Colorectal Cancers in Low- and Middle-Income Countries—Demographic Pattern and Clinical Profile of 970 Patients Treated at a Tertiary Care Cancer Center in India

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PURPOSE Globally, colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality. A relatively low burden of CRC has been reported from low- and middle-income countries (LMIC), and there is a paucity of publications related to CRC from LMIC.

PATIENTS AND METHODS A computerized comprehensive structured CRC clinical database was developed. All the patients with histopathologically proven CRC undergoing either curative and palliative multimodality management or surgical interventions between 2000 and 2019 were included in the study. A descriptive analysis of the demographic profile and clinical spectrum was performed.

RESULTS A total of 970 patients of CRC were treated between 2000 and 2019. Of these, 401 patients (41.3%) had colon cancer and 569 (58.7%) had rectal cancer. The male-to-female ratio was 1.79:1. The mean age at presentation was 47.7 years. A total of 337 (34.7%) patients qualified as young CRC ($\leq$ 40 years of age at diagnosis). The commonest symptom among patients with colon cancer was abdominal pain; 55.6% of patients had a right-sided primary tumor as compared with 42.2% with left-sided tumors. The commonest symptom among patients with rectal cancer was bleeding per rectum. The predominant location of the tumor was in the lower rectum (58%). Majority of patients with CRC presented with locally advanced stage II and III disease. The most common histologic subtype encountered for both colon and rectal cancers was adenocarcinoma (84.8% and 81.2%, respectively).

CONCLUSION This study has revealed certain important findings related to CRC in LMIC including a higher burden of young colorectal cancer, a relatively higher proportion of rectal cancers in comparison with colon cancer, a high percentage of patients with low-rectal cancer, and advanced stage at presentation.

INTRODUCTION

Globally, colorectal cancer (CRC) ranks third in terms of incidence and second in terms of mortality. In 2018, CRC was the most commonly diagnosed GI cancer across the globe with 1.8 million new cases and 881,000 deaths. Among men, it is the third commonest cancer and the fourth most common cause of cancer-related mortality, whereas among women, CRC stands second and third in terms of incidence and mortality, respectively.[1] The countries with a high Human Development Index have up to 3-fold higher incidence rates of CRC, and most of the published literature related to CRC originates from high-income countries (HIC).[2,3] A relatively low burden of CRC has been reported from low- and middle-income countries (LMIC), and there is a paucity of publications related to CRC from LMIC.[4,5] The age-standardized incidence rates of CRC reported in LMIC such as India are 7.2 and 5.1 per 100,000 population for men and women in comparison with global CRC incidence rates of 20.6 and 14.3 per 100,000 population, respectively.[6,7] Relatively higher mortality rates were reported for CRC in LMIC because of lack of screening, limited access to health care resources, and advanced stage at presentation.[8]

Recent epidemiologic studies have shown an increasing trend of CRC in LMIC including India because of demographic and economic transition, changing lifestyles, and dietary habits.[9] LMIC contribute to 60% of the global population with a significant proportion of the population belonging to young and middle-age groups. Currently available data of CRC in LMIC are mostly dependent on cancer registry data and few single-institutional publications consisting of a modest number of patients with CRC. As far as cancer registry data in LMIC is concerned, the population coverage is limited and registry data mostly cover basic demography and diagnosis only. There is a need to study large single- or multi-institutional cohorts of CRC from LMIC for a better understanding of the epidemiology, demographics, and clinical spectrum to formulate effective preventive and treatment strategies for

CONTEXT

Key Objective

Globally, colorectal cancer (CRC) stands among the top three cancers in terms of incidence and mortality. The exact incidence and mortality of CRC in low- and middle-income countries (LMIC) such as India are difficult to ascertain because of low coverage of population-based cancer registries and suboptimal data documentation. To the best of our knowledge, this is the largest single-center study from LMIC related to CRC patients' demography and clinical details.

Knowledge Generated

In LMIC, there is a higher burden of young-onset CRC, a relatively higher proportion of rectal cancers in comparison with colon cancer, a higher percentage of patients with low-rectal cancer, and advanced stage at presentation.

Relevance

This study highlights the importance of maintaining prospective disease-specific databases by clinical departments at cancer centers in LMIC to capture real-time, quality clinical data during the routine treatment process. This will help in planning future strategies for prevention, screening, and treatment of CRC in LMIC.

the future. Prospective comprehensive disease-specific clinical databases from high-volume tertiary care cancer centers in LMIC can provide valuable information regarding CRC in LMIC.

