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Clinicopathological patterns and survival outcomes of colorectal cancer among young adults in Malaysia: an institutional cohort study

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INTRODUCTION This study aimed to investigate the clinicopathological patterns and survival outcomes of patients with young-onset colorectal cancer (CRC) in Malaysia.

METHODS A total of 206 patients with young-onset CRC (age < 50 years at diagnosis) and 1,715 patients with late-onset CRC (age ≥ 50 years at diagnosis) diagnosed during 2002–2016 were included. The clinicopathological characteristics of patients with young-onset CRC were compared with those of patients with late-onset CRC during 2009–2013. Kaplan-Meier survival analysis was performed to determine the overall survival (OS) and disease-specific survival (DSS) in these patients.

RESULTS The overall proportion of young-onset CRC was 10.7%. The mean age for young-onset CRC was 39.5 ± 7.4 years, with a male-to-female ratio of 1.2:1. There were more Malay patients with young-onset CRC than late-onset CRC (44.0% vs. 19.9%, p = 0.004). Most CRCs were diagnosed at an advanced stage in both groups. However, young-onset CRC showed more aggressive tumour characteristics, such as poorer differentiation and mucinous subtype. Despite such differences, the OS and DSS in both groups were similar (five-year OS for young-onset CRC vs. late-onset CRC: 44.2% vs. 49.0%, p = 0.40; five-year DSS for young-onset CRC vs. late-onset CRC: 48.8% vs. 57.6%, p = 0.53; mean survival of young-onset CRC vs. late-onset CRC: 4.9 years vs. 5.4 years, p = 0.15). Advanced stage at diagnosis and the treatment modality used were independent prognostic factors.

CONCLUSION The unique ethnic and histological differences between patients with young- and late-onset CRC suggest that young-onset CRC may represent a distinct entity. However, despite such differences, both groups were equivalent.

Keywords: colorectal cancer, Malaysia, prognosis, survival rates, young adults

INTRODUCTION

Colorectal cancer (CRC) is currently the second most common cancer in Malaysia.[1] The age-standardised rate for CRC in Malaysia is about 14.6 per 100,000 population – much lower than that in developed countries in Europe and Northern America, where the age-standardised rate is in excess of 40 per 100,000 population.[1,2] However, the incidence of CRC is rising, possibly owing to rapid socioeconomic development leading to increasing adoption of Western diets and lifestyles.[2-4] The incidence of CRC among young adults in the United States is also increasing sharply.[5-8]

Many studies have sought to determine whether young-onset CRC has any unique clinicopathological features, with conflicting results.[9-13] Thus, it remains unclear whether young-onset CRC represents a distinct entity. Several studies have reported more aggressive tumour characteristics for young-onset CRC.[14,15] At present, there is a paucity of literature on young-onset CRC within the Asia-Pacific region. Institutional studies have reported a variable proportion of young-onset CRC, ranging from 6.7% in Taiwan to 39% in India.[16-19]

To the best of our knowledge, there are no studies on CRC among young adults in Malaysia. Malaysia epitomises a multi-ethnic Asian population, consisting predominantly of Malay, Chinese and Indian people. Identifying disparities in the ethnic distribution of young- and late-onset CRC would help to elucidate the interplay between genetics and environmental factors, and could guide clinical management. Keeping in mind the long-term consequences of CRC in young adults, we conducted a retrospective study at our hospital to determine the clinicopathological patterns and survival outcomes of young-onset CRC in Malaysia.

METHODS

This retrospective study was conducted at the University Malaya Medical Centre, a tertiary hospital in Malaysia. Consecutive patients diagnosed with CRC between 2002 and 2016 were identified and patients with young-onset CRC were included in the study. Young-onset CRC was defined as CRC affecting patients aged less than 50 years, as per previous studies that have considered young-onset patients to be those of pre-screening age, with an upper limit of 39–49 years.[20]

The medical records of patients with young-onset CRC were reviewed and the following data was retrieved for each patient: demographics (e.g. age, gender and ethnicity); tumour characteristics (e.g. TNM staging, tumour site, tumour cellular differentiation, grading, lymphovascular invasion,

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Table I. Demographic and pathological characteristics of patients with young-onset CRC (n = 206).

