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C-Reactive Protein (CRP)/Albumin Ratio (CAR) pre-treatment as a predictive factor of radiological response after neoadjuvant chemotherapy in Locally Advanced Rectal Cancer (LARC) patients at Dr. Soetomo General Hospital, Surabaya, Indonesia

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ABSTRACT

Background: Several serum inflammatory markers have been investigated as prognostic biomarkers for rectal cancer patients, including C-Reactive Protein (CRP)/Albumin Ratio (CAR). We aimed to examine the association between the CAR pre-therapy value and radiological response after neoadjuvant chemotherapy.
Methods: We recruited locally advanced rectal cancer patients who underwent FOLFOX first-line neoadjuvant chemotherapy (NAC) at Dr. Soetomo General Hospital (Surabaya, Indonesia) from January 2015 to December 2020. Before neoadjuvant chemotherapy treatment, the C-reactive protein (CRP) and albumin were measured. The chemotherapy response was performed by evaluating the CT scan result before and after the NAC was given. We used RESIST criteria to assess the radiological response after NAC treatment. Data were analyzed using SPSS version 23 for Windows.
Results: We included a total of 102 patients, with the female being the predominant gender with LARC (52%.0). The well-differentiated adenocarcinoma was the most common adenocarcinoma type found in this study (59.8%). We found 57 patients with positive responses and 45 patients with negative responses. Patients with well-differentiated status who had adenocarcinoma had a higher chance to have a positive response to NAC. Patients with low CAR values had a 2.13 times higher chance of having a positive chemotherapy response than patients with high CAR values (95% CI = 1.30-3.30).
Conclusion: There was a significant relationship between high CAR values and poor radiological response after neoadjuvant chemotherapy in locally advanced rectal cancer patients. The CAR value may be a potential biomarker to predict the radiologic response after NAC treatment.

Keywords: C-Reactive Protein, Albumin, Ratio, Locally Advanced Rectal Cancer, Radiological Response.
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INTRODUCTION

Rectal cancer is one of the most common types of malignancy and the second most common cancer in the large intestine.[1,2] Rectal cancer is defined as a malignancy that arises in the rectum. People were living with rectal cancer range from 39,910 per year in the US. Most rectal cancers are sporadic (70%), with a mean age of diagnosis after 50 years. A small proportion of patients (10%) showed a higher risk at less than 50 years.[3] Among all cancer sites, rectal cancer is the second leading cause of death in the United States. Approximately 18% of rectal cancer occurs at <50 years with an advanced stage and a poorer prognosis. Therefore, a better understanding of simple and objective prognostic factors for rectal cancer is important to improve the prognosis and monitoring of patients with rectal cancer.[4,5]

Surgical resection, either tumor resection or total mesorectal excision/ TME, is the best treatment option for rectal cancer patients.[6] However, surgery cannot be performed immediately in locally advanced rectal cancer (LARC) patients. Other therapies, such as neoadjuvant therapy or a combination of chemotherapy and/or radiotherapy, might be needed with the aim of downsizing or to downstaging the tumor, which will increase the possibility of sphincter-saving and residual free resection, subsequently reducing the local recurrence rate.[7–9]

Several serum inflammatory markers have been investigated as prognostic biomarkers in various cancers. C-reactive protein (CRP)/ albumin ratio (CAR) has been associated with the survival of rectal cancer patients. CRP is an acute-phase protein regulated by several proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 and interleukin-6. Meanwhile, albumin, synthesized in the liver, also decreases production due to inflammation. Albumin

is also a parameter of nutritional status and is associated with chronic inflammatory processes.[4,5] Albumin is a multipurpose drug carrier protein and improves the pharmacokinetic profile of peptides or protein-based drugs.[10] Various studies have also reported the role of pre-therapy serum albumin as a prognostic tool.[10,11]

In this study, we aimed to examine the association between the CAR pre-therapy value and radiological response after neoadjuvant chemotherapy and examine the potential of CAR value as a predictive factor of radiological response after neoadjuvant chemotherapy in locally advanced rectal cancer patients.

