# Carcinoembryonic antigen, C-reactive protein and albumin as prognostic indicators in colorectal carcinomas

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## I. INTRODUCTION

Colorectal carcinoma is the most common malignancy of the gastrointestinal tract and the second leading cause of cancer deaths. Five-year survival rate in patients with localized disease is 94%.[1]

Early detection and subsequent prompt treatment of colorectal carcinomas provide a better five years survival rate. Higher detection rate can be achieved if patients over 40 years of age with symptoms are submitted to a series of investigations including sigmoidoscopy, barium enema and colonoscopy. Colon cancer screening not only detects the disease at an early, more favorable stage, but also prevents disease by removing premalignant polyps.[2]

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.[3]

C- Reactive Protein (CRP) as proven, is a marker of chronic inflammation. And it is commonly used to evaluate systemic inflammatory response.[4] It has an annular pentameric structure and is synthesized in the liver. It is a non specific acute phase reactant, which has been reported to be a prognostic factor for colorectal carcinoma.[5]

It has been hypothesised that cancer originated at sites of chronic inflammation.[6] Chronic inflammation leads to cell proliferation and in turn to irreversible DNA damage. 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.

Pre-treatment serum albumin concentrations have been shown to be an independent prognostic factor in a number of malignant diseases. 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.

Colorectal cancer is responsible for approximately 15% of all cancer deaths,[7] and the corrected 5-year survival is less than 50%.[8]

This study was undertaken to determine the significance of C-Reactive protein (CRP), Carcinoembryonic antigen (CEA) and albumin levels in colorectal carcinomas (CRC).

## II. MATERIALS AND METHODS

All patients who underwent surgical treatment for colorectal carcinomas, admitted to the surgical wards of Kasturba Hospital, Manipal.

**Study period**

January 2009 to July 2011.

**Inclusion criteria**

All histologically proven cases of colorectal malignancies in any age group and both sexes.

**Exclusion criteria**

Patients subjected to non curative treatment. Patients with fever, arthritis, inflammatory bowel disease, uremia.
Emergency surgeries.

**Study design**

Cross sectional study conducted between the period of January 2009 to July 2011.

Preoperative CRP, CEA and albumin were assessed.

Further CRP, CEA and albumin assessment will be done during 1st (3rd to 5th week postoperatively) and 2nd (3rd to 6th month postoperatively) follow up visits.

**Method of CRP, CEA and albumin determination**

CRP, CEA and Albumin will be estimated in biochemistry laboratory using agglutination reaction and reviewed from the patient records.

CEA levels >4ng/ml was taken as positive (Yu-chen shiu et al, 2001).[27]

CRP levels of >6ng/dl was taken as significant (Yu-chen shiu et al, 2001).[27]

Albumin level <3.5g/ml was taken as hypoalbuminemia (Heys et al, 1998).[28]

## III. OBSERVATIONS AND ANALYSIS

A total of 69 patients with colorectal carcinoma were studied.

**Age distribution of colorectal carcinomas (n = 69)**

Out of the 69 patients diagnosed to have colorectal carcinomas, 41(59.4%) patients were below 60 years of age and 28(40.6%) patients were above 60 years. Mean age at presentation was 55.6 years. The youngest patient diagnosed was 28 years old while the oldest was 87 years old.

Out of the 69 patients diagnosed to have colorectal carcinomas, 43(62.3%) patients were males and 26(37.7.6%) patients were females. Male preponderance was seen in the present study, which was in concordance with the study by Yu-Chen Shiu[9] et al.

Only 5 cases out of the 69 patients in our study had a family history of colorectal carcinoma.

**Location of colorectal carcinomas**

Thirty (43.4%) of the 69 patients diagnosed to have colorectal carcinomas were located in the right colon, 27(39.1%) in the left colon, 11(15.9%) in the rectum and only 1(1.4%) involved both the left and right colon. The most common location of colorectal carcinoma was found to be the right colon.

**Histological differentiation of colorectal carcinomas**

The most common histological differentiation of colorectal carcinoma observed was moderately differentiated type, accounting for 30(43.4%) cases followed by well differentiated, 24 (34.8 cases) and least being the poorly differentiated type, 15(21.7%) cases.

