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Original research article

Association of preoperative c-reactive protein (CRP), carcinoembryonic antigen (CEA), Glasgow prognostic score (GPS) and car (CRP/albumin ratio) with staging, recurrence and survival in colorectal carcinoma: A prospective observational study

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Abstract

Colorectal carcinoma is the most common malignancy of the gastrointestinal tract. In India, colorectal cancer accounts for 7/1,00,000. Colorectal cancer only causes symptoms in 10% to 15% of patients early in the disease, and therefore screening is necessary for the early detection of colon cancer. Colonic cancers have a good prognosis provided they are detected early and treated aggressively. The search for better screening methods for cancers, including colorectal cancers, has led to tumor markers. An ideal tumor marker should be both specific and sensitive enough to detect small tumors for early diagnosis or during screening. This study was done to determine the significance and prognostic value of preoperative C-Reactive protein (CRP), Carcinoembryonic antigen (CEA) levels, GPS(Glasgow prognostic score) and CAR(CRP/Albumin ratio) in colorectal carcinomas (CRC). Correlation of CRP, CEA, CAR and GPS was done with staging and recurrence pattern of the disease.

Materials and Methods: This is a prospective observational study which included all the patients who underwent treatment for colorectal carcinomas, in the Department of Surgical Gastroenterology at Nizam's Institute of Medical Sciences, Hyderabad, over a period of 2 years from 1st March 2016 to 30th April 2018. The study population was Biopsy proven cases of Colorectal carcinomas treated at Nizam's Institute of Medical Sciences, Hyderabad during the study period.

Results and Analysis: A total of 146 patients with colorectal carcinoma were included in the study. 95(65.1%) patients were below 60 years of age and 51(34.9%) patients were above 60 years. Mean age at presentation was 45.6 years. 90(61.7%) patients were males and 56(38.3%) patients were females. Sixty five (44.6%) of the 146 patients diagnosed to have colorectal carcinomas were located in the right colon, 55(37.6%) in the left colon, 23(15.7%) in the rectum and only 3(2.1%) involved both the left and right colon. The most common histological differentiation of colorectal carcinoma observed was moderately differentiated type accounting for 64(43.8%) cases followed by well differentiated, 52 (35.6%) cases and least being the signet/poorly differentiated type, 30(20.6%) cases.

Out of all the parameters (pre-operative CEA,CRP,GCS,CAR), elevated CAR was the most sensitive marker associated with advanced stage, poor tumor differentiation, recurrence and cancer related mortality in CRC in this study. Preoperative CEA was the least sensitive marker for prognostication of CRC in this study. The results of univariate analyses demonstrated that pathological differentiation,stage (III, IV/0, I, II), and CAR (>0.034/<0.034) were associated with OS which were confirmed on multivariate analysis also. Patients with high CAR (>0.034) showed poorer OS than those with low CAR.

There was a significant difference in the survival period between patients with low CAR (321 ± 280 days) and patients with high CAR (261 ± 160) days;(P< 0.001, Mann–Whitney U test). Kaplan–Meier analysis and log-rank tests demonstrated a significant difference in 2 years OS between patients with low CAR and patients with high CAR. The 2 year survival in low CAR and high CAR groups were 96.6% and 88.3% respectively.

Conclusion: A definitive association between C- reactive protein and advanced disease was observed

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(presence of metastases (intraoperative / histopathological evidence). Higher CRP values were observed in patients with poorer differentiation of tumor and higher recurrence rates. No significant association could be demonstrated between preoperative CEA levels and Stage, tumor differentiation and recurrence. Persistent hypoalbuminemia is a feature of advanced disease and should be monitored serially and for longer period to arrive at a consensus.A low level of serum albumin is usually found in metastatic colorectal carcinoma patients.
CAR was the most sensitive marker which was associated with advanced stage, poor differentiation and higher recurrence and mortality in CRC. It can be concluded that the CAR could be applicable as a new inflammation-based prognostic system that could add a new dimension to prognostication and classification ability in CRC.
Keywords: Colorectal, C- reactive protein, prognosis, CRC.

Introduction

Colorectal carcinoma is the most common malignancy of the gastrointestinal tract. More than 145,000 new cases are diagnosed annually in the United States and more than 55,000 patients die of this disease each year, making colorectal cancer the second most lethal cancer in the United States [1]. The incidence is similar in men and women and has remained fairly constant over the past 20 years. The widespread adoption of current national screening programs should dramatically decrease the incidence of this common and lethal disease. Early detection along with improvements in medical and surgical care are thought to be responsible for the decreasing mortality of colorectal cancer observed in recent years [2].

In India, colorectal cancer accounts for 7/1,00,000. Cancer of the colon is not a very common disease in our country and the incidence is much lower than in the Western world [3]. This is primarily due to predominance of vegetarian dietary habits which has greater fiber content, less cholesterol, less animal fat as obtains in a predominantly non-vegetarian diet.

The presentation of the disease is also a varied factor, 38% of patients are diagnosed with regional disease and 20% to 25% have metastasis disease at diagnosis [4]. Colorectal cancer only causes symptoms in 10% to 15% of patients early in the disease, and therefore screening is necessary for the early detection of colon cancer [5].

Carcinoma of the colon is occurring with increasing frequency in the older age groups. There is an increased incidence in some geographical areas. It affects people from all strata of society but a certain section of the population is more prone to the disease. Colonic cancers have a good prognosis provided they are detected early and treated aggressively. Adequate screening techniques are not widely followed in our country, but if a patient over 40 years of age with bowel symptoms is submitted to a series of investigations including sigmoidoscopy, Barium enema and colonoscopy then a higher detection rate will result. The use of Carcino embryonic antigen as a diagnostic technique is not widely accepted. Surgical excision still remains the treatment of choice in carcinoma colon. Probably in no other cancer does surgery help so much than in this region. The use of antibiotics and improved pre and post operative care has diminished the operative mortality to acceptable levels.

Colorectal cancer screening requires testing asymptomatic individuals for the presence of premalignant adenomatous polyps or colorectal cancer. Colon cancer screening not only detects the disease at an early more favorable stage, but also prevents disease by removing premalignant polyps [6].

The search for better screening methods for cancers, including colorectal cancers, has led to tumor markers [7]. An ideal tumor marker should be both specific and sensitive enough to detect small tumors for early diagnosis or during screening [8]. The first tumor marker reported was Bence-Jones protein in the year 1847, but the general application of tumor markers for monitoring of cancer patients did not start until the discovery of Alpha fetoprotein and Carcinoembryonic antigen in 1965, the latter for colorectal cancers [9].

Since the discovery of CEA in 1965, various other substances have been found to be of some significance in colorectal cancers, most notably acute phase reactants, namely C-reactive protein, $Alpha_1$ antitrypsin, etc. The prognostic value and repeatability of these markers are being studied [10].

C- Reactive Protein (CRP) as proven, is a marker of chronic inflammation. And it is commonly used to evaluate systemic inflammatory response [11]. Its an annular pentameric disc in shape and synthesized in liver. It is a non specific acute phase reactant, which has been reported to be a prognostic factor for colorectal carcinoma [12].

It has been hypothesised that cancer originated at sites of chronic inflammation [13]. Chronic inflammation leads to cell proliferation and in turn to irreversible DNA damage. Also, it is proposed that Immune response of host is a consequence of tumor growth. Studies report that inflammatory bowel disease have an increased risk of developing colorectal carcinoma [14]. The presence of low-grade systemic inflammation, as determined by an elevation of high-sensitivity C-reactive protein (CRP), has been associated with an increased risk of cancers. Recent studies implicated, inflammation playing an important role in the occurrence and advancement of colorectal cancer [15].

During the past decade, a number of inflammation-based prognostic systems have been reported in the field of clinical oncology [16, 17]. Among them, it is well known that the Glasgow Prognostic Score (GPS)

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is one of the most valuable [18]. Because the GPS is based on two simple components—the serum levels of C-reactive protein (CRP) and albumin—which have their own cutoff values, the GPS can divide cancer patients into three independent groups before surgery. A recent study has revealed that the CRP/albumin ratio (CAR) is a useful tool for predicting the outcome of treatment for patients with hepatocellular carcinoma (HCC) [19]. In this study the authors attempted to address whether the CAR could be of prognostic value in patients with other types of cancer. In the present study, we investigated whether the CAR and GPS would be valuable in predicting stage, recurrence and postoperative survival of patients with colorectal cancer (CRC).