MATERIALS AND METHODS

Study Design and Subjects

This study is an associative test using a retrospective cohort analytic observational study design, associating the pre-therapy CAR value with the radiological response after neoadjuvant chemotherapy (NAC) in locally advanced rectal cancer patients. The study population was patients with locally advanced rectal cancer who underwent FOLFOX first-line neoadjuvant chemotherapy at Dr. Soetomo General Hospital (Surabaya, Indonesia) from January 2015 to December 2020. The subjects were recruited using a consecutive sampling method. The subjects in this study were given the FOLFOX regimen with a dose of oxaliplatin 85 mg/m^2 IV, leucovorin 400 mg/m^2 IV, fluorouracil 400 mg/m^2 IV, followed by fluorouracil i.v. in 46 hours (2400 mg/m^2). The cycle was repeated every 14 days. We excluded patients with no complete CRP and albumin value in this study. We also excluded patients with no CT scan evaluation before and after NAC treatment.

CRP, Albumin, and CAR Measurement

The CRP and albumin levels were measured before the NAC treatment was given. The normal range of CRP used in Dr. Soetomo General Hospital (Surabaya, Indonesia) was between 0 – 1.0 mg/dL. The CRP was considered high when the measurement was > 1 mg/dL. The normal albumin levels used in our hospital were between 3.5 – 5.2 g/dL. The patient was considered hypoalbuminemia when the albumin was less than 3.5 g/dL. The CAR was calculated by dividing the CRP by the albumin measurement. As previously described, the CAR value was divided into two groups: high CAR and low CAR, using the cut-off value of 0.1.[4]

Radiological Response to Chemotherapy

Radiological response to chemotherapy is an evaluation of the change in tumor size measured objectively through radiological examination (abdomen-pelvic CT scan) in 6-8 weeks after the patient received neoadjuvant chemotherapy. The patients underwent a CT scan (Hitachi Eclos, Japan) and the radiological results were read by a radiology specialist at Dr. Soetomo General Hospital (Surabaya, Indonesia). The expertise was recorded in the patient's medical record data.

The radiological response was determined using RECIST 1.1 criteria and each patient was divided into one of four categories: progressive disease, stable disease, partial response and complete response. Complete response was determined when all target lesions were disappeared and when any pathological lymph nodes had a reduction in short axis to less than 10 mm. Partial response was determined with at least a 30% decrease in the diameters of target lesions. Progressive disease was determined when there was a 20% increase in the sum of diameters of target lesions and must increase at least 5 mm. Stable disease was determined when neither sufficient shrinkage for a partial response nor adequate increase for a progressive response. Further, we divided the patient response into two groups: a positive response which consisted of patients with a complete response and partial response and a negative response which consisted of patients with stable disease and progressive disease.

Statistical Analysis

Discrete variables were tested using the Chi-square test. Statistical significance was determined when the P-value was less than 0.05. The statistical analysis was performed using the SPSS statistical software package version 23.0 (IBM Corp., Armonk, NY, USA) for Windows.

RESULTS

In this study, we included a total of 102 patients, with the female being the predominant gender with LARC (female: 53 patients; 52% vs. male: 49 patients; 48%). Based on the age category, we found that patients aged less than 50 years were the predominant age group in this study (53.9%), slightly higher than more than equal to 50 years group (46.1%). In this study, BMI measurement was also carried out on the patients. We found that most patients had normal BMI (92.1%). There were three underweight patients (2.9%), three patients with overweight BMI (2.9%), and two patients with obesity (2.1%). The demographic data are shown in Table 1.

Pathological results data obtained from the biopsy showed that there were 61 patients with well-differentiated adenocarcinoma (59.8%), 27 patients with moderately differentiated adenocarcinoma (26.5%), and 14 patients with poorly differentiated adenocarcinoma (13.7%). The patient's pre-chemo staging was determined using the TNM system, T tumor size, N regional lymph node nodules and M distant metastases. The staging is

Table 1. Demographic data of subjects in this study.

Characteristic	Total (N=102)	Percentage (%)
Sex		
Female	53	52.0
Male	49	48.0
Age (Years)		
< 50	55	53.9
≥ 50	47	46.1
Body Mass Index (BMI)		
Underweight	3	2.9
Normal	94	92.1
Overweight	3	2.9
Obese	2	2.1

Table 2. Cancer staging and pathologic examination results.