**Gross tumor size in colorectal carcinomas**

Thirty seven (53.2%) cases had tumor size of >5.2 cms while 32(46.4%) cases had tumor size of more than or equal to 5.2 cms at the time of diagnosis.

**Gross type of colorectal carcinomas**

The most common gross type observed was ulcerative type accounting for 49(71%) of the 69 cases. Twelve (12%) cases presented with polypoidal lesions and 8(17.4%) cases had infiltrative lesions.

**Distribution of colorectal carcinomas based on AJCC staging**

Most of the patients presented with stage III and stage IV disease accounting for 27(39.1%) and 20(29%) cases respectively. Eleven (15.9%) cases presented in stage I and II each.

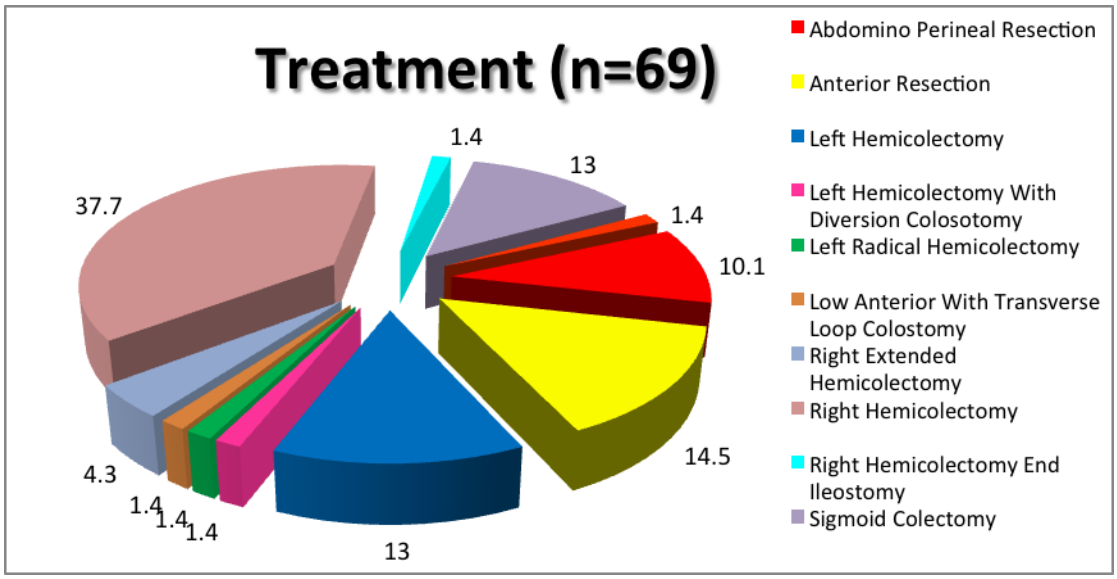
**Distribution of colorectal carcinomas based on Astler Coller staging**

Majority of the cases, 41 of 69 cases, were diagnosed to have Astler Coller stage C2 disease. Five cases had C1, 16 cases with B2 and 7 cases with B1 disease.

**Histopathological distribution of colorectal carcinomas**

The most common histo-pathological type was adenocarcinoma, accounting for 62(89.9%) of 69 cases in the study. Six (8.7%) cases had mucinous adenocarcinoma while only 1(1.4%) case had signet ring cell adenocarcinoma.

**Figure 1: Treatment modalities advocated for colorectal carcinomas**




Most common treatment advocated for the patients with colorectal carcinomas in the present study was observed to be right hemicolectomy accounting for 26(37.7%) cases, as the most common location for these tumors was right colon.