Methods and Material

This is a prospective observational study which included all the patients who underwent treatment for colorectal carcinomas, in the department of Surgical Gastroenterology at Nizam's Institute of Medical Sciences, Hyderabad, over a period of 2 years from 1st March 2016 to 30th April 2018.The study population was Biopsy proven cases of Colorectal carcinomas treated at Nizam's Institute of Medical Sciences, Hyderabad during the study period. All the patients more than 18 years of age undergoing treatment for biopsy proven colorectal carcinoma were included in this study. Colorectal carcinoma patients with fever, arthritis, inflammatory bowel disease, uraemia and Patients who have received neoadjuvant chemotherapy or chemoradiotherapy were excluded in this study.

Description of procedure followed in study (Methodology)

1. All biopsy proven cases of colorectal cancers will had preoperative estimation of C-Reactive protein, CEA and albumin, Glasgow prognostic score and CRP/Albumin ratio were derived from these parameters.
2. Co-relation of all these values were done with staging, recurrence and survival in colorectal cancer subjects.
3. Preoperative staging work up were done as per standard protocol with history and clinical examination, colonoscopy, CECT abdomen and Chest.
4. Patients were offered treatment as per staging workup and as per standard guidelines in form of curative/palliative surgery/chemotherapy.
5. Adjuvant therapy were given to patients as per standard guidelines.

Method of CRP, CEA and albumin determination

1. Serum CRP, CEA and Albumin were estimated in biochemistry laboratory using agglutination reaction and reviewed from the patient records.
2. CEA levels >4ng/ml was taken as positive (Yu-chen shiu *et al*, 2001) [15].
3. CRP levels of >6ng/dl was taken as significant (Yu-chen shiu *et al*, 2001).
4. Albumin level <3.5g/ml was taken as hypoalbuminemia (Heys *et al*, 1998)
5. The GPS was calculated as follows: patients with both an elevated level of CRP (>6 ng/dl) and hypoalbuminemia (Alb <3.5 g/dl) were allocated a score of 2, and patients showing one or neither of these blood chemistry abnormalities were allocated a score of 1 or 0, respectively.
6. The CAR was calculated as: CAR = serum CRP level (ng/dl)/serum albumin level (g/ dl). The cutoff values of CAR was determined using receiver operating characteristic (ROC) curve analyses. The recommended cutoff value was based on the most prominent point on the ROC curve for ‘‘sensitivity’’ and ‘‘1-specificity,’’ respectively. The ideal cutoff values was defined using the Youden index (maximum (sensitivity,specificity - 1). [20] The area under the ROC (AUROC) curve also was calculated.

Pathologic analysis

The specimen was processed after formalin fixation.

The pathologic parameters analysed include

1. Differentiation of tumor(well/moderately/poorly differentiated)
2. TNM stage of the tumor
3. Presence of lymphovascular invasion
4. Maximum tumor diameter

Follow up

Patients were followed up post surgery/palliative therapy every 3 to 6 months till recurrence, death or end of study period, whichever was earlier.

CEA, CXR, USG abdomen were done at each follow up visit. Surveillance colonoscopy was done at 1 year after surgery. CT abdomen or chest were done if recurrence was suspected at initial investigations.

Statistical Analysis

The data of the present study were entered into the computer and after its proper validation; check for error, coding & decoding it was compiled and analyzed with the help of SPSS 20 software for windows.

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Appropriate univariate and bivariate analysis were carried out with the use of Student's t-test, Mann–Whitney U test and Pearson correlation.
All numerical variable were summarized as mean ± standard deviation and median ± IQR (Interquartile range) based on normality. All categorical variable were summarized as percentages. Kaplan–Meier analysis and log rank test were used to compare the survival curves. P value <0.05 were considered significant. Parameters were recorded and arranged on Microsoft Excel spreadsheet (Microsoft, Seattle, WA) version 2010. All graphs and tables were made using Excel spreadsheet.

Sample size
As per study published by EF Leitch *et al* [21], and with the help of single proportion, at 80% power, 95% confidence interval and 5% margin of error, sample size for our study population is found to be 146.

Sample size was calculated using this formula:

$$\text{Sample Size} = \frac{\frac{z^2 \times p(1-p)}{e^2}}{1+\left(\frac{z^2 \times p(1-p)}{e^2 N}\right)}$$

Population Size = N | Margin of error = e | z-score = z
e is percentage, put into decimal form.

The z-score is the number of standard deviations a given proportion is away from the mean.

Desired Confidence Level	z-score
80%	1.28
85%	1.44
90%	1.65
95%	1.96
99%	2.58

A written and informed consent was taken from all the patients before including in the study. All the patients were worked up and treated as per the standard treatment guidelines for colonic cancer.

Outcomes of the study
Primary end point
Co-relation of preoperative C-Reactive protein (CRP), Carcinoembryonic antigen (CEA) levels, CRP/Albumin ratio (CAR) with Stage and Tumor differentiation in CRC.

Secondary end points
Recurrence (locoregional/systemic)
Survival at the end of study period
Bibliography was written in Vancouver system.

Results
Colorectal cancer is responsible for approximately 15% of all cancer deaths,and the corrected 5-year survival is less than 50%.' Variables that predict survival have been described previously. The most commonly used prognostic indicator has been the AJCC staging system, which describes the degree of spread of the tumour into the bowel wall and regional lymph mode metastases. Other prognostic factors have been identified, including vascular invasion (intramural and extramural), lymphatic invasion, nucleolar organizing regions, carcino-embryonic antigen levels in serum, inflammatory markers like CRP, and the histological grade of the tumour. It has also been recognized that weight loss is a prognostic factor, with weight-losing patients having a higher morbidity and mortality than non-weight-losing patients with colorectal cancer.
The impression that preoperative CEA determinations could function as a prognostic discriminant has been provided by a number of reports in which elevated CEA levels were associated with earlier relapse. Whether CEA levels were more predictive of recurrence than conventional pathologic staging methods could not be definitively established due to the small sample sizes in the various studies.
The elevation of serum CRP is undoubtedly correlated with the progression of CRC, however, whether it is an independent prognostic indicator of CRC remains controversial. Although the methods of measuring serum CRP and the cutoff values vary among institutes, the frequency of elevated serum CRP

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levels in patients with CRC ranges from 30.2% to 66.3%.
Pre-treatment serum albumin concentrations have been shown to be an independent prognostic factor in a number of malignant diseases-for example, in patients with prostatic cancer, melanoma and leukaemia. However, the role of albumin as an independent prognostic indicator in patients with localized, non-metastatic colorectal cancer has not, as yet, been adequately documented.
A total of 146 patients with colorectal carcinoma were included in the study

Age distribution

Table 1: Age distribution of colorectal carcinomas (n = 146)

Age	Frequency	Percentage
< 60 years	95	65.1%
60 years and more	51	34.9%

Out of the 146 patients diagnosed to have colorectal carcinomas, 95(65.1%) patients were below 60 years of age and 51(34.9%) patients were above 60 years. Mean age at presentation was 45.6 years. The youngest patient diagnosed was 21 years old while the oldest was 77 years old.

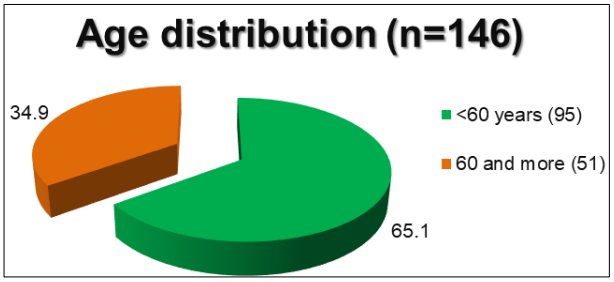

Fig 1: Age distribution in colorectal carcinomas

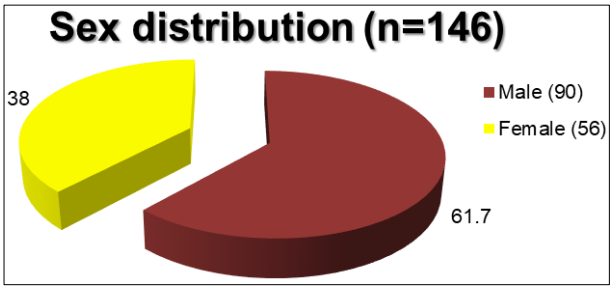

Fig 2: Sex distribution in colorectal carcinomas

Out of the 146 patients diagnosed to have colorectal carcinomas, 90(61.7%) patients were males and 56(38.3%) patients were females. Male preponderance was seen in the present study which is in concordance with the study by Yu-Chen Shiu [16] *et al.*

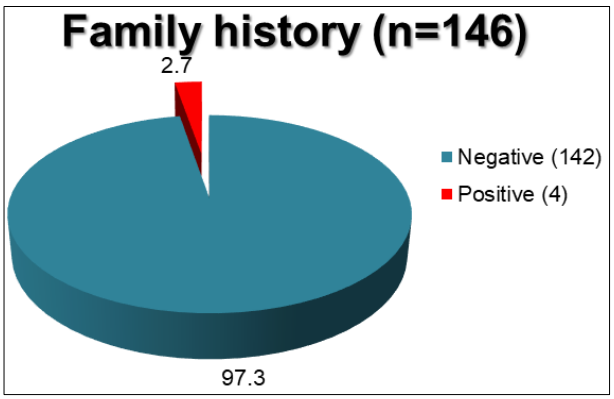

Fig 3: Family history in patients with colorectal carcinomas

Only 4 cases out of the 146 patients in our study had a family history of colorectal carcinoma.