Factor	No. (%)	Factor	No. (%)
Age* (yr)	39.5 ± 7.4	**Perineural permeation (n = 113)**	
Gender		Present	13 (11.5)
Male	111 (53.9)	Absent	100 (88.5)
Female	95 (46.1)	**Clinical presentation (n = 178)**	
Ethnicity		Altered bowel habit	84 (47.2)
Malay	76 (36.9)	Per-rectal bleeding	60 (33.7)
Chinese	92 (44.7)	Abdominal pain	56 (31.5)
Indian	28 (13.6)	Loss of weight	51 (28.7)
Other	10 (4.9)	Intestinal obstruction	32 (18.0)
TNM staging (n = 194)		Anaemia	11 (6.2)
Stage I	16 (8.2)	Tenesmus	10 (5.6)
Stage II	40 (20.6)	Metastatic symptoms/local invasion	7 (3.9)
Stage III	76 (39.2)	**Interval between onset of symptoms and diagnosis of CRC* (mth)**	4.4 ± 2.6
Stage IV	62 (32.0)	**Predisposing factor (n = 142)**	
Tumour site (n = 201)		None	108 (76.1)
Left	80 (39.8)	Family history of malignancy	26 (18.3)
Right	39 (19.4)	Previous history of other malignancy	4 (2.8)
Rectum	82 (40.8)	Familial adenomatous polyposis	4 (2.8)
Tumour histology (n = 192)		**Comorbidity (n = 197)**	
Adenocarcinoma	175 (91.1)	None	173 (87.8)
Mucinous adenocarcinoma	11 (5.7)	Diabetes mellitus	17 (8.6)
Signet cell adenocarcinoma	6 (3.1)	Hypertension	7 (3.6)
Grade (n = 176)		**Treatment modality (n = 197)**	
Well-differentiated	11 (6.3)	Surgery only	47 (23.9)
Moderately differentiated	133 (75.6)	Surgery with chemotherapy	99 (50.3)
Poorly differentiated	32 (18.2)	Surgery with concurrent chemoradiotherapy	42 (21.3)
Lymphovascular permeation (n = 140)		Chemotherapy only	6 (3.0)
Present	75 (53.6)	Radiotherapy only	3 (1.5)
Absent	65 (46.4)		

Some data is missing owing to the retrospective nature of the study; subtotal shown separately in individual categories. *Data presented as mean ± standard deviation. CRC: colorectal cancer

perineural invasion and tumour-infiltrating lymph nodes) and clinical characteristics (e.g. symptoms, duration of symptoms, predisposing factors [e.g. inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer and family history of CRC]); and treatment modality.

Separately, a control group consisting of 579 patients aged 50 years and above who were diagnosed with CRC during the period 2009–2013 was compared with 75 patients with young-onset CRC diagnosed during the same period. Patient characteristics and five-year survival outcomes between both groups were compared. The primary and secondary outcomes were five-year overall survival (OS) and five-year disease-specific survival (DSS).

The study was approved by the institutional ethics committee (MREC no. 2017615295).

Statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY, USA). Quantitative variables were expressed as mean ± standard deviation, while categorical variables were expressed as number and percentage. Differences between categorical variables were examined using chi-square test, while differences between numerical variables were examined using *t*-test or analysis of variance, where appropriate. Kaplan-Meier survival analysis was used to calculate the OS and DSS rates. OS was calculated from the date of histological diagnosis of CRC to the date of death from any cause, and DSS involved the absence of death attributable to CRC. Potential prognostic factors were tested individually using the log-rank test and multivariate logistic regression analysis was conducted using the Cox proportional hazards model. The significance level was set at $p < 0.05$.