PATIENTS AND METHODS

The treating institution is a comprehensive tertiary care cancer center catering to a diverse and mixed population from different socioeconomic segments. Patients presenting with CRC are evaluated in a multidisciplinary GI cancer clinic by a team of surgical, medical, and radiation oncologists; radiologists; and pathologists. The patients were diagnosed and managed as per the standard multimodality treatment protocols prevailing at that time.

A computerized comprehensive structured CRC clinical database was developed in 1999 to capture various domains including demographic and clinical profile, investigations, histopathology, staging, treatment details, and outcome data in a prospective fashion. All the patients with histopathologically proven CRC undergoing either curative or palliative multimodality management and surgical interventions between 2000 and 2019 were included in the study. The staging was performed as per the American Joint Committee on Cancer Cancer Staging System 8th edition. The database was managed by residents of the surgical oncology division under the supervision of faculty. All the relevant details were prospectively entered in a predesigned Microsoft Excel database

at the time of presentation and during various stages of treatment and follow-up. Periodic updates and audits of the database were performed for compliance and quality control. A descriptive analysis of the demographic profile and clinical spectrum including clinical presentation, family history, baseline parameters, tumor location, histopathology subtypes, and the stage was performed for the purpose of the current study using STATA 14 software. Age cutoff of 40 years was taken to classify patients as young colorectal cancer (YCRC) patients. The patients with hemoglobin concentration of < 10 gm/dL were labeled as anemic.

RESULTS

A total of 970 patients of CRC were treated between 2000 and 2019. Of these, 401 patients (41.3%) had colon cancer and 569 (58.7%) had rectal cancer. The colon versus rectal cancer ratio was 0.7:1. There was a male preponderance with a male-to-female ratio of 1.79:1. The mean age at presentation was 47.7 years (51 years for colon cancer and 45 years for rectal cancer). A total of 337 (34.7%) patients qualified as young CRC (≤ 40 years of age at diagnosis). Among young patients with CRC, rectal cancer was more frequently encountered than colon cancer (41.3% v 25.4%). As far as family history is concerned, 14.7% of patients with colon cancer and 6.7% with rectal cancer had a history of CRC in the family. The demographic details of the entire CRC cohort are shown in Table 1.

TABLE 1. Demographic Details of Patients With CRC

Variables	Colon Cancer, n (%)	Rectal Cancer, n (%)	CRC, n (%)
No. of patients	401 (41.3)	569 (58.7)	970 (100)
Sex			
Male	262 (65.3)	360 (63.3)	622 (64.1)
Female	139 (34.7)	209 (36.7)	348 (35.9)
Mean age, in years (range)	51.0 (17-85)	45.4 (12-88)	47.7 (12-88)
Young patients with CRC (≤ 40 years)	102 (25.4)	235 (41.3)	337 (34.7)
Family history of CRC	59 (14.7)	38 (6.7)	97 (10)

Abbreviation: CRC, colorectal cancer.

The commonest symptoms among patients with colon cancer were abdominal pain (75.8%) and altered bowel habits (56.9%) followed by weight loss and melena. Approximately 40% of the patients with colon cancer presented with a palpable abdominal lump. More than half (55.6%) of the patients had a right-sided primary tumor as compared with 42.2% with left-sided tumors. Multifocal and synchronous lesions were observed in 2.5% of patients. About half of the patients were found to be anemic on initial presentation. Serum carcinoembryonic antigen (CEA) levels of 260 patients with colon cancer were available in the database and levels were found to be elevated in 145 (36.1%) patients at presentation (Table 2).

The most common symptom among patients with rectal cancer was bleeding per rectum (83%) followed by altered bowel habits and pain during defecation. The mean duration of symptoms was 6.5 months. The predominant location of the tumor was in the lower rectum (58%) followed by the middle and upper rectum. Serum CEA levels of 239 patients were available in the database, of which 157 (27.6%) patients had elevated levels at presentation (Table 3).

As far as the stage at presentation was concerned, majority presented with locally advanced stage II and III disease (Tables 2 and 3). The most common histologic subtype encountered for both colon and rectal cancers was adenocarcinoma (84.8% and 81.2%) followed by mucinous adenocarcinoma. The incidence of signet ring cell histology

TABLE 2. Clinical Profile of Patients With Colon Cancer

Variables	N = 401, n (%)
Clinical presentation	
Abdominal pain	304 (75.8)
Altered bowel habits	228 (56.9)
Weight loss	151 (37.7)
Rectal bleeding	138 (34.4)
Location of tumor	
Right colon (caecum + ascending colon + hepatic flexure + proximal transverse colon)	223 (55.6)
Left colon (descending colon + splenic flexure + sigmoid colon)	169 (42.2)
Laboratory parameters	
Multifocal or synchronous	9 (2.2)
No. of patients with anemia	203 (50.6)
Mean albumin (range) (g/dL)	3.71 (1-5.5)
Patients with elevated serum CEA levels	145 (36.1)
Stage	
I	21 (5.2)
II	246 (61.3)
III	86 (21.5)
IV	48 (12)

Abbreviation: CEA, carcinoembryonic antigen.