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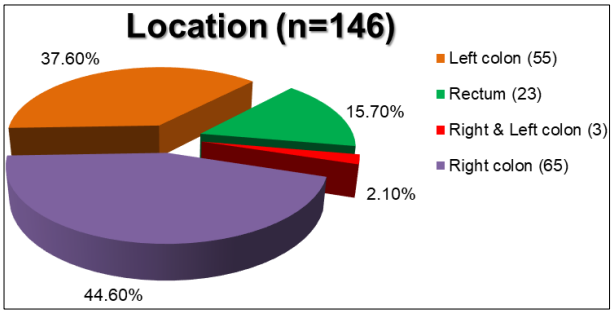

Fig 4: Location of colorectal carcinomas

Sixty five (44.6%) of the 146 patients diagnosed to have colorectal carcinomas were located in the right colon, 55(37.6%) in the left colon, 23(15.7%) in the rectum and only 3(2.1%) involved both the left and right colon. The most common location of colorectal carcinoma was found to be the right colon.

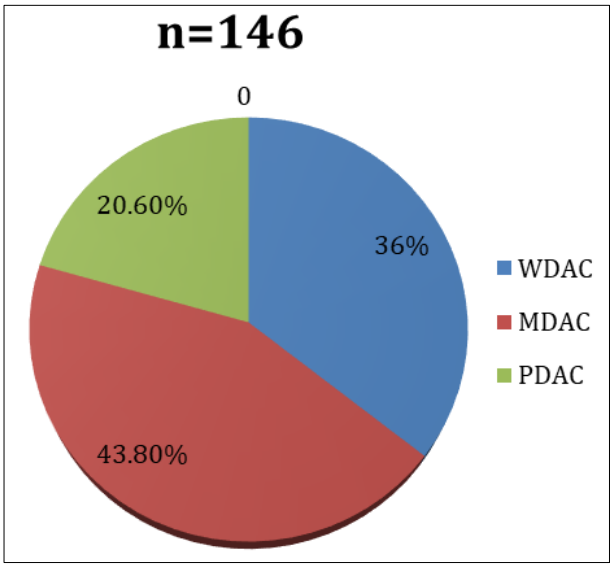

Fig 5: Histological differentiation of colorectal carcinomas

The most common histological differentiation of colorectal carcinoma observed was moderately differentiated type accounting for 64(43.8%) cases followed by well differentiated, 52 (35.6%) cases and least being the signet/poorly differentiated type, 30(20.6%) cases.

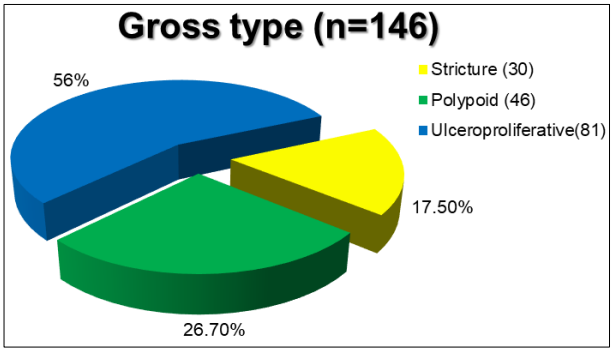

Fig 6: Gross type of colorectal carcinomas

The most common gross type observed was ulceroproliferative type accounting for 81(55.5%) of the 146 cases. Thirty nine (26.7%) cases presented with polypoidal lesions and 26(17.8%) cases had stricturous lesions.

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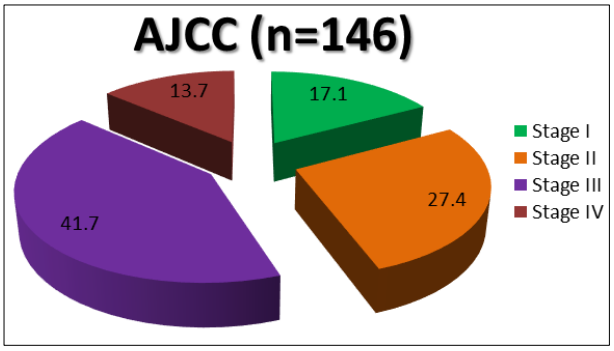

Fig 7: Distribution of colorectal carcinomas based on AJCC staging

Majority of the patients presented with advanced stage CRC, stage III and stage IV disease accounting for 61(41.7%) and 20(13.7%) cases respectively. Twenty five (17.1%) and 40 (27.4%) cases presented in stage I and II respectively.

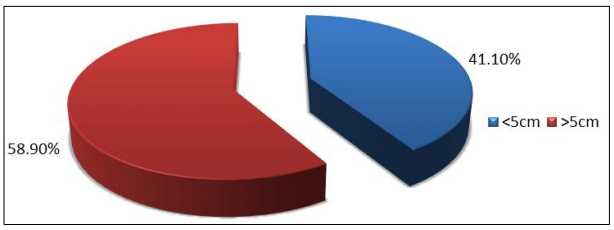

Fig 8: Maximum tumor diameter (MTD) of colorectal carcinomas

The maximum tumor diameter was divided into two groups- < 5cm and > 5cm.
60 patients (41.1%) had MTD <= 5 cm and 86 patients (58.9%) had MTD > 5cm.

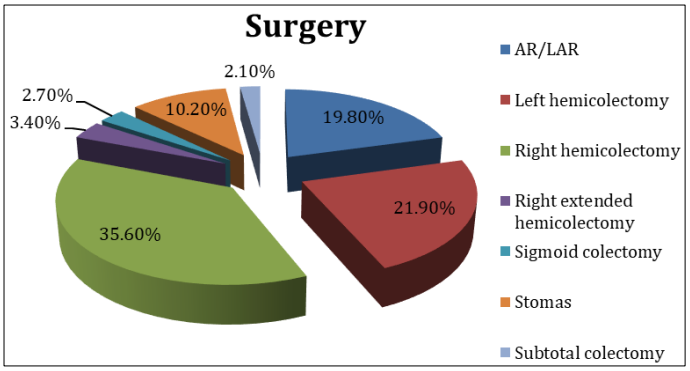

Fig 9: Surgery performed for colorectal carcinomas

Table 2: Surgical treatment given for colorectal carcinomas

Surgery	Frequency (n = 146)	Percentage
Anterior resection/LAR	29	19.8
Left radical hemicolectomy	32	21.9
Right extended hemicolectomy	5	3.4
Right radical hemicolectomy	52	35.6
Sigmoid colectomy	4	2.7
Subtotal colectomy	3	2.1
Stomas	15	10.2

Most common treatment advocated for the patients in the present study was observed to be right hemicolectomy accounting for 52(35.6) cases as the most common location for these tumors was right colon.

Preoperative analysis of CEA

- CEA was considered positive when it was more than 4.0ng/ml. It was raised in 56 patients (n=146, 38.3%) and within normal limits in 90 patients (61.7%) preoperatively.
- Of the 25 patients in Stage 1 (AJCC), 5 patients had raised CEA levels preoperatively (20%)
- Of the 40 patients in Stage 2 (AJCC), 11 patients had elevated CEA levels preoperatively (27.5%)

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- Of the 61 patients in Stage 3 (AJCC), 32 patients had elevated CEA levels preoperatively (52.4%)
- Of the 20 patients in Stage 4 (AJCC), 8 patients had elevated CEA levels preoperatively (40%)

Table 3: Association of preoperative CEA with AJCC staging system

Preoperative CEA	AJCC				p value
	I	**II**	**III**	**IV**	**0.536**
0-4	20	29	29	12	
	80%	72.5%	47.6%	60%	
>4	5	11	32	8	
	20%	27.5%	52.4%	40%	
Total	25	40	61	20	
	100.0%	100.0%	100.0%	100.0%	

No significant association could be demonstrated between preoperative CEA levels and AJCC staging system for colorectal carcinomas.

