ORIGINAL ARTICLE

PREDIAGNOSTIC CLINICAL PRESENTATIONS AND ABNORMAL LABORATORY REPORTS IN PATIENTS OF COLORECTAL CARCINOMA: A 5 YEARS' EXPERIENCE FROM A TERTIARY CARE HOSPITAL OF BANGLADESH

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Abstract:

Background: *Colorectal cancer (CRC) comprises a major public health issue globally. Understanding pre-diagnostic clinical features and abnormal laboratory reports in patients with Colo-rectal cancer could enlighten a way of opportunity for earlier diagnosis. This study was aimed to provide the pattern of relevant symptoms and abnormal laboratory results in patients with colorectal cancer before diagnosis.* **Methods:** *This cross sectional study held at department of gastroenterology of Rangpur medical College, Rangpur, Bangladesh from January 2019 to December 2023 over a 5 years period. Colonoscopy and histopathologically proven 1150 CRC patients were taken as study subjects.* **Results:** *Among the study subjects 73.47% (845) were male and 26.52% (305) were female. In the time before diagnosis of CRC, the most commonly observed symptom was abdominal pain 77.39%, (890) followed by altered bowel habit 46.95%, (540) among this study subjects. Other notable clinical features are Per rectal bleeding 20.69 % (238), abdominal lump 17.21% (198), Anemia/pallor 29.56 % (340) and weight loss in 23.21% (267). Laboratory reports of the patients before diagnosis were decreased hemoglobin in 47.04% (541) and high CRP in 65.56 % (754) and high ESR in 51.22%(589) patients. Stool examination shows RBC in 10.78 % (124) cases only. Ultrasonogram shows abdominal lump in 22.96% cases and SOL in liver in 12%. Plain X Ray abdomen shows acute and sub-acute intestinal obstruction in 11.30% cases. 217 (18.86%) patients presented within 6 months of symptom onset and 585 (50.86%) presented between 6 months to 02 years duration. About 35% of patients visited three or more physicians before diagnosis and rest (65%) of the study subjects consulted up to two physicians visit.* **Conclusion:** *From this study, it is evident that, if we will be aware of the CRC suggestive symptoms and laboratory reports, there is chance to promote referral for confirm diagnosis.*

Keywords: *Colorectal cancer (CRC), Pre diagnostic Clinical Presentations, Abnormal Laboratory Reports*

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Introduction:

Colorectal cancer (CRC) comprises a major public health issue globally with an estimated 1.2 million new cases and with 630,000 deaths per year, reaches 8% amongst all cancer related mortality[1]. Throughout the world this is the fourth most common cancer in male and the third most common in female [2]. CRC is primarily known to be common in developed and Western countries. However, the clinico-pathological patterns of colorectal cancer have been shown to be different in various geographical regions of the world. Although in the western world colorectal cancer is a disease of elderly and presented at an earlier stages,[3,4] colorectal cancer in Asian and African countries tends to present with advanced stages and shows poorer prognosis.[5,6] The diagnostic stage of the CRC often destine the prognosis and survival rate of a patient, with the best outcomes seen when patients diagnosed at an initial stage. However, the consequences of treatment of colorectal cancer in our country have been poor because most of the patients present with advanced stage and only palliative care can be given at that time[7,8]. This is partly due to lack of adequate data in this field as well as lack of public awareness about the significance of early diagnosis and treatment.

Throughout the world, at first most of the patients usually go to primary care physicians for their problem. Patients who experience alarm symptoms of colorectal cancer, including rectal bleeding, change in bowel habit, rectal or abdominal mass, and unexplained anemia can then be referred to a specialist for further evaluation.[9] However, most patients do not face alarm symptoms before the diagnosis of colorectal cancer. Besides these many patients with colorectal cancer experienced non-specific symptoms such as bodyache, weight loss or fatigue before their diagnosis.[10] They also visit other physicians for musculoskeletal, neurological, respiratory, endocrine dysfunction and for other non-specific symptoms.[11] These scenarios before diagnosis make a delay in timely diagnosis of CRC for most of the cases.

Based on previously reported data with colorectal cancer, blood test results for platelets, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and hemoglobin were analysed.[12] Reviewing of the literature, it was decided to take normal cut-offs values from reputed guidelines [13]

Understanding pre-diagnostic clinical features and abnormal laboratory reports in patients with CRC could enlighten a way of opportunity for early investigations and referrals and thus an earlier diagnosis of cancer could be possible.

