereszczyńska-Siemiątkowska U, Kędra B, Łukaszewicz M, Baniukiewicz A, et al. Serum interleukin 6 (IL-6) and C-reactive protein (CRP) levels in colorectal adenoma and cancer patients. Clin Chem Lab Med 2008;46:1423–8. https://doi.org/10.1515/CCLM.2008.278.

[37] Almeida AB, Faria G, Moreira H, Pinto-de-Sousa J, Correia-da-Silva P, Maia JC. Elevated serum C-reactive protein as a predictive factor for anastomotic leakage in colorectal surgery. International Journal of Surgery 2012;10:87–91. https://doi.org/10.1016/j.ijsu.2011.12.006.

[38] Perez RO, São Julião GP, Habr-Gama A, Kiss D, Proscurshim I, Campos FG, et al. The role of carcinoembriogenic antigen in predicting response and survival to neoadjuvant chemoradiotherapy for distal rectal cancer. Dis Colon Rectum 2009; 52:1137–43. https://doi.org/10.1007/DCR.0b013e31819ef76b.

[39] Hao C, Zhang G, Zhang L. Chapter Eleven - Serum CEA levels in 49 different types of cancer and noncancer diseases. In: Zhang LBT-P in MB and TS, editor. Glycans and Glycosaminoglycans as Clinical Biomarkers and Therapeutics - Part A, vol. 162, Academic Press; 2019, p. 213–27. https://doi.org/https://doi.org/10.1016/bs.pmbts.2018.12.011.

[40] Nikiteas NI, Tzanakis N, Gazouli M, Rallis G, Daniilidis K, Theodoropoulos G. Serum IL-6, TNFα and CRP levels in Greek colorectal cancer patients: Prognostics implications. World J Gastroenterol 2005; 11:1639–43. https://doi.org/10.3748/wjg.v11.i11.1639.

[41] Hermunen K, Soveri LM, Boisen MK, Mustonen HK, Dehlendorff C, Haglund CH, et al. Postoperative serum CA19-9, YKL-40, CRP and IL-6 in combination with CEA as prognostic markers for recurrence and survival in colorectal cancer. Acta Oncol (Madr) 2020; 59:1416–23. https://doi.org/10.1080/0284186X.2020.1800086.

[42] Yu YL, Fan CW, Tseng WK, Chang PH, Kuo HC, Pan YP, et al. Correlation Between the Glasgow Prognostic Score and the Serum Cytokine Profile in Taiwanese Patients with Colorectal Cancer. International Journal of Biological Markers 2021;36:40–9. https://doi.org/10.1177/17246008211022769.

[43] Li S, Huang M, Liu Q, Wang D, Wu R, Zhang X, et al. Serum Expression of β-Catenin Is a Potential Detection Marker in Patients with Colorectal Cancer. Dis Markers 2019;2019. https://doi.org/10.1155/2019/5070524.

[44] Kwon KA, Kim SH, Oh SY, Lee S, Han J-Y, Kim KH, et al. Clinical significance of preoperative serum vascular endothelial growth factor, interleukin-6, and C-reactive protein level in colorectal cancer. BMC Cancer 2010;10:203. https://doi.org/10.1186/1471-2407-10-203.