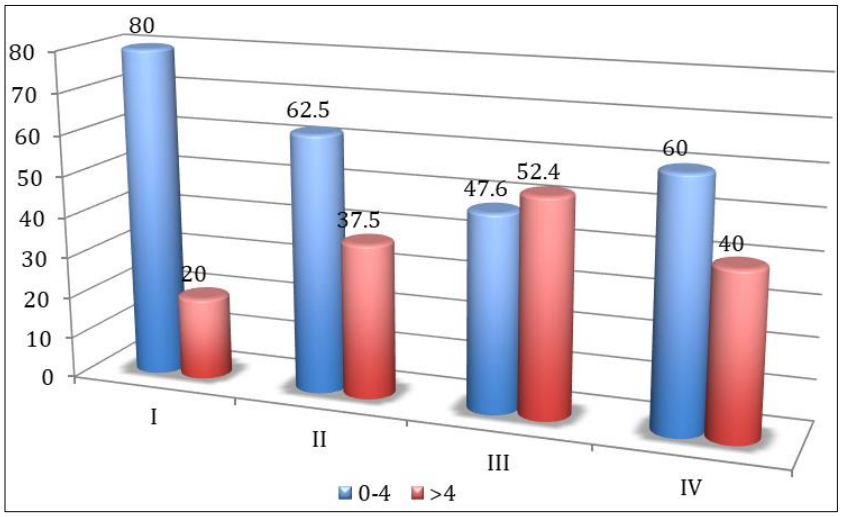

Fig 10: Preoperative CEA levels in colorectal carcinomas

Table 4: Association of preoperative CEA with tumor differentiation, lymphovascular invasion (LVI) and recurrence

	0-4(n=90)	**>4(n=56)**	**p value**
LVI	16(17.8%)	9(16.07%)	0.871
WDAC	31(34.4%)	21(37.5%)	0.786
MDAC	41(45.5%)	23(41.07%)	
PDAC	18(20%)	12(21.43%)	
Recurrence	8(8.9%)	4(7.1%)	0.346

No significant association could be demonstrated between preoperative CEA levels and LVI, tumor differentiation and recurrence.

Preoperative analysis of CRP levels

- CRP was considered significant when it was more than 6.0ng/dl. It was significant in 93 patients (n=146, 63.7%) and within normal limits in 53 patients (36.3%) preoperatively.
- Of the 25 patients in Stage 1 (AJCC), 9 patients had raised CRP levels preoperatively (36%)
- Of the 40 patients in Stage 2 (AJCC), 23 patients had elevated CEA levels preoperatively (57.5%)
- Of the 61 patients in Stage 3 (AJCC), 43 patients had elevated CRP levels preoperatively (70.5%)
- Of the 20 patients in Stage 4 (AJCC), 16 patients had elevated CRP levels preoperatively (80%)

Table 5: Association of preoperative CRP levels with AJCC staging system

Preoperative CRP	**AJCC**				**p value**
	I	**II**	**III**	**IV**	**<0.001**
0-6	16	17	18	4	
	64%	42.5%	29.5%	20.0%	
>6	9	23	43	16	
	36%	57.5%	70.5%	80.0%	
Total	25	40	61	20	
	100.0%	100.0%	100.0%	100.0%	

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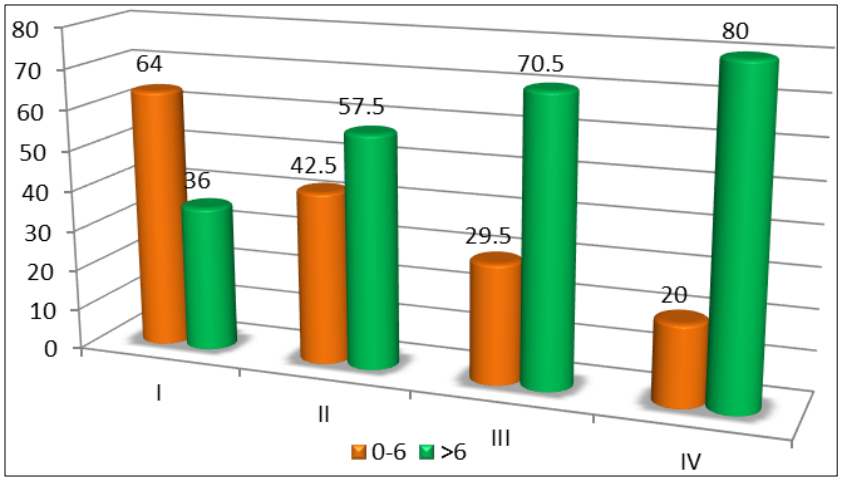

Fig 11: Preoperative CRP levels in colorectal carcinomas (%)

Significant association could be demonstrated between preoperative CRP levels and AJCC staging system for colorectal carcinomas.
Elevated preoperative CRP was more commonly associated with Stage III(70.5%) and Stage IV(80%) of CRC suggestive of association of elevated CRP with advanced and metastatic CRC.

Table 6: Association of preoperative CRP with tumor differentiation, lymphovascular invasion (LVI) and recurrence

	0-6(n=53)	**>6(n=93)**	**p value**
LVI	7(13.2%)	18(19.3%)	0.55
WDAC	25(47.1%)	27(29%)	0.18
MDAC	20(37.7%)	44(47.3%)	
PDAC	8(15.1%)	22(23.6%)	
Recurrence	2(3.7%)	10(10.7%)	0.16

No Significant association could be demonstrated between preoperative CRP levels and LVI, tumor differentiation and recurrence.

Preoperative analysis of albumin

- Albumin of 3.5 g/ml and less was considered as hypoalbuminemia. It was low in 56 patients (35.9%) and within normal limits in 90 patients (64.1%) preoperatively.
- Of the 25 patients in Stage 1 (AJCC), 4 patients had hypoalbuminemia preoperatively (1.6%)
- Of the 40 patients in Stage 2 (AJCC), 8 patients had hypoalbuminemia preoperatively (20%)
- Of the 61 patients in Stage 3 (AJCC), 32 patients had hypoalbuminemia preoperatively (52.4%)
- Of the 20 patients in Stage 4 (AJCC), 12 patients had hypoalbuminemia preoperatively (60%)

Association of preoperative Glasgow prognostic score with tumor staging and differentiation.
The GPS was calculated as follows: patients with both an elevated level of CRP ([1.0 mg/dl) and hypoalbuminemia (Alb\3.5 g/dl) were allocated a score of 2, and patients showing one or neither of these blood chemistry abnormalities were allocated a score of 1 or 0, respectively.(table 7)

Table 7: Out of 146 patients 53(36.3%) had GCS of 0, 37(25.3%) has GCS of 1 and 56(38.4%) had GCS of 2.

	GCS0(n=53)	GCS1(n=37)	GCS2(n=56)	p value
Stage I	**16(30.2%)**	**5(13.5%)**	**4(7.1%)**	**0.006**
Stage II	**17(32.1)**	**15(40.5%)**	**8(14.3%)**	
Stage III	**18(33.9%)**	**11(29.7%)**	**32(57.1%)**	
Stage IV	**2(3.8%)**	**6(16.2%)**	**12(21.4%)**	
Total	**53**	**37**	**56**	

Significant association could be demonstrated between preoperative GCS and AJCC staging system for colorectal carcinomas.
Higher GCS was more commonly associated with Stage III (57.1%) and Stage IV(21.4%) of CRC

Table 8: Association of preoperative Glasgow prognostic score with LVI, tumor differentiation and recurrence

	GCS0(n=53)	**GCS1(n=37)**	**GCS2(n=56)**	**p value**
LVI	7(13.2%)	8(21.6%)	10(17.8%)	0.546
Recurrence	2(3.7%)	4(10.8%)	6(10.7%)	0.827

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WDAC	25(47.1%)	13(35.1%)	11(19.6%)	0.086
MDAC	20(37.7%)	14(37.8%)	30(53.5%)	
PDAC	8(15.1%)	10(27.%)	12(21.4%)	

No Significant association could be demonstrated between preoperative GCS and LVI, tumor differentiation and recurrence

Association of preoperative CRP/Albumin ratio with tumor staging and differentiation.

The CAR is calculated as: CAR = serum CRP level (mg/dl)/serum albumin level (g/ dl). The recommended cut off value for CAR was calculated using the method described in materials and methods. The optimal cutoff value for CAR corresponded with the point on the ROC curve showing the best sensitivity (0.784) and specificity (0.456), respectively. The AUROC was 0.686 and the optimal cutoff value of 0.034 was indicated for these parameters.