Against this background, this study was aimed to provide a comprehensive and up-to-date description of the pattern of relevant symptoms and abnormal laboratory results in patients with colorectal cancer before diagnosis, and to identify when first signals of possible colorectal cancer might occur, so that timely steps can be taken.

Methods:

This was a cross sectional study held at endoscopy unit of department of Gastroenterology of Rangpur medical College, Rangpur, Bangladesh from January 2019 to December 2023 over a 5 years period. Patients who were diagnosed as colorectal cancer on colonoscopy and confirmed by histopathology were taken as study subjects. A total of 1150 CRC patients aged between 18-90 years were included for the study during the study period by purposive sampling method. We excluded the patients who were negative on histopathological reports or who had a colorectal tumor as metastatic deposits. After enrolling the subjects, data were collected by a questionnaire mentioning previous clinical features and available laboratory investigations up to 02 years before diagnosis. The questionnaires were filled by a trained physician both by face to face interview and also reviewing of previous investigation reports.

Numbers and percentages are used to express qualitative data, and the chi-square test was performed to assess the relationship between variables. Quantitative data are expressed as mean ± standard deviation. Statistical analysis was performed using the SPSS (version 25; IBM Corp). Statistical significance was set at a p-value of _0.05.

Ethical permission was taken from Ethical Review committee of Rangpur medical college(RMC/Rang/2024/2207-c). Informed written consent was also managed before enrolling each patient.

Results:

The study included 1150 patients with CRC, of whom 73.48% (845) were male and 26.52% (305) were female. More than half of the patients; 650 (56.52%) had an age at diagnosis ranging from 50 to 70 years. The majority of the CRC patient of this study have the following comorbidities; diabetes mellitus (10.17%), Hypertension(7.47%), IBS(20.17.%), IBD(2.08%), gall bladder diseases(3.05%) and hemorrhoids (7.73%). Family history were positive in 5.83 % of patients in our study. The duration of symptoms at presentation ranged from 06months to 2 years. 217 (18.86%) patients presented within 6 months of symptom onset and 585 (50.86%) presented between 6 months to 12 months duration. About 35% of patients visited three or more physicians visit before diagnosis and rest(65%) of the study subjects consulted up to two physicians visit.(Table-l)

Table-1

Clinico-demographic profile of the respondents:

Characteristics	Values	Number(n=1150)	Percentage(%)
Age at diagnosis(Years)	<50 years	189	16.43
	50-70 years	650	56.52
	>70 years	311	27.05
Gender	Male	845	73.48
	Female	305	26.52
Family History of CRC	Present	67	5.83
	Absent	1083	94.17
Comorbidities	Diabetes Miletus	117	10.17
	Hypertension	86	7.47
	Gall bladder diseases	35	3.04
	Irritable Bowel Syndrome	232	20.17
	Inflammatory Bowel Diseases	24	2.08
	Hemorrhoids	89	7.73
	None	567	49.30
Duration of symptom to diagnosis(Month)	<06	217	18.86
	06-12	585	50.86
	>12	348	30.26
Number of physician visits before diagnosis	≤02	748	65.04
	≥03	412	34.95