Category	Total (N=102)	Percentage (%)
TNM classification		
T (Tumor)		
T3	27	26.5
T4a	41	40.2
T4b	34	33.3
N (Nodule)		
N0	7	6.9
N1	27	26.5
N2	68	66.7
M (Metastasis)		
M0	102	100
Stadium		
IIb	3	2.9
IIc	3	2.9
IIIb	37	36.3
IIIc	59	57.8
Pathological grading		
Well-differentiated adenocarcinoma	61	59.8
Moderately differentiated adenocarcinoma	27	26.5
Poorly differentiated adenocarcinoma	14	13.7

Table 3. Radiological response after neoadjuvant chemotherapy.

Radiological Response	Total (N=102)	Percentage (%)
Positive Response	57	55.9
Complete Response	3	2.9
Partial Response	54	52.9
Negative Response	45	44.1
Progressive disease	19	18.6
Stable disease	26	25.5

based on the results of the abdomen-pelvic CT scan with details as shown in Table 2.

Based on the TNM table for pre-neoadjuvant chemotherapy in this study sample, the highest T distribution (tumor) was in the T4a group as many as 41 patients (40.2%) followed by the T4b and T3 groups. The most distribution of N (nodules) was in the N2 group as many as 68 patients (66.7%), while the highest stage was stage IIIc (57.8%), followed by the stage IIIb group (36.3%) and the stage IIc and IIb groups with the same number (2.9%) (Table 2).

The radiological response after NAC in this study is shown in Table 3. We found that there were 57 patients with a positive response and 45 patients with a negative response specifically there were 19 subjects (18.6%) with progressive disease, 26 subjects (25.5%) with stable disease, 54 subjects (52.9%) with partial response, and three subjects (2.9%) with complete response. The criteria from RECIST were used to evaluate the chemotherapy response after 4 cycles of neoadjuvant chemotherapy. Radiological examinations were performed to re-stag the tumor to assess the response to the chemotherapy regimen given. Radiological response assessment was determined using the

Table 4. Association between subject characteristic and radiological response.

Characteristic	Total (N=102)	Radiological Response		p	RR (95% CI)
		Positive (+) N (%)	Negative (-) N (%)		
Tumor Grade Adenocarcinoma					
Well-differentiated	61	47 (77.00)	14 (23.00)	0.001*	-
Moderate differentiated	27	12 (44.40)	15 (55.60)		
Poor differentiated	14	0 (0.00)	14 (100.00)		
Albumin Level					
< 3.5	48	30 (62.50)	18 (37.50)	0.369	1.20 (0.70-1.90)
≥ 3.5	54	29 (53.70)	25 (46.30)		
CRP Category					
High	61	43 (70.50)	18 (29.50)	0.002*	1.80 (1.30-2.70)
Normal	41	16 (39.00)	25 (61.00)		

CRP: C-Reactive Protein; RR: Relative Risk; CI: Confidence Interval; *Chi-Square: statistically significant if p-value less than 0.05

Table 5. The association between CAR with radiological response.

CAR category	Total (N=102)	Radiological Response		p	RR (95% CI)
		Positive (+) N (%)	Positive (+) N (%)		
High CAR	45	18 (40.0)	27 (60.0)	0.001	2.13 (1.30-3.30)
Low CAR	57	41 (71.9)	16 (28.1)		

CAR: CRP/Albumin Ratio; RR: Relative Risk; CI: Confidence Interval; *Chi-Square: statistically significant if p-value less than 0.05

results of the abdomen-pelvic CT scan, which was then interpreted by a radiology specialist (Table 3).

This study examines the association between the subject's characteristics and radiological response after NAC treatment. Based on the tumor histopathology, 47 patients (77.0%) with well-differentiated adenocarcinoma had a positive response to chemotherapy, while 14 patients (23.0%) had a negative response. In patients with moderately differentiated adenocarcinoma, we found 12 patients (44.4%) with a positive response and 15 patients (55.6%) with a negative response (Table 4). All patients with poorly differentiated adenocarcinoma had a negative response to chemotherapy. We found a significant relationship between histopathology and chemotherapy response (p=0.01) (Table 4).

