Section: Medical Oncology

Original Research Article

THE PREDICTIVE AND PROGNOSTIC VALUE OF C-REACTIVE PROTEIN/ALBUMIN RATIO (CAR) IN RESPONSE TO PALLIATIVE CHEMOTHERAPY IN STAGE IV COLORECTAL CANCER

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Abstract

Background: Colorectal cancer (CRC) is one of the most common causes of cancer-related death worldwide. C- reactive protein-to albumin (CRP/ALB) ratio (CAR) has been reported to be a more accurate prognostic value in patients with various malignancies which is calculated from the serum CRP and albumin concentration. The study aims to find the prognostic and predictive value of CRP/Albumin ratio in response to palliative chemotherapy in stage IV colorectal cancer. **Materials and Methods:** A prospective observational study was conducted on newly diagnosed Stage IV Colorectal cancer treated in Gastrointestinal clinic of Medical Oncology Department at Regional Cancer Centre for first line palliative chemotherapy. CAR was calculated at baseline, after first line palliative chemotherapy and at relapse. Response was correlated with the baseline CAR and the change in their levels after palliative chemotherapy. The baseline CAR and difference in the CAR after first line palliative chemotherapy was correlated with progression free survival and overall survival at 2 years. **Result:** The study included eighty two patients with newly diagnosed, treatment naïve Stage IV Colorectal Cancer. In this study, seventy-nine (96.3%) patients presented with metastatic colon cancer and three (3.6%) patients had carcinoma rectum. Palliative Chemotherapy regimens include FOLFOX in fifty-seven (69.5%), CAPEOX in twenty-four (29.2%) and FOLFIRI in one (1.2%) patient. Molecular targeted therapy using Anti VEGF agent Bevacizumab was given to thirty nine (47.5%) of patients. The baseline value of albumin, C-Reactive protein and CAR were studied. After palliative chemotherapy the value of albumin, CRP, CAR were taken. The mean CAR value was also studied for different regimens. The mean value of Albumin, CRP and CAR were also studied at relapse. The mean value of CRP, Albumin, and CAR were compared with baseline values. The progression free survival, overall survival was also assessed. **Conclusion:** The difference in CAR at base line and after chemotherapy and at relapse can be a predictor of response to chemotherapy in metastatic colorectal cancer. This study may help to predict and prognosticate patients to response to chemotherapy and relapse. The advantage is that it is simple, inexpensive and not time consuming. Moreover, it includes a nutritional marker which states the performance status of the patient.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common causes of cancer-related death worldwide.[1] About 20% present with distant metastasis at diagnosis and the survival of patients with unresectable stage IV CRC is very poor, with a median survival of 6-8 months with best supportive care without chemotherapy.[2] However, due to the development of chemotherapeutic and molecular targeting agents, the survival time has improved dramatically within the last decade, with a median survival of 24-30 months.[3-5]

Several parameters for predicting survival in patients with CRC have been identified, including patient characteristics, such as the performance status (PS), age and gender, and tumour

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characteristics, such as clinicopathological factors and the stage. The development of a new parameter able to more precisely predict the patient survival required to help select the optimal treatment, especially in patients with advanced disease. Many molecular parameters (such as proteins involved in cell cycle regulation, apoptosis and angiogenesis or RAS/RAF mutations) are associated with survival. These molecular parameters require sophisticated and expensive laboratory techniques.

Several combinations of these factors, including Glasgow Prognostic Score (GPS), neutrophil to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI), have also been reported to be useful prognostic factors in various malignant solid tumours, including CRC. The aim of this study is to examine the significance of Albumin to C-Reactive protein ratio (CAR) as a useful prognostic factor in patients with metastatic colorectal cancer.

MATERIALS AND METHODS

This was a prospective observation study conducted at department of medical oncology RCC Thiruvananathapuram for a period of 2 years after ethical clearence from IRB.