In the time before diagnosis of CRC, the most observed symptom was abdominal pain 77.39%, (890) followed by altered bowel habit 46.95%, (540) among this study subjects. Other notable clinical features are Per rectal Bleeding 20.69 % (238), abdominal lump17.21% (198), Anemia/pallor 29.56 %(340) and weight loss were in 23.21% (267). 11.65 % (134) of patients admitted in hospital with features of acute or subacute intestinal obstruction. (Figure-1).
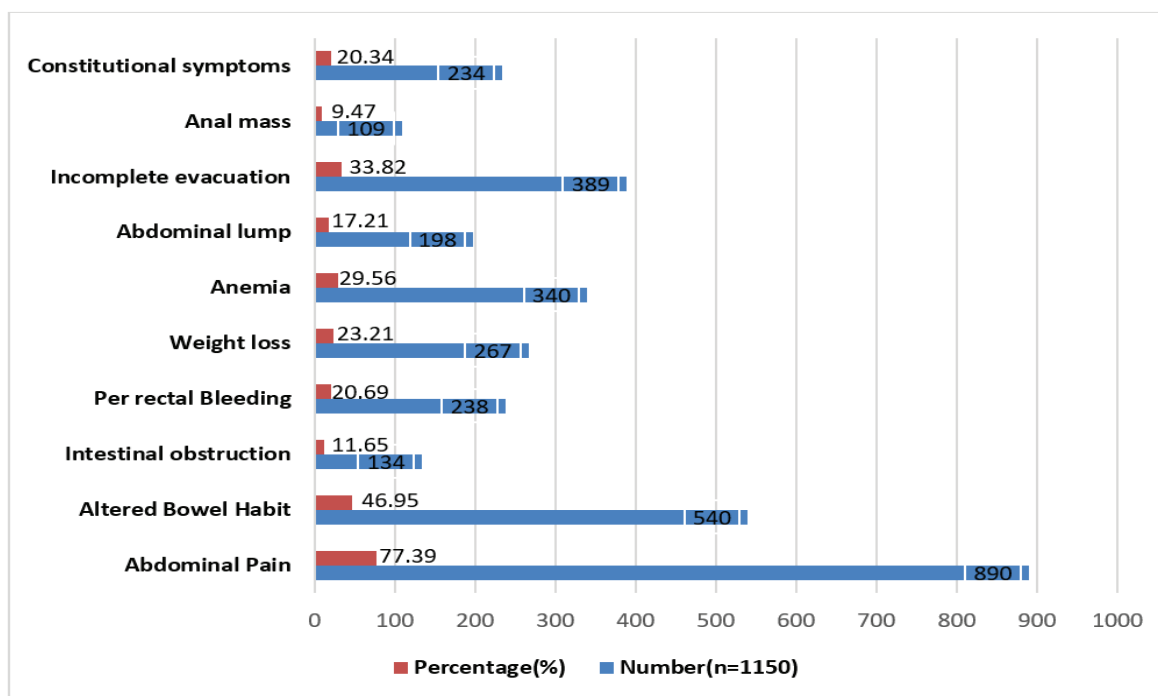

Figure-1: *Pre diagnostic Clinical Presentations of the respondents (n=1150)*

Table II

Association of age of the study subjects with pre diagnostic symptoms(n=1150)

Pre diagnostic symptoms	Total	Age (years)			p-value
		<50	50 - 70	>70	
Constitutional symptoms	234	52 (22.2)	126 (53.8)	56 (23.9)	0.024
Anal mass	109	32 (29.4)	45 (41.3)	32 (29.4)	<0.001
Incomplete evacuation	389	104 (26.7)	230 (59.1)	55 (14.1)	<0.001
Abdominal lump	198	52 (26.3)	113 (57.1)	33 (16.7)	<0.001
Anemia	340	97 (28.5)	165 (48.5)	78 (22.9)	<0.001
Weight loss	267	48 (18.0)	88 (33.0)	131 (49.1)	<0.001
Per rectal bleeding	238	94 (39.5)	91 (38.2)	53 (22.3)	<0.001
Intestinal obstruction	134	27 (20.1)	78 (58.2)	29 (21.6)	0.224
Altered Bowel Habit	540	131 (24.3)	309 (57.2)	100 (18.5)	<0.001
Abdominal Pain	890	147 (16.5)	510 (57.3)	233 (26.2)	0.463

Incomplete evacuation, abdominal lump is common among the age group 50-70 years and it is highly significant. Similarly weight loss is also significant among >70 years age group.(Table II).

Table III

Association of duration of symptoms with pre diagnostic presentations(n=1150)

Pre diagnostic symptoms	Total	Duration of symptoms			p-value
		<6	6 - 12	>12	
Constitutional symptoms	234	70 (29.9)	113 (48.3)	51 (21.8)	<0.001
Anal mass	109	72 (66.1)	21 (19.3)	16 (14.7)	<0.001
Incomplete evacuation	389	143 (36.8)	199 (51.2)	47 (12.1)	<0.001
Abdominal lump	198	155 (78.3)	33 (16.7)	10 (5.1)	<0.001
Anemia	340	212 (62.4)	71 (20.9)	57 (16.8)	<0.001
Weight loss	267	131 (49.1)	99 (37.1)	37 (13.9)	<0.001
Per rectal bleeding	238	163 (68.5)	50 (21.0)	25 (10.5)	<0.001
Intestinal obstruction	134	113 (84.3)	12 (9.0)	9 (6.7)	<0.001
Altered Bowel Habit	540	130 (24.1)	310 (57.4)	100 (18.5)	<0.001
Abdominal Pain	890	192 (21.6)	465 (52.2)	233 (26.2)	<0.001

Patients had presented within 06 months with abdominal lump, per rectal bleeding and intestinal obstruction. Whether patients with incomplete evacuation, altered bowel habit and abdominal pain had presented at later time.(Table III).