TABLE 3. Clinical Profile of Patients With Rectal Cancer

Variables	N = 569, n (%)
Clinical presentation	
Rectal bleeding	476 (83.7)
Altered bowel habits	282 (49.6)
Pain on defecation	155 (27.2)
Mean duration of symptoms, months	6.5
Location of tumor	
Upper rectum	59 (10.3)
Middle rectum	179 (31.5)
Lower rectum	331 (58.2)
Laboratory parameters	
No. of patients with anemia	222 (39)
Mean albumin (range) (g/dL)	4 (1-5.7)
Patients with elevated serum CEA levels	157 (27.6)
Stage	
I	86 (15.1)
II	349 (61.3)
III	117 (20.6)
IV	17 (3)

Abbreviation: CEA, carcinoembryonic antigen.

was higher among patients with rectal cancer (7.2%) in contrast to colonic tumors (0.8%) (Table 4).

DISCUSSION

CRC ranks among the top three common cancers globally and contributes to a substantial proportion of cancer-related mortality.[1] The global CRC burden is projected to increase by 60% by 2030 to 2.2 million new cases and 1.1 million CRC-related deaths. High-income countries report significantly higher incidence and mortality rates of CRC, and recent epidemiologic trends indicate an increasing CRC burden in LMIC, especially countries such as India going through a demographic and economic transition. The global disease burden and the related mortality are projected to rise in LMIC for both young and old populations.[10] The exact incidence and mortality of CRC in LMIC such as India are difficult to ascertain because of low coverage of population-based cancer registries, lack of uniformity in data acquisition and, limited availability of survival and follow-up data.[11] Few single-institutional studies with modest numbers from Indian centers published to date provide a snapshot of CRC burden in India.[4,5,7]

A significant number of patients with cancer are treated at tertiary care cancer centers in LMIC and structured prospective disease-specific clinical databases capturing critical parameters on a real-time basis by the treating clinicians is an excellent method of collecting quality clinical data. Generally, most of the clinical files are unstructured and there is no uniform or standard template for systematic data collection. The structured clinical

TABLE 4. Histopathology Details of Patients With Colorectal Cancer

Histopathology Type	Colon Cancer, n (%) (N = 401)	Rectal Cancer, n (%) (N = 569)
Adenocarcinoma	340 (84.8)	462 (81.2)
Mucin-secreting adenocarcinoma	33 (8.2)	57 (10)
Signet ring cell carcinoma	3 (0.8)	41 (7.2)
Other variants	25 (6.2)	9 (1.6)

databases can be used for patient care and for gathering quality data by the clinicians. The results of the current study prove the feasibility of such an approach.

As per recent reports, the incidence of CRC is increasing 2-fold every 5 years till 50 years of age followed by a 30% increase every 5 years after 55 years of age and beyond.[12] The median age at diagnosis of CRC varies from one geographical region to another. A Swedish study documented a median age of 71 years at diagnosis,[13] whereas an Indian study reported a mean age of 47.2 years.[7] In the current study, the mean age was 47.7 years at diagnosis indicating a relatively younger age of onset for patients with CRC in India. Global trends indicate that the incidence of YCRC is increasing by 2% per year. YCRC is generally characterized by advanced stage at presentation, aggressive biology, and predominantly left-sided colon or rectal location.[14,15] The global incidence of YCRC has been constantly on the rise, especially in high-income regions such as Europe and North America, whereas the rates are either stable or declining in the older population.[16] The results of the current study show that almost one third of the patients of the entire CRC cohort belonged to the age group of < 40 years. Subset analysis revealed a higher proportion of patients with rectal cancer (41.3%) as compared with patients with colon cancer (25.4%) among the YCRC group. Whether this rising incidence of YCRC will translate into higher mortality is still unanswered[17] and we need long-term studies with follow-up.