RESULTS

A total of 1,921 patients were diagnosed with CRC from 2002 to 2016, of which 206 patients had young-onset CRC. The overall frequency of young-onset CRC was 10.7%. The demographics and pathological characteristics of patients with young-onset CRC are shown in Table I. The mean age of patients with young-onset CRC was 39.5 ± 7.4 years, with a male-to-female ratio of 1.2:1. A majority of patients with young-onset CRC were diagnosed at an advanced stage (71.2%). Tumours were mostly left-sided (39.8%) or in the rectum (40.8%), and were predominantly

adenocarcinoma (91.1%). Most tumours were moderately differentiated (75.6%), but among patients with very young-onset CRC (age < 30 years), tumours were more likely to be poorly differentiated (p = 0.003).

The two most common symptoms were altered bowel habit (47.2%) and per-rectal bleeding (33.7%). Intestinal obstruction was associated with left-sided tumour (p < 0.001), abdominal pain and anaemia were associated with right-sided tumour (p < 0.05), and per-rectal bleeding and tenesmus were associated with rectal tumour (p < 0.05). Surgery with chemotherapy was the most common treatment modality (50.3%) and was mainly used for advanced CRC (p < 0.001).

A comparison of patient characteristics among those with young- and late-onset CRC is shown in Table II. There were no significant differences between the genders. However, the ethnic composition between young- and late-onset CRC was markedly different. Young-onset CRC consisted of more Malay patients when compared with late-onset CRC (44.0% vs. 19.9%, p = 0.004). In both groups, CRC was diagnosed at the late stage and was primarily located in the left colon or rectum. Young-onset CRC was more likely to be mucinous adenocarcinoma and poorly differentiated histological subtypes (p < 0.01). Not unexpectedly, young-onset CRC had better premorbid function than late-onset CRC (p < 0.005). A majority (81.7%) of patients with young-onset CRC received combination therapy when compared to those with late-onset CRC (55.1%). However, this difference did not reach statistical significance.

The OS and DSS rates are shown in Fig. 1. There was no statistically significant difference in the five-year OS (young-onset CRC vs. late-onset CRC: 44.2% vs. 49.0%, p = 0.40) and five-year DSS (young-onset CRC vs. late-onset CRC: 48.8% vs. 57.6%, p = 0.53; mean survival of young-onset CRC vs. late-onset CRC: 4.9 years vs. 5.4 years, p = 0.15) rates between the two groups. A sub-analysis comparing individual disease stages between age groups showed no statistically significant difference across all stages for OS and DSS.

Univariate logistic regression analysis (Table III) showed that advanced stage, ASA grade and treatment modality were significantly associated with reduced OS and DSS. Age, gender, ethnicity, tumour site and histological subtype were not significantly associated with OS and DSS. Multivariate logistic regression analysis identified advanced stage and the treatment modality used as independent prognostic factors.

Table II. Comparison of patients with young- and late-onset CRC from 2009 to 2013.