The patients were put into 2 categories based on this- with CAR>0.034 and CAR <0.034. (table 9)

Table 9: Out of 146 patients 86 patients had CAR>0.034 and 60 patients had CAR <0.034

	CAR<0.034(n=60)	**CAR>0.034(n=86)**	**p value**
Stage I	22(36.7%)	3(3.5%)	<0.001
Stage II	29(48.3%)	11(12.8%)	
Stage III	8(13.4%)	53(61.6%)	
Stage IV	1(1.7%)	19(22.1%)	
Total	60	86	

Significant association could be demonstrated between preoperative CAR and AJCC staging system for colorectal carcinomas.

Elevated preoperative CAR (>0.034) was more commonly associated with Stage III (61.6%) and Stage IV(22.1%) of CRC suggestive of association of elevated CRP with advanced and metastatic CRC.

Table 10: Association of preoperative CRP/Albumin ratio with LVI, tumor differentiation and recurrence

	CAR <0.034(n=60)	CAR >0.034(n=86)	p value
LVI	6(10%)	19(22.1%)	0.003
Recurrence	1(1.7%)	11(12.8%)	<0.001
WDAC	37(61.7%)	15(17.4%)	<0.001
MDAC	20(33.3%)	44(51.2%)	
PDAC	7(11.7%)	23(26.7%)	

Significant association could be demonstrated between elevated preoperative CAR and LVI, tumor differentiation and recurrence. Elevated CAR >0.034 was associated with higher incidence of LVI, recuurence and poorer tumor differentiation.

Recurrence and mortality

There were 12 recurrences (8.2%) and 12 deaths (8.2%) in the study. Out of 12 recurrences, 9 were systemic and 3 were locoregional. Out of 3 locoregional recurrences 2 patients had R2 resection at index surgery. 10 deaths were due to metastatic disease and 2 were due to post operative complications.

Table 11: Association of elevated preoperative CEA, CRP, CAR with recurrence and mortality

	CEA >4	**CRP> 6**	**CAR>0.034**
Recurrence(n=12)	4(33.3%)	10(83.4%)	11(91.7%)
Mortality(n=12)	4(33.3%)	9(75%)	10(83.4%)

Both recurrence and mortality were seen in majority of patients who had elevated CRP and CAR preoperatively indicating a strong association between them.

Out of all the parameters(pre-operative CEA,CRP,GCS,CAR), elevated CAR was the most sensitive marker associated with advanced stage, poor tumor differentiation, recurrence and cancer related mortality in CRC in this study as shown by ROC curve below.

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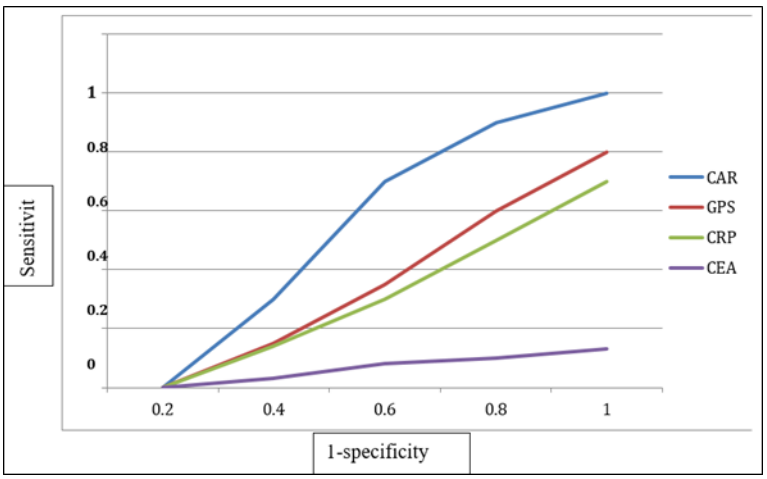

Fig 12: Specificity

Preoperative CEA was the least sensitive marker for prognostication of CRC in this study.
Since CAR was the most reliable prognostic marker, hence its relationship to clinicolaboratory characteristics were also studied using mean ± SD, Mann–Whitney U test which is depicted in the table below:

Table 12: Variables

Variable	CAR<0.034(n=60)	CAR>0.034(n=86)	p value
Age (yrs)	55 ± 11	59 ± 12	0.030
MaximumTumor diameter(mm)	39 ± 17	55 ± 24	<0.001
CRP	2.7±0.8	15.2 ± 8	<0.001
Albumin	3.9 ± 0.4	2.9 ± 0.6	<0.001
Survival period(Days)	321 ± 280	261 ± 160	<0.001

There were significant differences between the two groups in maximum tumor diameter, CRP, albumin and survival period. CAR >0.034 was associated with larger tumors and lesser overall survival.

During the observation period, 12 patients died of cancer-related disease. Univariate and multivariate analyses were performed to evaluate the relationship between clinical characteristics and OS shown in table below.(table 13)

Table 13: Univariate Multivariate

Variable	p value	HR	95%CI	p value	HR	95%CI
Age(<60/>60 yrs)	0.526	0.891	0.622–1.173			
Tumor location(colon/rectum)	0.937	0.986	0.700–1.390			
Pathological differentiation(PD/MD,WD)	0.001	2.216	1.274–3.514	0.003	1.811	1.229–2.669
CEA(>4/<4)	0.263	1.283	0.830–1.984			
Stage(III,IV/I,II)	0.001	4.756	3.304–6.576	0.001	3.067	1.997–4.774
CAR(>0.034/<0.034)	0.001	4.512	2.927–6.954	0.001	2.613	1.621–4.212

HR-hazard ratio, CI-confidence interval

The results of univariate analyses demonstrated that pathological differentiation, stage (III, IV/0, I, II), and CAR (>0.034/<0.034) were associated with OS which were confirmed on multivariate analysis also. Patients with high CAR (>0.034) showed poorer OS than those with low CAR.
There was a significant difference in the survival period between patients with low CAR (321 ± 280 days) and patients with high CAR (261 ± 160) days; (P< 0.001, Mann–Whitney U test; Table 12). Kaplan–Meier analysis and log-rank tests demonstrated a significant difference in 2 years OS between patients with low CAR and patients with high CAR (Fig. 13). The 2 year survival in low CAR and high CAR groups were 96.6% and 88.3% respectively.

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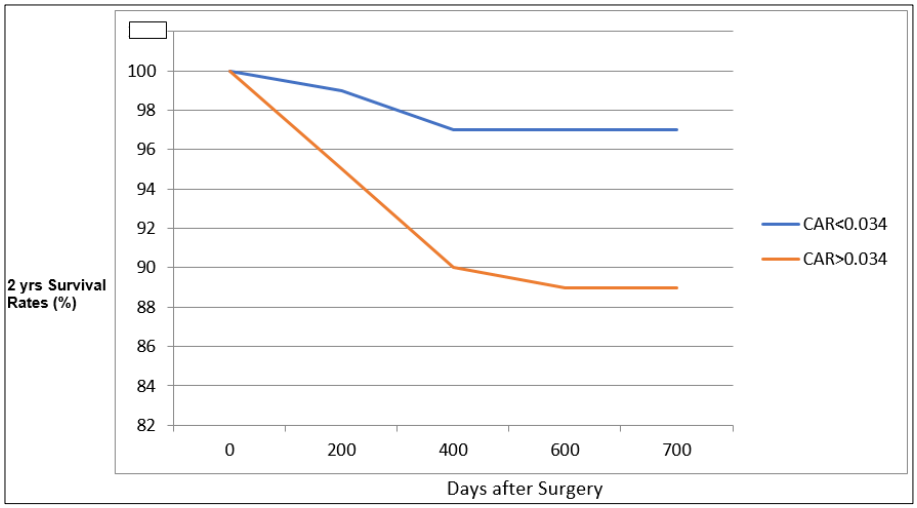

Fig 13: CAR Difference

Plasma CEA levels at the time of diagnosis was one of the first criteria compared in our study and we learnt that as per a study done in 1978 by McIntire *et al*, [87] showed that 60-90% of the patients had elevated CEA at prima presentation. Recent studies by I Tarantino *et al*, [88] and Giovanni Li Destri el al, [89] showed elevated preoperative CEA in 22.4% and 27.3% respectively. In the present study, we had incidence of preoperative elevated CEA in 38.3% of patients. (Table 14)

Table 14: Comparison of CEA levels at the time of presentation in various studies

Robert McIntire (1978)	60-90%
I Tarantino(2012)	22.4%
Giovanni Li Destri(2015)	27.3%
Present study(2018)	38.3%

As per a study by Holyoke *et al*, [47], it showed that 18% of the patients in Duke's Stage A disease had an elevated prima CEA level, 53% in Stage B1, 62% in Stage B2, 65% in Stage C1 and 79% in Stage C2. This study did show that a larger percentage of patients in advanced disease state tend to have elevated CEA at the time of primary presentation however all of them did not have elevated CEA at the time of diagnosis. This is in concordance with our study. This finding is similar to the statistical figures reported by other workers and we are in a position to draw the conclusion that CEA elevation alone cannot be taken as a serum marker for carcinoma colon, since they are not necessarily elevated in all patients diagnosed to have carcinoma colon, but patients with advanced disease states at the time of presentation have a higher propencity to have elevated CEA. (Table 15 & 16)

Table 15: Study done by Holyoke *et al*.