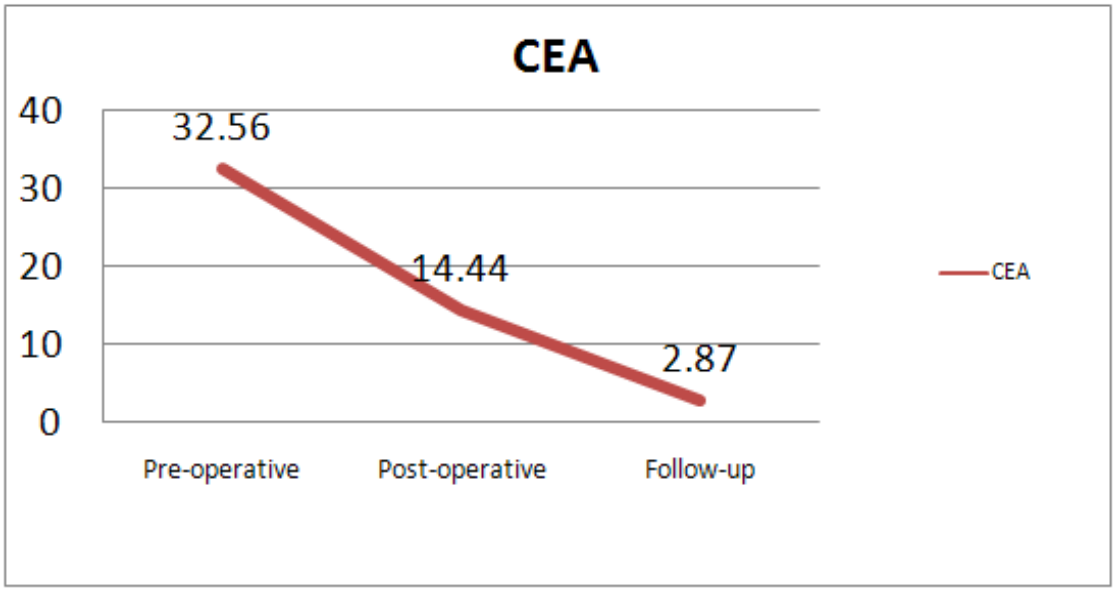
**Table 1: Association of mean preoperative, postoperative and followup CEA levels in colorectal carcinomas**

| | Mean | Standard deviation | n | p – value | Post hoc test |
|---|---|---|---|---|---|
| **Preoperative CEA** | 32.56 | 57.64 | 65 | **<0.001** | **1>2**<br>**1>3** |
| **Postoperative CEA** | 14.44 | 48.74 | 65 | | |
| **Followup CEA** | 2.87 | 1.43 | 65 | | |

Statistically significant

A satistically significant association was seen between mean preoperative, postoperative and followup CEA levels in colorectal carcinomas.

**Figure 2: Association of mean preoperative, postoperative and followup CEA levels in colorectal carcinomas**




Repeated Measures ANOVA followed by post hoc Bonferroni test was performed to assess any significant difference in CEA levels in the 3 visits. It was found that there was statistical difference in the mean CEA level at the 3 visits. However, Post hoc test showed that the mean pre-CEA was significantly higher than the post CEA and at follow-up. No difference was seen post op and follow-up CEA levels.

No statistically significant association could be demonstrated between histopathological types of colorectal carcinomas and preoperative, postoperative and followup CEA levels.

**Table 2: Association of gross types of colorectal carcinomas and CRP levels**

| **Significant CRP** | **Gross type** | | | **p value** |
|---|---|---|---|---|
| | **Infiltrative (8)** | **Polypoid (12)** | **Ulcerative (49)** | |
| **Preoperative** | 3 | 5 | 23 | **0.856** |
| | 37.5% | 41.7% | 46.9% | |
| **Postoperative** | 1 | 1 | 13 | **0.28** |

| | | | | |
|---|---|---|---|---|
| | 12.5% | 8.3% | 27.7% | |
| **Followup** | 0 | 1 | 8 | **0.30** |
| | .0% | 8.3% | 21.1% | |

No statistically significant association could be demonstrated between gross types of colorectal carcinomas and preoperative, postoperative and followup CEA levels.