Factor	No. (%)		p-value
	Young-onset CRC (n = 75)	Late-onset CRC (n = 580)	
Gender			0.292
Male	33 (44.0)	315 (54.3)	
Female	42 (56.0)	265 (45.7)	
Ethnicity			0.004
Malay	33 (44.0)	115 (19.8)	
Chinese	30 (40.0)	392 (67.6)	
Indian	7 (9.3)	66 (11.4)	
Other	5 (6.7)	7 (1.2)	
TNM staging	[n = 71]	[n = 483]	0.82
Stage I	3 (4.2)	46 (9.5)	
Stage II	13 (18.3)	130 (26.9)	
Stage III	31 (43.7)	161 (33.3)	
Stage IV	24 (33.8)	146 (30.2)	
Tumour site	[n = 72]	[n = 523]	0.364
Left	31 (43.1)	250 (47.8)	
Right	16 (22.2)	123 (23.5)	
Rectum	25 (34.7)	150 (28.7)	
Tumour histology	[n = 68]	[n = 486]	0.002
Adenocarcinoma	61 (89.7)	466 (95.9)	
Mucinous adenocarcinoma	7 (10.3)	10 (2.1)	
Signet cell adenocarcinoma	–	2 (0.4)	
Other	–	8 (1.6)	
Grade	[n = 63]	[n = 406]	0.002
Well-differentiated	6 (9.5)	27 (6.7)	
Moderately differentiated	47 (74.6)	360 (88.7)	
Poorly differentiated	10 (15.9)	19 (4.7)	
ASA grading	[n = 71]	[n = 483]	0.82
I	3 (4.2)	46 (9.5)	
II	13 (18.3)	130 (26.9)	
III	31 (43.7)	161 (33.3)	
IV	24 (33.8)	146 (30.2)	
Treatment	[n = 71]	[n = 490]	0.74
Systemic	2 (2.8)	54 (11.0)	
Surgery	11 (15.5)	166 (33.9)	
Surgery + systemic	58 (81.7)	270 (55.1)	

Some data is missing owing to the retrospective nature of the study; subtotal shown separately in individual categories. ASA: American Society of Anesthesiologists physical status classification system; CRC: colorectal cancer

DISCUSSION

The incidence of CRC among young adults is on the rise and has become a major public health concern.[8,21] However, data on this subpopulation, particularly within the Southeast Asia region, is scarce and conflicting. As a result, the approach towards young-onset CRC in Malaysia is largely guided by experience. Our study aimed to better define the clinicopathological characteristics of young-onset CRC, utilising two potential strengths: a hospital-based study, with more complete clinical information, and the multi-racial composition of Malaysia, in view of similar environmental exposure across all ethnicities.

In our study, young-onset CRC represented about 11% of all patients with CRC. The proportions of young-onset CRC in developing countries were noted to be higher than those in developed countries.[8-11,16,18,19,22,23] This puzzling difference may be due to lifestyle and dietary patterns that individuals are exposed to during their childhood and younger adulthood years, which were different from those of preceding generations.[24]

