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CLINICOPATHOGICAL SIGNIFICANCE OF SERUM PROLACTIN, CA19-9 AND C – REACTIVE PROTEIN IN COLORECTAL CANCER

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ABSTRACT: The incidence of colorectal cancer in India ranks fourth in men and third in women. Carcinogenesis is a process that involves a combination of mutations in oncogenes, tumour suppressor genes or epigenetic changes in DNA such as methylation. Our study aim to assess the clinicopathogical significance of serum Prolactin, CA19-9 and C – reactive protein in colorectal cancer. Population based case control study, which includes 120 participants and 120 healthy volunteers during the time period of one year. In our study we found, CA19-9 tumor markers reflected more specificity as compared to sensitivity and efficiency. Prolactin were significantly higher when compared with control. Further prolactin levels were significantly elevated in different stages of CRC malignancy as compared to controls. Our values demonstrated the progressive increase corresponding to clinical staging, tumor size and notable in relation to nodal status of colorectal squamous cell carcinomas. Our results may provide new approaches in the diagnosis, prognosis, and monitoring the risk factors and combines both gross as well as microscopic information to determine the probable diagnosis of colorectal cancer.

INTRODUCTION: The incidence of colorectal cancer in India ranks fourth in men and third in women. Colorectal cancer is a disease of old age, but its incidence has been rising among younger population compared to older ones [1]. Colorectal cancers occur sporadically and are characterized by sequenced carcinogenesis process that involves the progressive accumulation of mutations in a period that lasts 10-15 years [2]. The clinical presentation of CRC is dependent on the site of tumour and extent of tumor. Patients with early-stage cancers are asymptomatic and diagnosis is mostly made through screening.

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Common symptoms associated with colorectal cancer include abdominal pain, rectal bleeding, altered bowel habit and involuntary weight loss [3, 4]. Carcinogenesis is a process that involves a combination of mutations in oncogenes, tumour suppressor genes or epigenetic changes in DNA such as methylation. A genetic model that depicts the switch from healthy colonic epithelia through increasingly dysplastic adenoma to malignant cancer has been proposed. This model recognizes a number of vital oncogenes and tumour suppressor genes, which drives the adenoma to carcinoma transition [5].

There are several additional features, derived from both clinical and pathological information, which have prognostic significance. In present study clinicopathogical significance were relate by analysing serum prolactin, CRP and CA 19-9 levels. CRP is a significant marker of inflammation

that is known to represent a critical component of tumor development and progression. Prolactin (PRL), a cytokine hormone accumulates in the tissue microenvironment and elicits its action in an autocrine or paracrine manner to regulate diverse physiological activities that include reproduction, growth, development, metabolism and immunomodulation. CA 19-9, is a carbohydrate chain which is expressed on tumor cells and is known to play a role in adhesion between tumor cells and endothelial cells [6, 7]. CA19-9 is a monoclonal antibody that is ligand for E-selectin. Our study aim to assess the clinicopathogical significance of serum Prolactin, CA19-9 and C – reactive protein in colorectal cancer.

MATERIAL AND METHODS:

Study Design: Population based case control study, which includes 120 participants and 120 healthy volunteers during the time period of one year at the Ashwini rural medical college, hospital and research center. Solapur, Maharashtra. Information on tumor size, lymph node status, lymphatic or vascular vessel invasion, mucinous cell type and tumor differentiation was retrieved from pathological records.

This study population was divided into two groups;

1. Patients with disease dissemination (stage I-III with recurrences and stage IV).
2. Patients with non- dissemination (stage I-III without recurrences).

Ethical clearance was obtained from the institutional Ethical Committee. The DCGI Registration no. ECR/782/Inst/MH/2015/RR-18.

Inclusion Criteria: Patients with known colorectal carcinoma were considered to be eligible and were included in this study.

a) The patients willingly gave the consent to be included in the study.

b) The patients diagnosed of having colorectal cancer were confirmed by the accepted gold standard i.e. Histopathological report.

Exclusion Criteria: To avoid false positive results care was taken by excluding patients with renal hepatobilliary disorders, systemic lupus erythematosus, lymphoproliferative disorders, collagen disorders, acquired immunodeficiency syndrome as well as malignancies other than colorectal cancer.