**Table 3: Association of histopathological type of colorectal carcinomas with CRP levels**

| **Significant CRP** | **Histopathology** | | | **p value** |
|---|---|---|---|---|
| | **Adenocarcinoma (62)** | **Mucinous (6)** | **Signet Ring cell (1)** | |
| **Preoperative** | 27 | 4 | 0 | **0.366** |
| | 43.5% | 66.7% | 0% | |
| **Postoperative** | 14 | 1 | 0 | **0.81** |
| | 23.3% | 16.7% | 0% | |
| **Followup** | 8 | 1 | 0 | **0.81** |
| | 15.7% | 25% | 0% | |

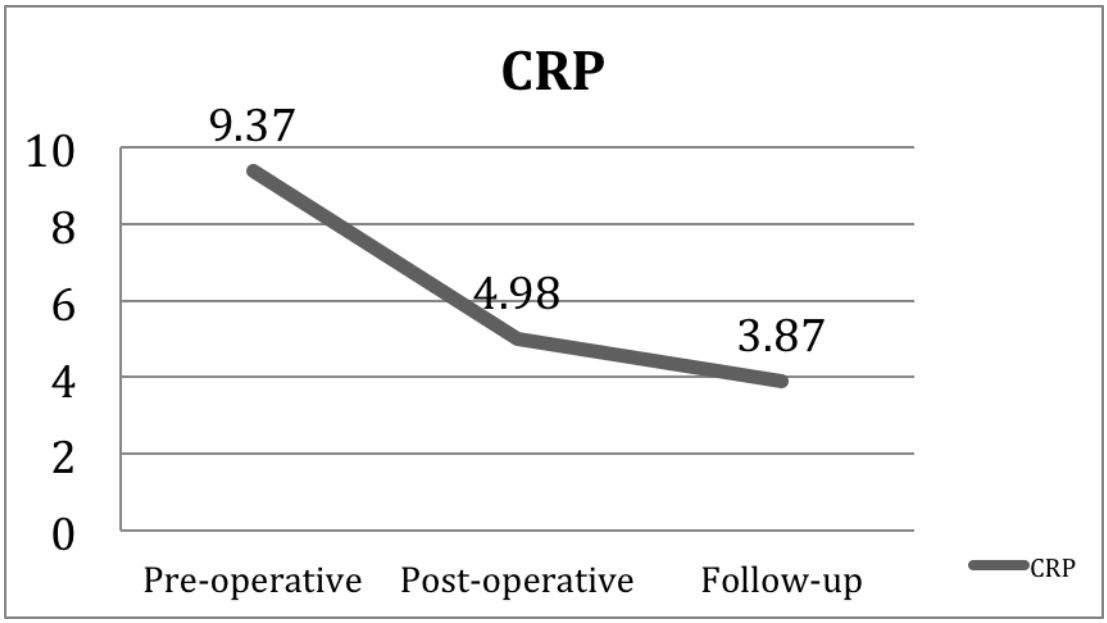
No statistically significant association could be demonstrated between histopathological types of colorectal carcinomas and preoperative, postoperative and followup CEA levels.

**Table 4: Association of mean preoperative, postoperative and followup CRP levels in colorectal carcinomas**

| | **Mean** | **Standard deviation** | **n** | **p – value** | **Post hoc test** |
|---|---|---|---|---|---|
| **Preoperative CRP** | 9.37 | 11.25 | 55 | **<0.001** | **1>2>3** |
| **Postoperative CRP** | 4.98 | 5.60 | 55 | | |
| **Followup CRP** | 3.87 | 4.56 | 55 | | |


A satistically significant association was seen between mean preoperative, postoperative and followup CEA levels in colorectal carcinomas.

**Figure 3: Association of mean preoperative, postoperative and followup CRP levels in colorectal carcinomas**




Repeated Measures ANOVA followed by post hoc Bonferroni test was performed to assess any significant difference in CRP levels in the 3 visits. It was found that there was statistical difference in the mean CRP level at the 3 visits. Post hoc test showed that the mean preoperative CRP was significantly higher than the postoperative CRP and at follow-up. Similarly the mean CRP postoperative was significantly higher than follow-up.