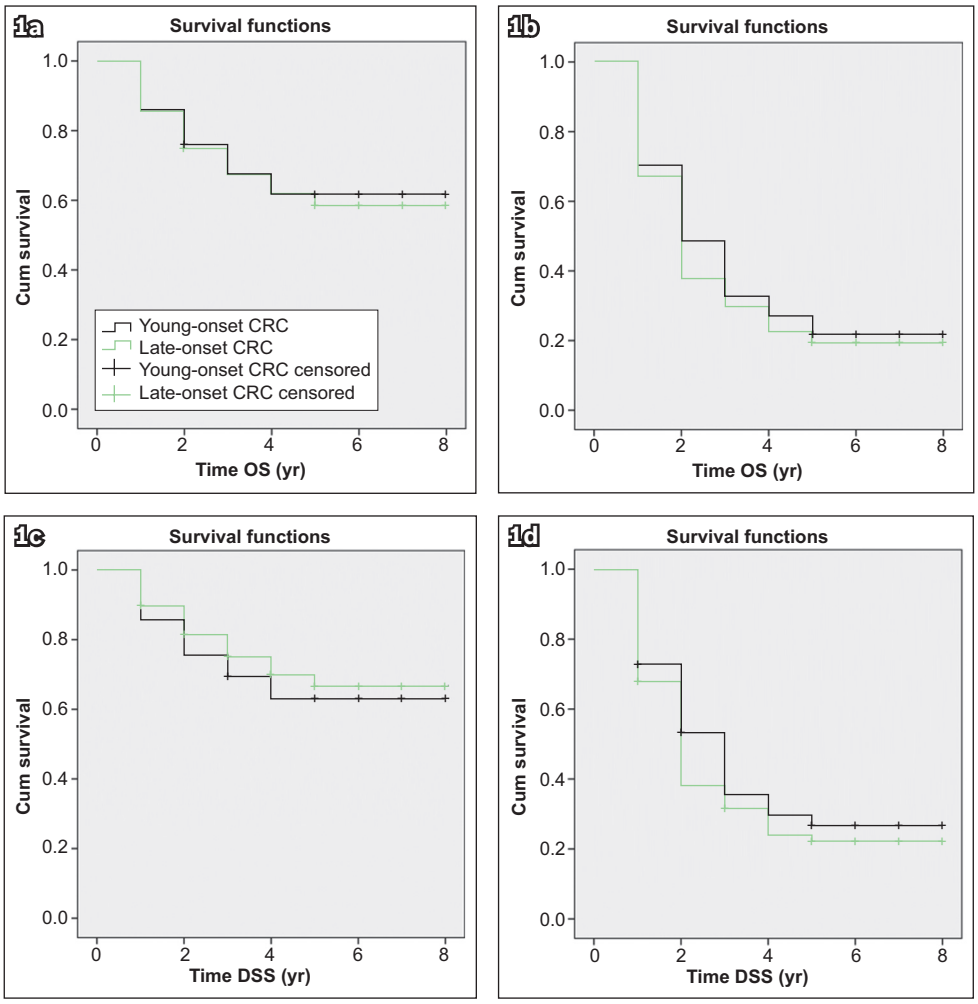

Fig. 1 Kaplan-Meier graphs show (a) OS in Stages I–III; (b) OS in Stage IV; (c) DSS in Stages I–III; and (d) DSS in Stage IV CRC. CRC: colorectal cancer; DSS: disease-specific survival; OS: overall survival

Table III. Univariate and multivariate logistic regression analyses of overall survival and disease-specific survival according to various factors.

Prognostic factors	Significance in univariate analysis (p-value)		Exp (B)	95% CI	Significance in multivariate analysis (p-value)
	Overall survival	Disease-specific survival			
Age	–	–	1.066	0.762–1.492	0.707
Gender	0.450	0.251	–	–	–
Ethnicity	0.222	0.214	–	–	–
ASA grading*	0.001	0.493	–	–	–
Disease stage*	< 0.001	0.008	–	–	–
Stage II	–	–	1.145	0.507–2.590	0.744
Stage III*	–	–	2.715	1.282–5.752	0.009
Stage IV*	–	–	7.126	3.466–14.648	< 0.0001
Tumour site	0.674	0.220	–	–	–
Treatment modality*	< 0.001	0.006	0.853	0.751–1.687	0.002
Histology	0.257	0.265	–	–	–

*p < 0.05 was statistically significant. ASA: American Society of Anesthesiologists physical status classification system; CI: confidence interval

In other words, in historically low-risk regions for CRC, where rates in the older population have remained low, CRC incidence has increased significantly in newer generations.[25] Even among developed countries, CRC among young adults is rising.[5,7,21,26] This can also be attributed to changes in lifestyle and environmental factors, with evidence of strong birth cohort effects on the incidence of CRC.[6,7] The rise in young-onset CRC parallels with the obesity epidemic, as obesity significantly increases the risk of developing CRC.[27,28] Moreover, complex epigenetic interactions between obesity, sedentary lifestyles and changes in

dietary patterns, such as increased intake of fat with decreased intake of fibre, could also contribute to the rise in young-onset CRC.[27,29-32] Recently, alterations in the gut microbiome have been implicated in the causation of CRC.[33,34] Separately, diet and antibiotic use are also known to change the population of gut microbiome.[35-38] It would not be unreasonable to link all three factors to the increasing incidence of CRC in the younger cohort. Population-based studies would be helpful in further characterising national epidemiological trends with regard to young-onset CRC.