A higher CRC burden including YCRC in LMIC will have implications for planning treatment and screening strategies. The issues of concern in this population include psychosexual, fertility, quality-of-life (QOL), and long-term effects of therapy. The majority of LMIC currently lack comprehensive CRC screening programs, and when these programs are planned, younger age at presentation needs to be factored in regarding age of onset for CRC screening.[18] Majority of the patients in the current study presented with symptomatic disease in the form of rectal bleeding, altered bowel habits, abdominal pain, abdominal mass, and anemia.[19] The mean duration of symptoms in the patients with rectal cancer in the current study was 6.5 months, which indicates a delayed diagnosis and referral at the primary and secondary level of care. The majority of the population with rectal cancer symptoms can be misdiagnosed as having hemorrhoids in LMIC because

of lack of access to quality health care facilities. Anemia is one of the major types of clinical presentation, especially in patients with right-sided colon cancer. In a study by Väyrynen et al,[20] preoperative anemia was found in 43% of patients, whereas in the current study, 50.6% and 39% of the patients with colon and rectal cancer had anemia. Preoperative serum CEA is a useful tool for prognostication, monitoring response to systemic therapy in metastatic CRC, and detection of relapse during follow-up. A study by Baqar et al[21] found that preoperative serum CEA level of ≥ 5 ng/mL was an independent risk factor for recurrence after surgery and death because of CRC. In the current study, 31% of the patients with CRC (36.1% of the patients with colon cancer and 27.6% of the patients with rectal cancer) had elevated serum CEA levels at presentation, which correlates with advanced stage and guarded prognosis.

Recent literature has shown that the sidedness of colon cancer has prognostic and therapeutic implications. Right-sided colon cancers carry a relatively adverse prognosis in contrast to left-sided colon cancers in terms of overall survival.[22] A comparative study from HIC found that the incidence of left-sided colon cancer was higher (53%) as compared with right-sided colon cancer (47%).[23] The results of the current study revealed that 55.6% of the patients with colon cancer had right-sided tumors as compared with 42.2% with left-sided tumors. Therefore, the survival of the majority of the Indian patients with colon cancer is expected to be poorer as compared with their Western counterparts.

Rectal cancers have been traditionally classified as upper-, mid-, and lower-rectal cancers depending on the distance from the anal verge. The location of rectal cancer has therapeutic and prognostic implications. In general, upper-rectal cancers are treated on the lines of colon cancer and outcomes are comparable with left-sided colon cancers. However, cancers of the middle and lower third of the rectum usually require a multimodality treatment approach in the form of preoperative radiation or chemoradiation for locally advanced tumors.[24] Low-rectal cancers are challenging to treat because of the proximity to the sphincter and quality-of-life issues following sphincter ablative surgery. The majority of patients with rectal cancer in HIC present with cancers involving the upper third of the rectum,[25,26] but there is a lack of data from LMIC regarding the location of tumors and impact on treatment outcomes. In the current study, 58% of patients with rectal cancer presented with lower third tumors and only 10% of the patients presented with upper third rectal tumors. As far as histopathologic subtypes of CRC are concerned, adenocarcinoma is the predominant type reported from western countries and 1%-2% of patients have signet ring cell histology subtype, which is considered an aggressive biologic variant.[27] Histopathologic subtype analysis of the current study revealed a higher incidence (7.2%) of signet

ring cell subtype among patients with rectal cancer indicating adverse intrinsic biology.

As far as the stage at presentation is concerned, a significant proportion of patients with CRC present with early-stage (stage I and II) disease in HIC because of screening programs, higher levels of awareness, and access to health care, whereas LMIC, in general, report a significant burden of advanced stage at presentation. As expected, in the current study, 68% of patients with colon cancer and 71% with rectal cancer had T3/T4 tumors, and 12% of patients with colon cancer and 3% with rectal cancer presented with metastatic disease. Managing patients with CRC with advanced stage is challenging and resource-intensive. Hence, strategies for increasing awareness, early detection, and low-cost screening methods need to be evolved in LMIC to overcome these challenges.

In conclusion, to the best of our knowledge, this study is one of the largest single-center studies from LMIC related to CRC patients' demography and clinical details. This study has revealed certain important findings related to CRC in LMIC including a higher burden of YCRC, a relatively higher proportion of rectal cancers in comparison with colon cancer, a high percentage of patients with low-rectal cancer, and advanced stage at presentation. There are certain limitations of the current study including an element of referral bias and data being hospital-based rather than population-based. However, high-quality population-based cancer data can only be generated through population-based cancer registries with high population coverage and accurate documentation. Unfortunately, the majority of LMIC lack high-quality cancer registry programs and mostly gather basic demographic data. The coverage of the population by cancer registries ranges between 5% and 20% in most of LMIC. The current experience has proved the value of maintaining prospective disease-specific databases by clinical departments at comprehensive cancer centers to capture real-time quality clinical parameters during the routine course of treatment. It is feasible to implement prospective disease-specific clinical database programs in cancer centers of LMIC without major financial burden, and they can be easily implemented with existing infrastructure and human resources. More cancer centers in LMIC should implement structured prospective disease-specific database programs to generate quality cancer-related data from LMIC which will help in planning future strategies for prevention, screening, and treatment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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