Based on study by Shibutani et al,[6] assuming a power of 80% and 5% level of significance we need minimum sample size of 83 as per the formula $n = (Z\alpha + Z\beta)\ 2\ [\log(RH)]2q0q1\ Z\alpha = 1.96,\ Z\beta = 0.8416$, RH= 1.857, $q1 = 0.448$ and $q0 = 1 - q1$

Newly diagnosed cases of Stage IV Colorectal cancer treated in Gastrointestinal clinic of Medical Oncology Department at Regional Cancer Centre who was planned for first line palliative chemotherapy were included in this study. Those patients satisfying the inclusion criteria was selected. A complete blood counts with differentials, renal function tests, liver function tests, serum albumin, serum CRP, serum CEA, tissue diagnosis with complete histology, CT of thorax, abdomen and pelvis will be done as part of routine evaluation and reports was done as per institutional protocol. CAR was calculated as, CAR = C- Reactive Protein / Albumin CAR was calculated at baseline, after first relapse and after first line palliative chemotherapy. Response was then correlated with the baseline CAR and the change in their levels after palliative chemotherapy. The baseline CAR and difference in the CAR after first line palliative chemotherapy was correlated with progression free survival and overall survival at 2 years. Progression Free Survival (PFS) was taken from the date of initiation of treatment to the date of of death or last follow up. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow up.

Inclusion Criteria

- Newly diagnosed patients with metastatic CRC
- Patients planned for first line palliative chemotherapy with FOLFOX -6 or CapeOX .
- Patients in the age group between 18 to 70 years

Exclusion Criteria

- Non metastatic colorectal cancer
- Patients with history of previous malignancy
- Patients with active infection
- Pregnant and lactating women

Statistical methods: The demographic variables were summarized using appropriate descriptive statistics (frequencies, percentages, mean, median and Standard Deviation). The significant differences in inflammatory and nutritional markers at two different time points were tested using paired t-test. The cut-off value of CAR was obtained using ROC analysis. The survival probabilities were estimated using the Kaplan-Meier method and the corresponding significant differences by the Log-rank test. The risk for survival was estimated using the Cox proportional hazards modal. A p-value less than 0.5 was considered statistically significant.

RESULTS

A prospective observational study was conducted on newly diagnosed stage IV colorectal cancer. A total of 82 patients were studied.

Table 1: Baseline characteristics of patients.

Age (years)	56(median)	percentage
Gender		
Male	36	44
Female	46	56
Location of primary tumour		
Colon	79	96.3
Rectum	3	3.6
Histology		
Well, moderately differentiated	76	96.6
Poorly, mucinous	6	7.3
First line Chemotherapy		
FOLFOX+ Bevacizumab	35	42.7
CAPEOX + Bevacizumab	4	4.8
FOLFOX	22	26.8
CAPEOX	20	24.3
FOLFIRI	1	1.2
Molecular Targeted therapy		
Bevacizumab	39	47.5
Pre-treatment C-reactive protein level(mean)	1.145 g/dl	
Pre-treatment albumin level(mean)	3.7 g/dl	
Pre-treatment CAR (mean)	1.13	

The median age of the patients studied was 56 years.

Table 2: Classification of the patients according to sex

Gender	Number	Percentage
Male	36	43.9
Female	46	56.1
Total	82	100

Figure 1: sex distribution of the patients

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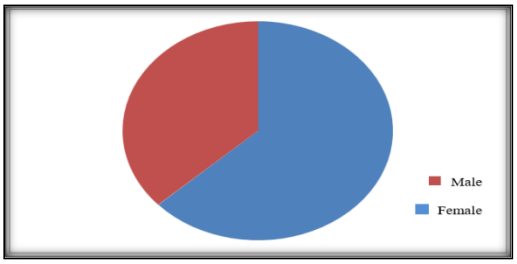

Table 3: Location of the primary tumour

Location	Number	Percentage
Colon	79	96.3
Rectum	3	3.7
Total	82	100

Figure 2: Location of primary tumour

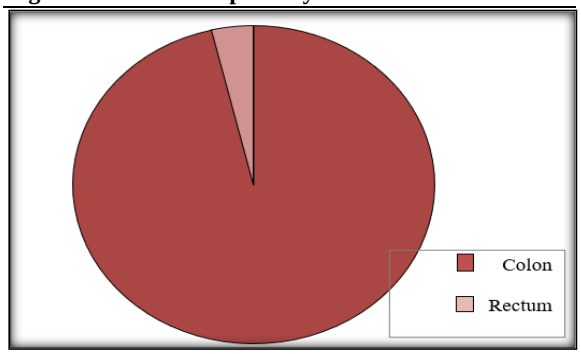

Table 4: First line chemotherapy

Chemotherapy	Number	Percentage
FOLFOX+Bevacizumab	35	42.6
CAPEOX+Bevacizumab	4	4.8
FOLFOX	22	26.8
CAPEOX	20	24.39
FOLFIRI	1	1.2
Total	82	100