METHODS: Prolactin was estimated by an enzyme immunoassay sandwich with final fluorescent detection (ELFA), CRP by NycoCard Reader immunometric assay and CA 19-9 (cancer antigen 19-9) level by two-step immunoassay sandwich method with a final fluorescent detection (ELFA) technique using commercial kit.

Statistical Data Analysis: The analysis of data was done by using student t test and SPSS-17 software. The difference in mean values of various parameters were calculated and expressed in terms of p value.

- Sensitivity, specificity, predictive value and efficiency of each marker was reported.
- Correlations between the parameters was evaluated in all study subjects and calculated by Pearson's method.

RESULTS: The results shows that these two tumor markers were significantly increased in mean level as compared with control. Further these levels showed significant rise as the stage advances **Table 1.** The Pearson correlation showed positive correlation ship. CA19-9 tumor markers reflected more specificity as compared to sensitivity and efficiency. Prolactin were significantly higher when compared with control.

Further prolactin levels were significantly elevated in different stages of CRC malignancy as compared to controls. Our values demonstrated the progressive increase corresponding to clinical staging, tumor size and notable in relation to nodal status of colorectal squamous cell carcinomas **Table 2**.

We also observed stage wise significant elevation in prolactin with higher sensitivity as compared to specificity. Our results depicts that the CRP mean values when compared stage-wise, showed significantly raised levels ($p<0.001$) as the stages advances.

TABLE 1: MEAN LEVEL OF PROLACTIN, CA19-9 AND CRP IN COLORECTAL CANCER (CRC) AND CONTROLS WITH THEIR SIGNIFICANT P VALUE USING UNPAIRED T TEST

Parameters	Case of CRC Mean ± SD	Control Mean ±SD	p value
CA 19-9(ng/ml)	56.30 ± 7.31	22.68 ± 8.37	p<0.001
CRP	24.08 ± 4.74	3.36 ± 0.66	p<0.001
Prolactin (ng/ml)	36.94 ± 3.94	20.27 ± 5.92	p<0.001

p<0.001 - Highly significant p<0.01 - More significant p<0.05- Significant p>0.05- Not significant.

TABLE 2: ANALYSIS OF VARIANCE SHOWING THE PARAMETERS IN THE DIFFERENT STAGES OF COLORECTAL CANCER WITH THEIR P VALUE

Parameters	CRC Cases stage wise distribution					p value
	Stage 0	Stage I	Stage II	Stage III	Stage IV	
CA 19-9	41.62±1.41	45.45±2.34	55.40±3.90	60.05±3.74	64.84±3.11	p<0.001
Prolactin	32.66±3.49	34.69±2.53	36.85±3.10	37.12±3.63	40.76±4.87	p<0.001
CRP	12.6±0.88	17.74±2.58	24.52±2.57	26.06±2.66	28.33±3.47	p<0.001

TABLE 3: MEAN LEVEL OF CRC WITH RECURRENCES PATIENTS AND CONTROLS WITH THEIR SIGNIFICANT P VALUES BY USING UNPAIRED T TEST

Parameters	Case of CRC with Recurrences Mean ± SD	Control Mean ±SD	p value
CA 19-9	54.64±4.80	22.68± 8.37	p<0.01
Prolactin	26.29±3.08	20.27±5.92	p<0.05
CRP	26.58±3.33	3.36±0.66	p<0.001

TABLE 4: SENSITIVITY, SPECIFICITY AND EFFICIENCY OF DIFFERENT STUDY PARAMETERS

Parameters	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Efficiency
CA 19-9	82.5%	91.66%	90.82%	83.96%	87.08%
Prolactin	91.66%	91.66%	91.66%	91.66%	91.66%
CRP	95%	90.83%	91.2%	94.78%	92.91%