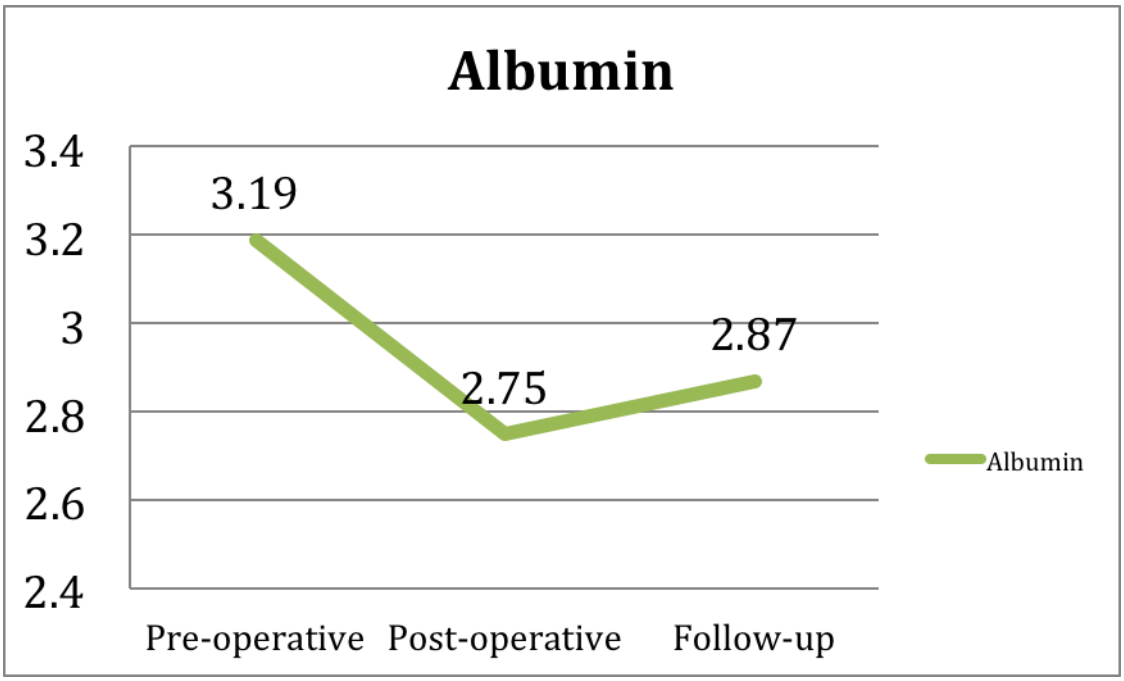
**Table 5: Association of mean, preoperative and followup albumin levels in colorectal carcinomas**

| | Mean | Standard deviation | n | p – value | Post hoc test |
|---|---|---|---|---|---|
| **Preoperative albumin** | 3.19 | .85 | 66 | **<0.001** | **1>2**<br>**1>3** |
| **Postoperative albumin** | 2.75 | .74 | 66 | | |
| **Followup albumin** | 2.87 | .58 | 66 | | |

**Statistically significant**

A satistically significant association was seen between mean preoperative, postoperative and followup CEA levels in colorectal carcinomas.

**Figure 4: Association of mean preoperative, postoperative and followup albumin levels in colorectal carcinomas**




Repeated Measures ANOVA followed by post hoc Bonferroni test was performed to assess any significant difference in albumin levels in the 3 visits. It was found that there was statistical difference in the mean albumin level at the 3 visits. However, post hoc test showed that the mean preoperative albumin was significantly higher than the postoperative albumin and at followup. No difference was seen postoperative and followup albumin levels.

## IV. DISCUSSION

As per a study by Holyoke et al[10] in 1975, 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.

The proportion of patients with elevated CEA level was 56.5% and 80.4% in Astler Coller B and C groups respectively as per our study. There was a significant increase in the proportion of patients with raised CEA level through the progressive stages of disease ($P<0.05$) and also there was increase in the level of CEA perse. This is in strong agreement with the data from other groups, Wanebo et al[11], Goslin et al[12] and Janusz et al[13].