CRP measurement showed that in the study, 61 patients low high CRP levels while the remaining 41 patients had high CRP levels. In the high CRP level group, 43 patients (70.5%) had a positive response and 18 patients had a negative response (29.5%). In the low CRP level group, 16 patients (39.0%) with a positive response and 25 patients (61.0%) with a negative response. There was a significant relationship between CRP level and radiological response (p=0.020). Patients with normal/not high CRP had a 1.8 times higher chance of having a positive chemotherapy response than patients with high CRP levels (95% CI = 0.836-1.620) (Table 4).

We examined the albumin level and examined the association with chemotherapy response. The cut-off value to determine the albumin level was 3.5 g/dL. There were 54 patients with albumin level ≥ 3.5 g/dL and 48 patients with albumin levels < 3.5 g/dL. Furthermore, in the group with albumin levels < 3.5 g/dL, there were 30 patients (62.5%) with positive chemotherapy responses and 18 patients (37.5%) with negative chemotherapy responses. In patients with albumin levels ≥ 3.5 g/dL, 29 (53.7%) patients had positive chemotherapy responses and 25 patients (46.3%) had negative chemotherapy responses. There was no significant association between albumin level and chemotherapy response (p=0.369). Patients with albumin < 3.5 g/dL had a 1.2 times higher chance to have negative chemotherapy response compared to patients with albumin levels ≥ 3.5 g/dL (95% CI = 0.836-1.620). Characteristics of research subjects are shown in Table 4.

The CRP/Albumin Ratio (CAR) variable was divided into two using the cut-off of 0.1: low CAR and high CAR. This study found that the predominant group was the low CAR level group (low: 57 patients; 55.9% vs. high: 45 patients; 44.1) (Table 5). In the low CAR group, there were 41 patients with a positive response and 16 patients with a negative response. Furthermore, in the high CAR group, there were 18 patients with a positive response and 27 patients with a negative response. Our analysis showed a significant relationship between CAR and radiological response (p=0.001). Patients with low CAR values had a 2.13 times higher chance of having a positive chemotherapy response than patients with high CAR (95% CI = 0.836-1.620). The distribution of CAR on the radiological response towards chemotherapy is shown in Table 5.

DISCUSSION

This study examined the association between the pre-therapy CAR value and the radiological response after neoadjuvant chemotherapy. The CRP/Albumin Ratio (CAR) value was divided into two categories, namely low CAR and high CAR, using the cut-off value previously described.[4] From our analysis, we found a significant association between CAR and the response to chemotherapy. A study conducted by Partl R et al., in 2020 concluded that the increased pre-therapy CRP has a poor outcome in patients.[12] These results are in line with a systematic review and meta-analysis using 3,431 colorectal patients, which revealed a significant relationship between the increased CAR values and poor patient prognosis.[4] This study also concluded that a high CAR value indicates a poorer prognosis in colorectal cancer patients than a low CAR value, indicating that CAR is a valuable prognostic indicator to predict the radiologic response after NAC treatment. This phenomenon might happen because the inflammatory process is one of the important factors in tumor development.

Locally Advanced Rectal Cancer (LARC) is rectal cancer that has reached T3 and T4 or a tumor that has invaded locoregional lymph nodes. Locally advanced rectal cancer (LARC) was established based on the tumor classification parameters cT3-T4, N -/+, and M0, which have a 5-years survival rate of 50-65%, with a local recurrence rate of around 30-40%, and a high incidence of metastases.[13] Locally Advanced Rectal Cancer (LARC) can also be defined as a tumor that invades or spreads close (< 2 mm) to the mesorectal fascia. In addition, because LARC is cancer of the rectum that reaches T3 and T4, which means that the tumor is adjacent to adjacent organs such as the pelvic bone, proximity of the sphincter or peritoneum, vagina, prostate and also the autonomic nerves, making surgical resection an option challenging because it can cause patient morbidity.[14] The use of neoadjuvant chemoradiotherapy is recommended for all newly diagnosed rectal adenocarcinomas with a clinical-stage (c) T3 or T4 based on transrectal Endoscopic Ultrasound (EUS) or pelvic Magnetic Resonance Imaging (MRI). In this study, the chemotherapy treatment used was FOLFOX because it controlled the accuracy of the dose and the cycle of chemotherapy administration. Meanwhile, in patients taking capecitabine therapy, it is difficult to review the accuracy of taking the drug while the patient is at home.