In our study, available previous blood reports of the most of the patient before diagnosis were decreased haemoglobin in 47.04% (541) and high CRP in 65.35%(366/560) and high ESR in 51.22%(589) patients. Stool examination shows RBC in 10.74%(52/ 484) cases only. Ultra sonogram shows abdominal lump in 22.96% cases and SOL in liver in 12%. Plain X Ray abdomen shows acute and sub-acute intestinal obstruction in 11.30% cases.(Table-IV).

Table-lV
Laboratory reports of study subjects:

Investigation	Number(n=1150)	Percentage(%)	Mean ±standard deviation
Hemoglobin((<11 g/dL for males, <10 g/dL for females) [9]	541/1150	47.04	Male:9.83±1.15 g/dL Female:8.56±1.34g/dL
Thrombocytosis(>400 × 10^9/L) [9]	186/1150	16.17	(510±104)x10 ^{9}/L
Erythrocyte sedimentation rate (>40mm) [9]	589/1150	51.22	70±11 mm
C Reactive protein(>10mg/L)	366/560	65.35	19±8 mg/L
Stool RME for RBC	52/484	10.74	
Ultrasonogram of Abdomen:			
Abdominal lump	264/1150	22.96	
SOL in liver	138/1150	12	
Plain X Ray Abdomen:			
Intestinal obstruction	130/1150	11.30	

The rectum was the most frequent site for colorectal cancer 289 (25.13%) cases followed by cecum 245 (21.30%), recto-sigmoid junction and ascending colon both were 176 (15.30%) cases respectively. The ano-rectum was involved in 15 (1.30%) cases. (Figure-2)
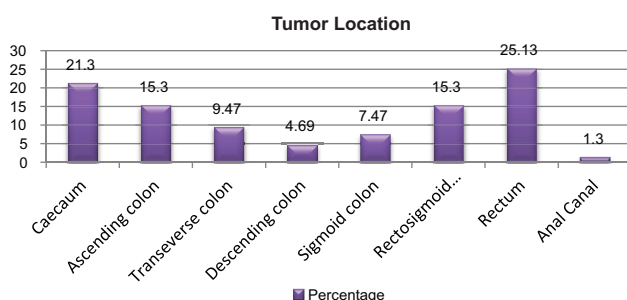

Figure-2: *Site of the tumor at diagnosis*

In our study, out of 1150 cases the most common histopathological variety were adenocarcinoma 74.43% (856). The remaining commoner varieties were Adeno-squamous (15.13%) and squamous cell carcinoma (9.39%). (Figure-3)
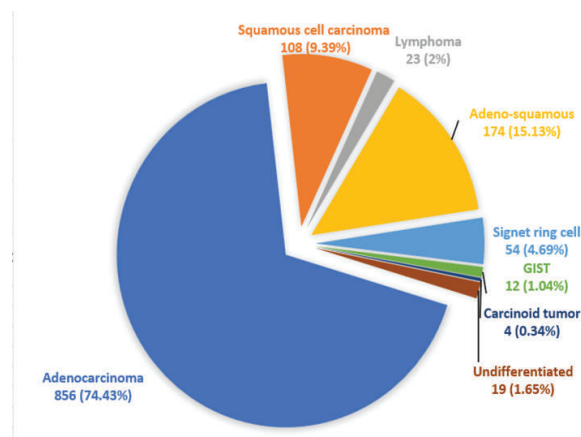

Figure-3: *Histopathological varieties of the tumor of the respondents(n-1150)*

Discussion:

In this study, the majority of patients presented late with advanced stage of cancer which is in keeping with other studies in developing countries.[14,15] Delayed presentation may be attributed to lack of awareness about colon cancer, low level of education, low accessibility to healthcare facilities and absence of screening programs for general population in this region.