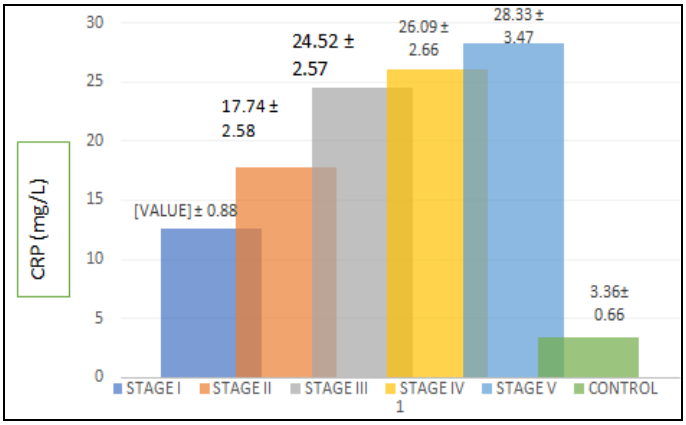

FIG. 1: MEAN LEVEL OF CRP IN COLORECTAL CANCER (CRC)

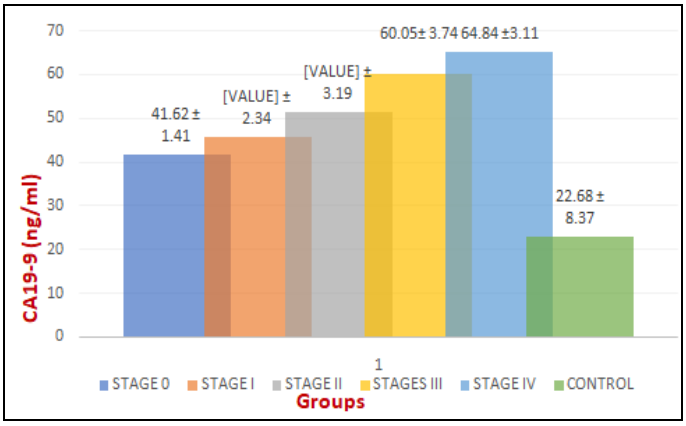

FIG. 2: MEAN LEVEL OF CA19-9 IN COLORECTAL CANCER (CRC)

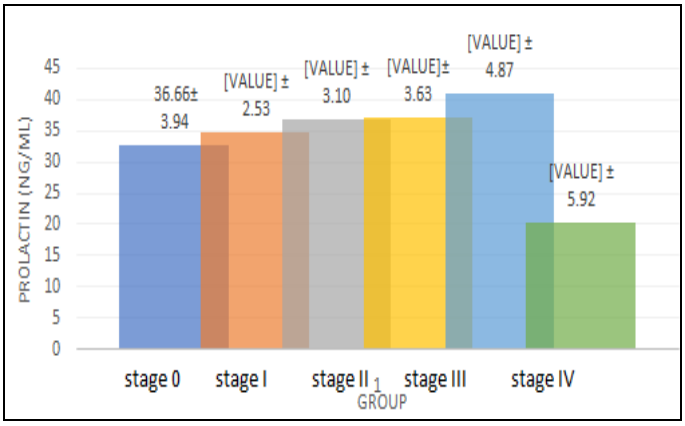

FIG. 3: MEAN LEVEL OF PROLACTIN, IN COLORECTAL CANCER (CRC)

DISCUSSION: Our study shows that Ca19-9 levels in pretreatment would be useful for prediction of prognosis, and postoperative serial assay of CEA level. It also provide an opportunity for early detection of recurrent disease. We Envisaged that these parameters may play a crucial role in colorectal carcinogenesis and metastasis. The positive correlation shows comprehensive comparison of prognostic value of tumor and levels of protein factor [8]. The significantly increased levels of CRP in CRC conditions when compared to controls might be from a generalized increased CRP synthesis throughout the body of cancer patients. Prolactin has shown excellent sensitivity as compared to specificity. The elevated levels of CRP in colorectal cancer have been associated with tumor stage and recurrence and reduced survival rate [9, 10, 11]. Circulating prolactin has been found to have prognostic impact in colorectal cancer patients. Clinicopathological correlation will be helpful in treating disease during early stages of development of colorectal cancer.

CONCLUSION: In the view of clinicopathological significance the serum prolactin, CRP and CA19-9 level in CRC were significantly corelated with each other. Our results may provide new approaches in the diagnosis, prognosis, and monitoring the risk factors and combines both gross as well as microscopic information to determine the probable diagnosis of colorectal cancer.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest.

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