**Table 6: Comparison of preoperative CEA levels in various studies.**

| Study | Stage A | | Stage B | | Stage C | |
|---|---|---|---|---|---|---|
| | Total no. of patients | No. of patients with raised preoperative CEA | Total no. of patients | No. of patients with raised preoperative CEA | Total no. of patients | No. of patients with raised preoperative CEA |
| **Wanebo et al 1978[161]** | 58 | 2 (4%) | 51 | 13 (25%) | 63 | 28 (44%) |
| **Robert Goslin et al 1980[49]** | 7 | - | 71 | 11 (15%) | 46 | 21 (46%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Janusz J. et al 1982[162]** | 53 | 13 (25%) | 41 | 12 (30%) | 127 | 75 (59%) |
| **Present study 2011** | - | - | **23** | **13 (56.5%)** | **46** | **37 (80.4%)** |

The present study was compared with the study done by Yu-Chen Shiu *et al*[9]. 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, 14 patients in Stage 4 disease had significant CRP preoperatively (n=20, 70%), 44.9% of the patients had positive pre-operative significant CRP levels. In the study by Yu-Chen Shiu et al[9], CRP level was considered as an independent variable. But, in our study, there was a positive relation of change in CRP with stage IV disease. CEA elevation along with CRP elevation had shown statistical significance in the present study. Furthermore it was concluded that though CEA alone could not be used as a prognostic tool, the combined values of CEA 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[9] study which is in vehement approval of the data from the present study. (Table 7)

**Table 7: Comparison of various factors in present study with Yu-Chen et al[9]**

| | | **Yu-Chen Shiu et al 2001[27]** | | | | **Present Study 2011** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **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=41 | 22 (57.9) | 19(61.3) | **0.775** |
| | **>60** | n=107 | 45(21.2) | 62(29.2) | | n=28 | 16 (42.1) | 12 (38.7) | |
| **Gender** | **Male** | n=140 | 66(31.3) | 74(34.9) | 0.56 | n=43 | 12 (31.6) | 14 (45.2) | **0.247** |
| | **Female** | n=72 | 37(17.5) | 35(16.5) | | n=26 | 26 (68.4) | 17 (54.8) | |
| **Family History** | **Negative** | n=192 | 94(44.3) | 101(47.6) | 0.71 | n=64 | 35 (92.1) | 29 (93.5) | **0.818** |
| | **Positive** | n=17 | 9(4.2) | 8(3.8) | | n=5 | 3 (7.9) | 2 (6.5) | |
| **Differentiation** | **Well** | n=2 | 1(0.5) | 1(0.5) | 0.16 | n=24 | 15 (39.5) | 9 (29) | **0.55** |
| | **Moderate** | n=180 | 90(42.5) | 90(42.5) | | n=30 | 16 (42.1) | 14 (45.1) | |
| | **Poor** | n=30 | 12(5.7) | 18(8.5) | | n=15 | 7 (18.4) | 8 (25.8) | |
| **Gross type** | **Polypoid** | n=54 | 35(16.5) | 19(9) | 0.015 | n=12 | 7 (18.4) | 5 (16.1) | **0.856** |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Ulcerative** | n=143 | 60(28.3) | 83(39.2) | n=49 | 26 (68.4) | 23 (74.2) | |
| | **Infiltrative** | n=15 | 8(3.8) | 7(3.3) | n=8 | 5 (13.2) | 3 (9.7) | |