Duke's stage	**CEA elevation**
A	18%
B1	53%
B2	62%
C1	65%
C2	79%

Table 16: Present study

AJCC	**CEA elevation**
I	20%
II	27.5%
III	52.4%
IV	40%

The present study was compared with the study done by Yu-Chen Shiu *et al*, [15]. According to their study, the CRP level, differentiation and gross type were the independent prognostic factors. It also showed that CRP was significant for Stage III and IV disease, but not for stage II. In the present study, 70% and 80% patients in Stage 3 and 4 disease had significant CRP preoperatively, 63.7% of the patients had positive pre-operative significant CRP levels. In the study by Yu-Chen Shiu *et al*, [15], CRP level was considered as a marker for advanced disease which was shown by our study also Furthermore it was concluded that though CEA alone could not be used as a prognostic tool, the combined values of CEA

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and CRP was a strong predictor of prognosis in colorectal carcinomas. Primary tumor size and levels of CRP showed a strong statistically significant co-relation in Yu Chen Shiu's [15] study which is in vehement approval of the data from the present study as shown by CRP/Albumin ratio. (Table 5)

Table 17: Comparison of various factors in present study with Yu-Chen *et al*.

		Yu-Chen Shiu *et al*				**Present Study**			
			Patient number (%)				**Patient number (%)**		
			CRP<6	**CRP>6**	**p value**		**CRP<6**	**CRP>6**	**p value**
Age	<60	n=105	58(27.4)	47(22.2)	0.055	n=95	50(34.2)	45(30.8)	**0.775**
	>60	n=107	45(21.2)	62(29.2)		n=51	30(20.5)	21(14.5)	
Gender	Male	n=140	66(31.3)	74(34.9)	0.56	n=90	48(32.9)	42(28.7)	**0.247**
	Female	n=72	37(17.5)	35(16.5)		n=56	26(17.8)	30(20.5)	
Differentiation	Well	n=2	1(0.5)	1(0.5)	0.16	n=52	25(47.1)	27 (29)	**0.18**
	Moderate	n=180	90(42.5)	90(42.5)		n=64	20 (37.7)	44 (47.3)	
	Poor	n=30	12(5.7)	18(8.5)		n=30	8 (15.1)	22(23.6)	

		Yu-Chen Shiu *et al* 2001				**Present Study**			
			Patient number (%)				**Patient number (%)**		
			CRP<6	**CRP>6**	**p value**		**CRP<6**	**CRP>6**	**p value**
Size (cm)	<5	n=103	66(31.1)	37(17.5)	<0.001	n=60	42 (28.7)	18 (12.3)	<0.001
	>5	n=109	37(17.5)	72(34)		n=86	22 (15.1)	64 (43.9)	
AJCC Staging	Stage I	n=29	22(10.4)	7(3.3)	0.002	n=25	16(10.9)	9(6.1)	<0.001
	Stage II	n=64	32(15.1)	32(15.1)		n=40	17(11.6)	23(15.7)	
	Stage III	n=67	33(15.6)	34(16)		n=61	18(12.3)	43(29.5)	
	Stage IV	n=52	16(7.5)	36(17)		n=20	4(2.7)	16(10.9)	

As for comparison between the present study and the one by Yu-Chen Shiu,with regards to male preponderance of the disease, relatively low positive family history and histologically being moderately differentiated adenocarcinoma, our study was in approval of the data shown in that study.

The present study, showed that CRP and CRP/Albumin ratio (CAR) had a statistically significant relationship with respect to the stage of the disease and recurrence rates during followup. This again was true as per previous studies from various centres including the Yu-Chen Shiu study.

CRP, as for the statistics, was not regarded as an independent prognostic factor in our study, however there was a positive relation with the burden of disease. We believe in the observation made by Neilson *et al*, [90] were they considered the increase in CRP to poorer survival of the patient. They also concluded with the proportionate increase in morbidity in patients with raised CRP values. But, as said, to condition this statement, a better study population would be ideal with a longer follow up.

A study done by Mcmillan *et al*, [31] reported, age, stage (Duke's) and CRP<1mg/dl, as independent variables for prognosis. A similar study reported by Chung and Chang, [91] proposed the prediction of CRP levels with the outcome of colorectal cancer and decreased immunity. We agree on their observation regarding the outcome as our study is relating the CRP levels with advanced stage of the disease. Also we assume that inflammatory response increases as tumor increases in size and becomes bigger and more advanced. 52.4% and 60% patients in stage 3 and 4 had low albumin levels preoperatively suggestive of association of hypoalbuminemia with advanced CRC.

This is concordance with the study as per Heys *et al*, [92] which showed that serum albumin was an individual prognostic indicator in detecting advanced colorectal disease preoperatively, outcome and recurrence rates. Pretreatment serum CRP and Albumin levels are indicative of inflammation and nutritional status. Recently, Chen *et al*. [93] and Kinoshita *et al*. [86] reported that the CAR was better than the GPS in predicting the prognosis of patients with renal cell or hepatocellular carcinoma.

A recent study by Masahide Ikeguchi [94] in 2017 showed that in locally advanced unresectable colorectal carcinomas with high vs. low CAR well represented the difference in survival of patients who received chemotherapy. Among chemotherapy treated patients with a high CAR, the median survival time (5 months) was almost the same as that of patients who did not undergo chemotherapy (3 months). They concluded that patients with locally advanced CRC and distant metastasis who have a low CAR may benefit from intensive treatment, in terms of survival, even if prior to treatment their disease was considered to be unresectable.

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Shibutani M *et al*, [95] in 2016 studied the prognostic significance of the preoperative ratio of C-Reactive Protein to Albumin in patients with colorectal cancer and concluded that the group with high CRP/ALB ratio had significantly worse relapse-free survival (p=0.0003) and cancer-specific survival (p=0.0026) rates than those of the low CRP/ALB ratio group. Our study findings are similar to these studies though the patient number and follow up duration is lesser in our study.

We conclude, based on our results that the preoperative CRP/ALB ratio is a useful prognostic marker in patients with colorectal cancer who undergo potentially curative surgery. Moreover, the CRP/ALB ratio may be superior to the GPS and CEA for predicting survival.

We suggest that among patients with locally advanced CRC, those with a low preoperative CAR may be candidates for aggressive, intensive chemotherapy, and some of them may have improved survival. Conversely, among patients with unresectable, locally advanced CRC with distant metastasis and a high CAR, an alternative treatment strategy should be considered to ensure a good quality of life rather than compromising it to prolong survival.

Summary and Conclusions

146 patients were included in our study with the earliest followup at 3 weeks postoperatively and the latest at 6 months.

Following were the conclusions made in the present study -

C- reactive protein (CRP)

- A definitive association between C- reactive protein and advanced disease was observed (presence of metastases (intraoperative / histopathological evidence).
- Higher CRP values were observed in patients with poorer differentiation of tumor and higher recurrence rates.

Carcinoembryonic antigen (CEA)

- Since the plasma CEA levels did not rise in all patients with colorectal carcinoma, this marker cannot be taken as a sole diagnostic criterion.
- No significant association could be demonstrated between preoperative CEA levels and Stage, tumor differentiation and recurrence.

Albumin

- Preoperative hypoalbuminemia should raise the suspicion of advanced disease state and appropriate investigations should be done to identify sites of metastases.
- Persistent hypoalbuminemia is a feature of advanced disease and should be monitored serially and for longer period to arrive at a consensus.
- A low level of serum albumin is usually found in metastatic colorectal carcinoma patients.

CRP/Albumin ratio (CAR)

- CAR was the most sensitive marker which was associated with advanced stage, poor differentiation and higher recurrence and mortality in CRC.
- It scored above CRP alone and GPS as the CAR was based on values of both CRP and albumin which have their own prognostic significance in advanced colorectal cancer.