Table 5: Studied factors and p value at baseline and 6 months

Factor	Baseline value	Value at 6 months	p-value
Albumin (g/dl)	3.6	4.0	0.001
CRP (g/dl)	3.6	1.9	0.001
CAR (ng/dl)	1.1	0.5	0.001

Table 6: Mean values of studied factors at baseline and relapse

Factor	Baseline value	Value at relapse	p-value
Albumin (g/dl)	3.6	3.3	0.001
CRP (g/dl)	3.9	5.0	0.022
CAR (ng/dl)	1.1	1.2	0.001

Paired t test was used to find the significant correlation between CAR, CEA at baseline and after first line chemotherapy. Also studied any significant difference between CAR, CEA at relapse. There is statistically significant p value found between CAR, CEA at baseline and first line chemotherapy. The study found no significant relations between CEA at baseline and after relapse.

Comparison of CAR with baseline clinical features

Table 7: Comparison of CAR with Sex

	Sex	Mean	P-value
Car baseline	Male	1.13755	0.875
	Female	1.09442	

Table 8: Comparison of CAR with age

	Age (years)	Mean	P-value
CAR	<60	1.03258	0.492
BASELINE	≥60	1.22182	

Table 9: Comparison of CAR with chemotherapy

	CAR Mean value	P-value
FOLFOX+B	1.09878	0.329
CAPEOX+B	1.91237	
FOLFOX	.83646	
CAPEOX	1.33361	
Total	1.12569	

When studied CAR with base line characterstics like age, sex, chemotherapy no statistically significant association was found. For study purpose age was categorized as above 60 years and below 60 years.

Survival Analysis

Figure 3: ROC analysis showing CAR CUT OFF VALUE

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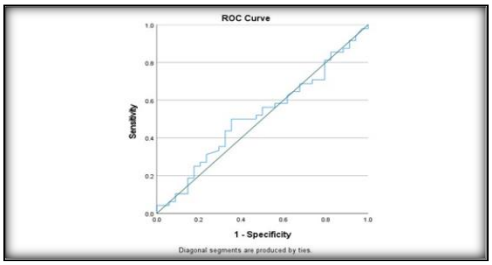

Figure 4: Cut off value for CAR: 0.76

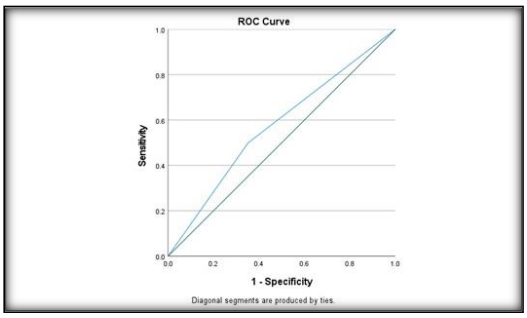

Table 10: Overall survival

Time (Months)	Surv Prob %	SE %
12	98.6	1.4

At 12 months survival probability was 98.6% with a standard error of 1.4%.

Table 11: Median overall survival

Median Survival (months)	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
23.000	2.713	17.683	28.317

Median overall survival was found to be 23 months with a standard error of 2.713.

Table 12 Survival probability with CAR CUT OFF VALUES

Time (Months)	UPTO 0.76		>0.76		P-value
	Surv Prob %	SE %	Surv Prob %	SE %	
12	94.5	3.8	96.8	3.2	0.970

At 12 months the survival probability was found to 96.8% at CAR more than .76 and 94.5 at CAR less than .76. it is statistically non-significant. (p value .970).

Figure 5: Overall survival curve

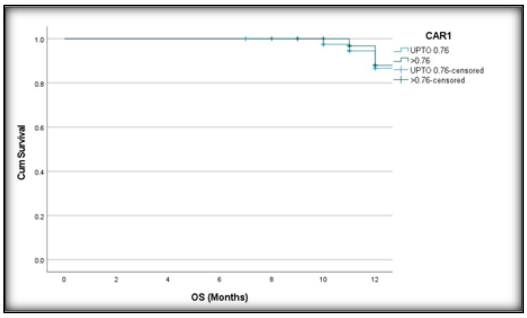

Table 13: Progression free survival

Time (Months)	Surv Prob %	SE %
12	39.6	5.9

Table 14: Median Progression free survival

Median survival (months)	Std. Error	95% Confidence Interval	
		Lower Bound	Upper Bound
11.000	.500	10.020	11.980

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At 12 months the progression free survival probability was 39.6 with standard error of 5.9. The median progression free survival was 11 months.