| | | **Yu-Chen Shiu et al 2001** | | | | **Present Study 2011** | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Patient number (%)** | | | | **Patient number (%)** | | |
| | | | **CRP<6** | **CRP>6** | **p value** | | **CRP<6** | **CRP>6** | **p value** |
| **Location** | **Right colon** | n=63 | 26(12.3) | 37(17.5) | 0.066 | n=30 | 17 (44.7) | 13 (41.9) | **0.367** |
| | **Left colon** | n=79 | 35(16.5) | 44(20.8) | | n=27 | 13 (34.2) | 14 (45.2) | |
| | **Rectum** | n=70 | 42(19.8) | 28(13.2) | | n=11 | 8 (21.1) | 3 (9.7) | |
| **Size (cm)** | **<5.2** | n=103 | 66(31.1) | 37(17.5) | <0.001 | n=37 | 21 (55.3) | 16 (51.6) | **<0.001** |
| | **>5.2** | n=109 | 37(17.5) | 72(34) | | n=32 | 17 (44.7) | 15 (48.4) | |
| **AJCC Staging** | **Stage I** | n=29 | 22(10.4) | 7(3.3) | 0.002 | n=11 | 4 (10.5) | 7 (22.6) | **0.006** |
| | **Stage II** | n=64 | 32(15.1) | 32(15.1) | | n=11 | 9 (23.7) | 2 (6.5) | |
| | **Stage III** | n=67 | 33(15.6) | 34(16) | | n=27 | 19 (50) | 8 (25.8) | |
| | **Stage IV** | n=52 | 16(7.5) | 36(17) | | n=20 | 6 (15.8) | 14 (45.2) | |
| **CEA (ng/ml)** | **<4** | n=106 | 64(30.2) | 42(19.8) | 0.001 | n=19 | 11 (28.9) | 8 (25.8) | **<0.001** |
| | **>4** | n=106 | 39(18.4) | 67(31.6) | | n=50 | 27(71.1) | 23(274.2) | |

As for comparison between the present study and the one by Yu-Chen Shiu,[9] with regards to male preponderance of the disease, relatively low positive family history and histologically being moderately differentiated adenocarcinoma, out study was in approval of the data shown in the previous studies.

Most of the lesions, colonscopically, appeared to be ulcerative, which again was in concordance with our study, however location and size of the primary tumour did not yield comparable results.

The present study, however, did show that CEA and CRP 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,[14] 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.

When relating to the cancer specific survival, our patients were followed for a short period (about 3 to 6 months), which does not render us any conclusion. A similar study reported by Chung and Chang,[15] 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.

50 out of the 69 patients in our study had elevated CEA preoperatively (72.4%). 33 out of 43 patients with intraoperative/histopathological evidence of metastases had elevated CEA preoperatively (76.7%). 31 of the 43 patients with intraoperative/histopathological evidence of metastases had hypoalbuminemia preoperatively (72.1%). 44 patients of the 69 in the present study had preoperative hypoalbuminemia (63.7%).

17 of the 20 patients in AJCC Stage IV had hypoalbuminemia preop (85%) with a strong association (p=0.027). Postoperative period Stage IV disease patients persisted to have hypoalbuminemia, 19 of the 20 patients in this group persisted to have low albumin levels (95%).

This is concordance with the study as per Heys et al[16] published in *J.R.Coll Surg.Edinb*; 1998 which showed that serum albumin was an individual prognostic indicator in detecting advanced colorectal disease preoperatively, outcome and recurrence rates.

## V. CONCLUSIONS

69 patients were included in our study with the earliest followup at 3 weeks postoperatively and the latest at 6 months. Serial preoperative, postoperative and followup CEA, CRP and albumin levels were analyzed.

Following were the conclusions made in the present study -

**C- reactive protein (CRP)**

- Polypoidal lesions seemed to have higher CRP levels as compared to patients with ulcerative lesions and infiltrative lesions.
- Higher CRP values were observed in patients with poorer differentiation of tumor.
- There was statistical significance between CRP and CEA values as prognostic indicators.
-

**Carcinoembryonic antigen (CEA)**

- Poor histology carcinoma patients tend to have higher preoperative CEA levels as compared to the others. (signet ring>> mucinous>> adenocarcinoma)
- Our current findings indicate that an abnormal pre and postoperative serum CEA level observed, significantly correlated with the depth of tumor invasion, the status of lymph node metastasis, advanced MAC stage, and higher postoperative relapse.

**Albumin**

- Hypoalbuminemia was also strongly associated with poorer prognosis and poor histopathological variants.
- Persistent hypoalbuminemia is a feature of advanced disease and should be monitored serially and for longer period to arrive at a consensus.

To conclude, CEA, CRP and albumin were found to have statistical significance as preoperative and postoperative indicators of prognosis of colorectal carcinomas and should be followed up serially in all patients who have undergone surgery with curative intent.

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