It can be concluded that the CAR could be applicable as a new inflammation-based prognostic system that could add a new dimension to prognosticationand classification ability in CRC. In addition, further studies are required to indicate the superiority of the CAR to the other inflammation-based prognostic systems; the CAR would have an advantage of prognostication for cancer patients because of its high AUROC. Adjustment of the CAR to well-accepted systems, such as TNM staging and performance status would facilitate firmer classification of patients for whom the indications for surgery and chemotherapy may be obscure.

Limitations of the study

- Single centre, observational study
- Smaller sample size
- Short term follow up

References

1. Hawk ET, Limburg PJ, Viner JL. Epidemiology and prevention of colorectal cancer. Surg clin N Am. 2002;82:1943.
2. National Comprehensive Cancer Network. Colorectal cancer screening clinical practice guidelines in oncology. J NCCN. 2003;1:72.
3. Mohan KM. Epidemiology of digestive tract cancers in India. V. Large and small bowel. Indian J

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

Gastroenterology 1999 Jul-Sep; 18(3):118-21.
4. Daniel WC, Stewart S, Burtis AC, Ashwood ER. Tumor markers. In Textbook Of clinical Chemistry. 2nd edition:98.
5. Gold P, Freedman SO. Demonstration of tumor specific antigens in human colonic carcinoma by immunohistologic tolerance and absorption techniques. New Eng J Med. 1971; 285:138-141.
6. Gold P, Freedman SO. Specific CEAS of the human digestive system. J Exp. Med. 1972;136:100-129.
7. Seregeni E, Ferrari l, Martinelli A, Bombardieri E. Diagnostic and prognostic tumor markers in the GIT. Seminars in Surgical Oncology. 2001;20:147-166.
8. Madjic O, Knapp W. Cluster report: CD66. In Leucocytes typing IV. Oxford, England: Oxford University Press. 1989, 838.
9. Gold P, Krupey J, Ansari H *et al*. Position of the CEA of human digestive system in ultra structure of tumor cell surface. Journal of the National Cancer Institute. 1970;45(2):219-225.
10. Rosenthal KL, Palmer JL, Harris JA, *et al*. Antibody-induced redistribution of CEA on the cell surface: utilization in separation of CEA and isoantigen A. Journal of Immunology. 1975;115(4):1049-1053.
11. Yeh. CRP as a mediator of disease. Circulation. 2004;109:11-14.
12. Significance of preoperative elevation of CRP as an indicator for prognosis in CRC. Am J Surg. 1998;176:335-8.
13. Ulcerative colitis and Crohn's disease as colorectal cancer risk. GUT. 1994;35:1590-2.
14. Preoperative elevation of serum CRP is related to impaired immunity in patients with CRC. Am J of Clin Oncol. 2000;23:262-6.
15. Shiu YC, Lin JK, Huang CJ, Jiang JK, Wang LW, Huang HC, *et al*. Is C reactive protein a prognostic factor of colorectal cancer?. Diseases of the colon and rectum. 2001;51:4,443-449.
16. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev. 2013;39:534-40.
17. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophillymphocyteratio: experience in patients with cancer. Crit Rev Oncol Hematol. 2013;88:218-30.
18. Forrest LM, McMillan DC, McArdle CS, Angerson WJ, Dunlop DJ. Comparison of an inflammation-based prognostic score(GPS) with performance status (ECOG) in patients receivingplatinum-based chemotherapy for inoperable non-small-cell lungcancer. Br J Cancer. 2004;90:1704-6.
19. Kinoshita A, Onoda H, Imai N, *et al*. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score,predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol. 2015;22:803-10.
20. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;3:32-35.
21. EF Leitch1, 2, M Chakrabarti1,2, JEM Crozier1, RF McKee1, JH Anderson *et al*. Comparison of the prognostic value of selected markers of thesystemic inflammatory response in patients with colorectal cancer. British Journal of Cancer. 2007:97:1266-70.
22. Posner MC, Steele GD. Adeno carcinoma colon and rectum. In: Pemberton JH, editor. Shackelford's Surgery of Alimentary Tract, Vol 4. 5th ed. W.B. Saunders. p. 219-26.
23. Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. Indian Journal of Gastroenterology. 1999;18:118-21.
24. Rao DN, Ganesh B. Estimate of cancer incidence in India in 1991. Indian Journal of Cancer 1998;35:10-18.
25. Eaden J, Abrams K, Mayberry J *et al*. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. Gut. 2001;48:526.
26. Surg Clin N Am. 2002;82:1094(a),1096(b).
27. Casciato DA. Colorectal Carcinoma. Manual of Clinical Oncology. 5th edition. 2004;195.
28. Schreiber H, Rowley DA. Inflammation and cancer. In: Gallin JI, editor. Inflammation: Basic Principles and Clinical Correlates.3rd ed. Philadelphia: Lippincoptt Williams & Wilkins. 1999;317-20:324-26.
29. Erlinger TP, Platz EA, Rifai N, Helzlsouer KJ, *et al*. C-reactive protein and the risk of incident colorectal cancer. Journal of the American Medical Association. 2004;291(5):585-590.
30. Mercer DW, Talamo TS. Multiple markers of malignancy in sera of patients with colorectal carcinoma: Preliminary clinical studies. Clin Chem. 1985;31:1824-28.
31. McMillan DC, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surge. 2003;90:215-19.
32. Pignatelli M, Durbin H, Bodmer WF. CEA functions as an accessory adhesion molecule mediating colon epithelial cell-collagen interactions. Proceeding of the National Academy of Sciences (USA). 1990;87(4):1541-1545.
33. Thompson DM, Krupey J, Freedman SO. The radioimmunoassay of circulating CEA of the human

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

digestive system. Proceeding of the National Academy of Sciences (USA). 1969;64(1):161-167.
34. Oikawa S, Nakazato H, Kosaki G, *et al*. Primary structure of human CEA deduced from cDNA sequence. Biochemical and Biophysical Research Communications. 1987;142(2):511-518.
35. Slayter HS, Coligan JE. Electron microscopy and physical characterization of the Carcinoembryonic antigen. Biochemistry. 1975;14(11):2323-2330.
36. Von Kleist S, Migule I, Halla B, *et al*. Possible function of CEA as cell contact inhibitory molecule. Anticancer Research. 1995;15(5B):1889-1894.
37. Allin KH, Bojesen SE, Nordestgaard BG, *et al*. Baseline C-Reactive Protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol. 2009;27:2217-2224.
38. Beauchemin N, Huang JQ. Studies on the functions of CEA. In: Yachi A, Shively JE, eds. The CEA gene family. New York: Elsevier.1989;49.
39. Zamcheck N, Doos WG, Prudente R, *et al*. Prognostic factors in colon carcinoma: correlation of serum CEA level and tumor histopathology. Human Pathology. 1975;6(1):31-45.
40. Goslin R, Steele G Jr, McIntire J, *et al*. The use of preoperative plasma CEA levels for the stratification of patients after curative resection of colorectal carcinoma. Annals of Surgery. 1980;192(6):747-751.
41. Benchimol S, Fukes A. CEA, a human tumor marker, functions as an intercellular adhesion molecule. Cell. 1989;57(2):327-334.
42. Von Kleist S, Migule I, Halla B *et al*. Possible function of CEA as cell contact inhibitory molecule. Anticancer Research. 1995;15(5B):1889-1894.
43. Onetto M, Paganuzzi M, Secco GB, *et al*. Preoperative CEA and prognosis in patients with colorectal cancer. Biomedicine and Pharmacotherapy. 1985;39(7):392-395.
44. Proceeding of the First International Conference on the clinical uses of CEA. Cancer. 1978;42(3 suppl):1397-1659.
45. Baron JA, Cole BF, Sandler RS *et al*. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J med. 2003;348:891-9.
46. Herbeth B, Bagrel A. A study of factors influencing plasma CEA levels in an unselected population. Oncodevelopmental Biology and Medicine. 1980;1 (4-5):191-198.
47. Holyoke ED, Herrera MA, Chu TM, *et al*. CEA monitoring of palliative treatment of colorectal carcinoma. Annals of Surgery. 1977;185(1):23-48.
48. Goslin R, Steele G Jr, Macintyre J, *et al*. The use of preoperative plasma CEA levels for the stratification of patients after curative resection of colorectal carcinoma. Annals of Surgery. 1980;192(6):747-751.
49. Onetto M, Paganuzzi M, Secco GB, *et al*. Preoperative CEA and prognosis in patients with colorectal cancer. Biomedicine and Pharmacotherapy. 1985; 39(7):392-395.
50. Wolmark N, Fisher B, Wieand HS *et al*. The prognostic significance of preoperative CEA levels in colorectal carcinoma. Annals of Surgery 1984; 199(4):375-382.
51. Kohler JP, Simonowitz D, Paloyan D, *et al*. Preoperative CEA level: a prognostic test in patients with colorectal cancer. American Surgeon. 1980;46(8):449-452.
52. Zamcheck N, Doos WG, Prudente R, *et al*. Prognostic factors in colon carcinoma: correlation of serum CEA level and tumor histopathology. Human Pathology. 1975;6(1):31-45.
53. Goodyear MDE, Sutherland DJ, Malkin A *et al*. Prognostic value of postoperative levels of CEA for recurrence and survival in primary breast cancer. Review on Endocrine-Related cancer. 1984;14:149-153.
54. Alvarez JA, Marin J. Sensitivity of monoclonal antibodies to CEA, tissue polypeptide antigen, AFP, CA 19-9 in the diagnosis of colorectal adenocarcinoma. Disease of Colon and Rectum. 1995;38(5):535-542.
55. Goldenberg DM, Neville M, Carter AC, *et al*. CEA: its role as a marker in the management of cancer: an NIH consensus development statement. Annals of Internal Medicine.1981;94(3):407-409.
56. Fuks A, Shuster J, Gold P, *et al*. Theoretical and practical considerations of the utility of the radioimmunoassay for CEA in clinical medicine In: Sells S, ed. Cancer Markers. Clifton, NJ: Humana Press. 1980. p. 315-327.
57. Armigate NC, Davidson A, Tsikos D, *et al*. A study of reliability of CEA blood levels in the following course of colorectal cancer. Clinical Oncology. 1984;10(2):141-147.
58. Wonebo JH, Stearns M, Schwartz MK *et al*. Use of CEA as an indicator of early recurrence and as a guide to a selected second- look procedure in patients with colorectal cancer. Annals of Surgery 1978; 188(4):481-493.
59. Benson AB, Schrag D, Somerfield MR, *et al*. American Societyof Clinical Oncology recommendations on adjuvant chemotherapyfor stage II colon cancer. J Clin Oncol. 2004;22(16):3408-19.
60. National Comprehensive Cancer Network. http://www.nccn.org (2015). Accessed 16 Jan 2015.
61. Engstrom PF, Benson AB 3rd, Saltz L. Colon cancer clinicalpractice guidelines in oncology. J Natl Compr Canc Netw. 2003;1:40-53.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