In our study we have noticed a preponderance of left-sided tumors, especially rectum and recto-sigmoid junction, which is consistent with other studies in some developing countries [16,17]. Whereas in developed countries right-sided tumors are predominant. The reason for this anatomical difference among these countries is not clear. But studies from this countries showed that the more right sided tumor the more delayed presentation of cancer symptoms. [18,19]

Abdominal pain and altered bowel habit were the commonest symptom for colorectal cancer in our study which is in similarity with other study findings in Asian countries. [20] In our study, the next common clinical features were per rectal bleeding which were also predominant in other studies in African countries. [5,21] It is evident by literature that, the more right sided tumor the late presentation and the more left sided tumor the earlier detection of CRC. Right sided tumors usually manifested with anemia and left side tumor presented with per rectal bleeding and intestinal obstruction. Hence, right sided tumor presented lately and left sided tumors presented at an earlier stage[10]. Weight loss, pallor and constitutional symptoms are also accounting a notable portion of clinical presentation in our study. These findings are nonspecific but common in CRC. That's why these findings should be kept in mind while clinical visit of a

patient. These data correlate with pre-diagnostic clinical feature study by Moullet et al. 2022[18]. If our primary care physicians and specialists are aware of these features, earlier search of CRC could be warranted.

Low hemoglobin were found in 47.04% of patients in this study which is consistent with previous studies elsewhere in the world.[18, 24]Although high inflammatory markers and thrombocytosis are non-specific for cancer, the abnormality should prompt other investigation tools, especially when risk factors and suggestive clinical features or blood tests are positive.[22,23] We found that, 10.74% patient had RBC in their stool test. This finding was not in consistent with study done by Abu- Freha et al.2022 in Israel (3.38%). This dissimilarity was possibly due to their population-based study and ours were CRC specific data.[24] Abdominal lump in Ultrasonogram were found in 22.69% in our study. Martínez-Ares et al.2005 found in 28.9% patients which was quite similar. Abdominal Ultrasonogram can be used as a screening tool for CRC suspected cases in general practice, though it is a highly subjective test.[25]

In a retrospective study in Korea, 49.6% of colon cancer patients had e"3 comorbidities.[26] The most common comorbidities we found in our study were IBS in 20.17% and DM in 10.17%. In a Taiwanese study showed 23% prevalence of IBS in CRC, which in concordance with this study. [27]

In this study, a family history of colorectal cancer was reported in 5.83% of cases, a figure which is closely related to 4.10% in USA by Herkinsen et al. 2015 [28] and 4.3% reported by Azadeh et al. [29] in Iran. This finding suggests that genetic risk factors are also an important risk factor in the development of CRC throughout the world. Based on this important observation, it is suggested to start genetic screening for CRC patient's family in our country and all developing countries as well.

Similar to previous studies, we have found that about 35% of patients visited more than 03 physicians for consultation of relevant symptoms and abnormal tests in patients with colorectal cancer in the year before final diagnosis. These previous studies had analyzed number of physician consultations during the pre-diagnostic period.[30,31]In our study, patients visited for gastrointestinal and other nonspecific constitutional symptoms indicates that if we can make awareness regarding those clinical features, we can make earlier referral for further investigations of CRC.

A recent study in England showed that GPs did not make adequate referrals for 82% of patients presenting with per rectal bleeding. Other study also found that, lack of knowledge of standard referral criteria and concerns of over-referring leads to late referral of patients with CRC suggestive clinical features.[31]

Increasing primary care physicians' awareness of the less cancer-specific symptoms and abnormal blood tests (such as low hemoglobin and high CRP) may prompt convenient check-up of symptoms and abnormal laboratory reports. Moreover, the more employment of CRC specialized diagnostic points has the possibility to speed up diagnosis colorectal cancer. [32]

Conclusion:

This study found evidence for increasing trends of physician visits for colorectal cancer-related clinical presentations and abnormal laboratory test results before diagnosis of CRC. From this study, it is evident that people who present with alarm symptoms such as rectal bleeding, change in bowel habit, and anemia will benefit from earlier referrals for cancer-specific investigations.

Limitations: This was a single center based study with limited numbers of patients and study subjects confined to only northern part of Bangladesh.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study

Ethical consideration:

The study was conducted after approval from the ethical review committee Rangpur Medical College, Rangpur, Bangladesh. The confidentiality and anonymity of the study participant was maintained.

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