DISCUSSION

The CRP/ALB ratio was used to predict the prognosis in various cancers. CRP is an inflammatory marker and albumin is a nutritional marker used in the study. Thus as a combination of these two proteins, CAR may reflect the severity of inflammation, which is believed to be correlated with tumour progression. Various other markers studied in colorectal cancer to predict outcome include neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, GPS, modified GPS.

Our study is a single institution prospective observational study of treatment naïve Stage IV Colorectal cancer treated in Gastrointestinal clinic of Medical Oncology Department at Regional Cancer Centre who is planned for first line palliative chemotherapy from 1/7/2021 to 31/12/2022. We assessed the baseline value of albumin to CRP ratio, CEA at baseline and after first line palliative chemotherapy and at relapse.

The demographic variables were summarized using appropriate descriptive statistics (frequencies, percentages, mean, median and Standard Deviation). The significant differences in inflammatory and nutritional markers at two different time points were tested using paired t-test. The cut-off value of CAR was obtained using ROC analysis. The survival probabilities were estimated using the Kaplan-Meier method and the corresponding significant differences by the Log-rank test. The risk for survival was estimated using the Cox proportional hazards modal. A p-value less than 0.5 was considered statistically significant.

In the present study there is no significant association was found between baseline CAR/Alb ratio and age. Here we categorised patients as above age 60 and below age 60. A multicentre study conducted by Hashimoto et al. found that high pre-operative CAR was an independent predictor of postoperative complications in patients aged 85 years or older who underwent primary tumour resection for CRC.[7] In the study Xue Feng Ni etal, an elevated CRP/Alb ratio was significantly associated with advanced age .[8]

In the present study there is no significant difference was found with CRP/Alb ratio and sex difference with p value 0.0875. Xue Feng etal8 studied CRP/Alb ratio with sex difference. Mao song etal found a minor of male cases dominance (n=70) was observed compared with their female counterparts (n=53) overall, but no significant difference of gender distribution was identified between the two groups.[9]

We have given different chemotherapy regimens based on patients' tolerance. Majority of patients were treated with FOLFOX regimes (42%). In the present study we examined that no significant difference with different chemotherapy regimens. It was found that there exists no significant difference between CAR and chemotherapy-(p value 0.329). Meta – analysis of the effect of CAR on overall survival by Chun-Kai Liao et al studies with a total 6193 participants reported the association of pre-treatment CAR with overall survival.[10-14]

In the present study the CAR cut-off was 0.6 and there was no significant difference exist between CRP level and overall survival (p value 0.97). Masatsune Shibutani et al,[6] the overall survival rate was significantly worse in the pre-treatment CAR group than in the low pre-treatment CAR group (p value 0.0009).

Meta – analysis conducted by Jia yuan Wu etal, six studies comprising 2904 patients reported the outcomes for disease free survival(DFS) and the pooled result indicated that elevated CAR was associated between poor DFS (HR=1.80 95%CI P<0.001).[11] In the present study also assessed DFS in relation to CAR at 12 months patients a survival probability 45% was seen in CAR less than 0.6 and 32% in CAR more than 7%. The p value was non-significant (0.21).

In a study by Xu Feng et al,[8] determined whether CRP/Alb ratio as a predictor of response to chemotherapy. This study is the first to show that CRP/Alb ratio was superior to other inflammation-based prognostic scores in predicting 6-month survival rates in patients with metastatic colorectal cancer. In the present study also showed statistically significant difference CRP/Alb ratio baseline and at 6months as a predictor response to chemotharaty with a p value of 0.001.

CONCLUSION

Metastatic colorectal is cancer one of the most common causes of cancer related death at our institution. There was statistically significant corelation with CAR at baseline and CAR after first line palliative chemotherapy There is no statistical significant relation between overall survival and progression free survival in relation with CAR values. This study may help to predict and prognosticate patients to response to chemotherapy and relapse. The advantage is that it is simple, inexpensive, and not time consuming. Moreover, it includes a nutritional marker which states the performance status of the patient.

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