62. Srivastava G, Renfro LA, Behrens RJ, *et al*. Prospective multicenterstudy of the impact of oncotype DX colon cancer assayresults on treatment recommendations in stage II colon cancerpatients. Oncologist. 2014;19(5):492-7.
63. Maak M, Simon I, Nitsche U, *et al*. Independent validation of aprognostic genomic signature (ColoPrint) for patients with stageII colon cancer. Ann Surg. 2013;257(6):1053-8.
64. Fakih MG, Padmanabhan A. CEA monitoring in colorectal cancer.What you should know. Oncology (Williston Park). 2006;20(6):579-87.
65. Bassel Nazha, Elias Moussaly, Mazen Zaarour, Chanudi Weerasinghe, Basem Azab.Hypoalbuminemia in colorectal cancer prognosis:Nutritional marker or inflammatory surrogate?. World J Gastrointest Surg. 2015;7(12):370-377.
66. Falconer JS, Fearon KC, Ross JA, *et al*. Acute phase protein response and survival in colon cancer. Cancer. 1995;75:2077-82.
67. Wigmore SJ, McMahon AJ, Sturgeon CM, Fearon KCH. Acute phase protein response,survival and tumor recurrence in patients with colorectal cancer. BJS. 2001;88:255-60.
68. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer. 2004;4(1):71-78.
69. Mantovani A, Allavena P, Sica A, and Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-444.
70. Wisastra R, Dekker FJ. Inflammation, cancer and oxidative lipoxygenase activity are intimately linked. Cancers. 2014;6(3):1500-1521.
71. De Visser KE, Eichten A, Coussens LM. Paradoxical roles ofthe immune system during cancer development. Nat Rev Cancer. 2006;6(1):24-37.
72. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357(9255):539-545.
73. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331(6024):1565-1570.
74. Gao Y, Huang D. The value of the systematic inflammation-based GlasgowPrognostic Score in patientswith gastric cancer: a literature review. J Cancer Res Ther. 2014;10(4):799-804.
75. Zhang X, Zhang W, Feng LJ. Prognostic significance of neutrophil lymphocyte ratio in patients with gastric cancer: a meta-analysis. PLoS One. 2014;9(11):e111906.
76. Yang JJ, Hu ZG, Shi WX, Deng T, He SQ, Yuan SG. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. World J Gastroenterol. 2015;21(9):2807-2815.
77. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, *et al*. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-6222.
78. Feng JF, Huang Y, Chen QX. Preoperative platelet lymphocyte ratio (PLR) is superior to neutrophil lymphocyte ratio (NLR) as a predictive factor in patients with esophageal squamous cell carcinoma. World J Surg Oncol. 2014;12:58.
79. Kinoshita A, Onoda H, Takano K, Imai N, Saeki C, Fushiya N, *et al*. Pretreatment serum C-reactive protein levelpredicts poor prognosis in patients with hepatocellular carcinoma. Med Oncol. 2012;29(4):2800-2808.
80. Wong VK, Malik HZ, Hamady ZZ, Al-Mukhtar A, Gomez D, *et al*. C-reactive protein as a predictor of prognosis following curative resection for colorectal liver metastases. Br J Cancer. 2007;96(2):222-225.
81. Ishino Y, Saigusa S, Ohi M, Yasuda H, Tanaka K, Toiyama Y, *et al*. Preoperative C-reactive protein and operative blood loss predict poorprognosis in patients with gastric cancer after laparoscopy-assisted gastrectomy. Asian JEndosc Surg. 2014;7(4):287-294
82. Crumley AB, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastriccancer? World J Surg. 2010;34(10):2393-2398.
83. Borda F, Borda A, Jimenez J, Zozaya JM, Prieto C, Gomez M, *et al*. Predictive value of pre-treatment hypoalbuminemia inprognosis of resected colorectal cancer. Gastroenterol Hepatol. 2014;37(5):289-295.
84. Espinosa E, Feliu J, Zamora P, Gonzalez Baron M, Sanchez JJ, Ordon ez A, *et al*. Serum albumin and other prognostic factors related to response and survival in patients with advanced non–small cell lung cancer. Lung Cancer. 1995;12(1-2):67-76.
85. Asher V, Lee J, Bali A. Preoperative serum albumin is an independent prognostic predictor of survival in ovarian cancer. Med Oncol. 2012;29(3):2005-2009.
86. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, *et al*. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol. 2015;22(3):803-810.
87. McIntire J, Goslin R, Steele G Jr, *et al*. The use of preoperative plasma CEA levels for the stratification of patients after curative resection of colorectal carcinoma. Annals of Surgery.

ISSN:0975 -3583,0976-2833 VOL14, ISSUE 05, 2023

1980;192(6):747-751.
88. Tarantino I, Warschkow R, Worni M, Merati-Kashani K, Köberle D, *et al*. Br J Cancer. 2012;107(2):266-274.
89. Giovanni Li Destri, Antonio Salvatore Rubino, Rosalia Latino, Fabio Giannone, Raffaele Lanteri. Int Surg. 2015;100(4):617-625.
90. Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N. Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. Ann Surg Oncol. 2000;7:617-623.
91. Chung YC, Chang YF. Serum C-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. Eur J Gastroenterol Hepatol. 2003;15:369-373.
92. Heys SD, Walker LG, Deehan DJ, Eremin OE. Serum albumin: a prognostic indicator in patients with colorectal cancer. J R Coll Surg Edinb. 1998;43:163-168.
93. Chen Z, Shao Y, Fan M, *et al*. Prognostic significance of preoperative C-reactive protein: albumin ratio in patients with clear cell renal cell carcinoma. Int J Clin Exp Pathol. 2015;8(11):14893-14900.
94. Ikeguchi M, Ashida K. Indian J Surg Oncol (2017) 8: 263. Shibutani M, Maeda K, Nagahara H, *et al*. Prognostic significance of the preoperative ratio of C-reactive protein to albumin in patients with colorectal cancer. Anticancer Res 2016;36:995-1001.