This study only included rectal cancer patients diagnosed with adenocarcinoma based on pathology results. Based on the tumor histopathology, we found that patients with well-differentiated adenocarcinoma had a higher percentage of positive radiological response after NAC. Moderately differentiated adenocarcinoma had a lower chance of having a positive response. In addition, we found that all patients with poorly differentiated adenocarcinoma had a negative response towards NAC treatment in this study. These results clearly showed that the level of cell differentiation was a crucial factor affecting the effectiveness of the chemotherapy. Our result concordance with the research conducted by Wardhana

AA and Lesmana T, which concluded that well-differentiated adenocarcinoma had a positive relationship to chemotherapy response.[15] In contrast, the poorly differentiated adenocarcinoma was associated with a negative chemotherapy response. This is consistent with the theory, which states that patients with poorly-differentiated adenocarcinoma have a worse prognosis than those with well-differentiated adenocarcinoma.[15,16]

This study found a significant association between albumin levels and radiological response towards NAC treatment. Patients with high albumin levels had a higher chance of having a positive response than patients with low albumin levels. A previous study conducted by Heys SD et al., showed that albumin could be used as a prognostic factor in colorectal cancer patients.[11] The most common plasma protein, albumin, makes up almost half of the total protein composition. Albumin is the most widely used nutritional indicator and is also involved in the inflammatory response, acting as an acute-phase protein. Low albumin concentrations indicate malnutrition, which can negatively impact tumor immunity in the tumor microenvironment, drug carrier limitation, and the decrease of the pharmacokinetic profile of the drugs. The results of research by Lai CC et al., also supports the role of albumin as a prognostic modality that can be used to predict the poor prognosis of colon cancer and the survival rate in colon cancer patients.[17] Hypoalbuminemia is an independent risk factor for postoperative mortality, morbidity, and complications related to wounds, lungs, urinary system, and anastomoses. Previous studies reported that compared to normal albumin levels, patients with hypoalbuminemia had a lower 5-year survival rate (normal, 78% vs. hypoalbuminemia, 60%) and had lower 5-year recurrence-free rate or 5-years relapse-free survival than normal albumin level (normal, 78.9% vs. hypoalbuminemia, 73.5%).[17-19]

This study also found a statistically significant association between CRP levels and NAC response. Elevated CRP is a secondary response to tumor necrosis, local tissue damage, and inflammation in malignancy patients. CRP is produced in hepatocytes as a systemic response to cytokines in the bloodstream, particularly IL-6, which is released from leukocytes in the tumor microenvironment. IL-6 can also indirectly assist the binding of CRP to phospholipids in tumor cells, activate the classical C1q pathway of the complement system and act as an opsonin, leading to tumor cell lysis.[20] There was evidence that CRP was not only a marker of inflammation but has a role in regulating tumor microenvironment, tumor cell growth and survival; this results in changes in response to hormones and chemotherapy drugs.[21]

We found that CRP and albumin can be used as independent prognostic indicators in cancer patients from the above findings. CRP and albumin are more appropriate indicators to be used as complementary indicators as predictors of prognosis in solid tumors. The CAR is a promising prognostic factor in cancer patients because it is associated with poor survival rates, including OS and DFS patients. These markers reflect the systemic inflammatory response in cancer patients and have been reported as significant prognostic indicators. A high CAR indicates that C-Reactive Protein (CRP) is high and albumin levels are low, which may represent a condition leading to a poor response to chemotherapy.

CONCLUSION

There was a significant relationship between high CAR values and poor radiological response after neoadjuvant chemotherapy in locally advanced rectal cancer patients. The CAR value may be a potential biomarker to predict the radiologic response after NAC treatment.

CONFLICTS OF INTEREST

No competing interests were declared regarding this study.

ETHICAL CLEARANCE

Ethical approval was obtained from the Ethics Committee of Dr. Soetomo General Hospital, Surabaya, Indonesia (Ref. No: 0651/LOE/301.4.2/X/2021).

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AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis, drafting the manuscript until interpreting the final report through publication.

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