According to our National Cancer Registry data, individuals with Chinese ethnicity had the highest CRC incidence (27.35), followed by those with Malay (18.95) and Indian (17.55) ethnicities.[39] Other institutional studies in Malaysia have reported similar findings.[40,41] These ethnic differences could be attributed to genetic factors, as similar patterns were observed in Singapore and Brunei.[18,42] The disparity in the incidence between Chinese and Indians living in Southeast Asia mirrors the rates in the countries of origin, despite both groups having migrated more than three generations ago.[43] When we compared the ethnic composition between young- and late-onset CRC, there were markedly fewer Chinese and more Malay individuals in the younger group. Although the exact causation has not been identified, an increasingly Westernised lifestyle adopted by Malay people over recent years could have led to an increase in young-onset CRC.[44,45] However, it is unlikely that lifestyle factors alone could result in such differences, thus supporting the theory that young-onset CRC may represent a distinct entity.[46,47] This warrants further research to better understand the molecular differences between young- and late-onset CRC.

The clinicopathological characteristics described in this study are in keeping with the current understanding of young-onset CRC, which usually presents with altered bowel habit and per-rectal bleeding.[9-11,14] The diagnostic challenge here is to distinguish benign causes of per-rectal bleeding from malignant causes. It is challenging for clinicians to thoroughly investigate per-rectal bleeding among young adults owing to cost constraints in public hospitals. However, when per-rectal bleeding is associated with other symptoms, such as altered bowel habit, investigation for more sinister causes is warranted. It is also a common misconception that young-onset CRC is usually hereditary. In our study, only 18.3% of patients with young-onset CRC had a family history of cancer, which was lower than the average incidence of 22.8% reported in a review.[14] This suggests that in a majority of cases, young-onset CRC is sporadic, and the lack of suspicion in these individuals may lead to a delay in diagnosis, resulting in late presentation and poorer outcomes.[14,48] While most studies report that young-onset CRC is more often diagnosed at advanced stages when compared with late-onset CRC, late presentations occurred in both groups in our study.[10] Currently, there are no nationwide, population-based screening programmes for CRC in Malaysia.[49,50] Hence, public awareness on CRC and participation rate for opportunistic screening in Malaysia remained low.[51] Strategies to increase awareness of the symptoms of CRC among the general population along with implementation of screening programmes in Malaysia are necessary for early detection of CRC, which could lead to improved survival.

Nevertheless, late presentations only partially account for the poorer prognosis in young patients. Many studies have reported that patients with young-onset CRC tend to have poorer histological features.[9,10,12,52] Our findings, which show that young-onset CRC shows a trend towards mucinous adenocarcinoma subtype and poor differentiation with lymphovascular permeation, are consistent with this. However, there is no consensus that more aggressive histological subtypes are indicative of poorer prognosis, and we have shown similar survival outcomes for patients with young- and late-onset CRC.[9-11,14,53] The possible explanations are that more patients with young-onset CRC received combination therapy, hence compensating for worse tumour biology, or that younger patients had fewer comorbidities and better baseline life expectancy independent of the cancer diagnosis.[53] Treatment modality was pivotal in influencing OS and DSS for both young and old cohorts, where combination therapy (both systemic and surgery) was superior to monotherapy for achieving better survival outcomes. Our study showed a trend for more patients with young-onset CRC receiving combination therapy than those with late-onset CRC. However, this finding did not reach statistical significance, which could be attributed to Type II error owing to the limited sample size.

In view of the advanced presentation of CRC in both groups, we fully support efforts to establish nationwide CRC screening, as it has been shown to reduce incidence, particularly in high-prevalence countries. However, the costs and benefits of screening in Malaysia are unclear at this stage owing to its low yield compared to Western populations and limited resources.[54-56] Hence, in a resource-limited setting, guidance on identification of susceptible individuals and a tailored approach to screening modalities, through consensus or guideline-guided screening policies, are essential. Although the Malaysian clinical practice guidelines provide some guidance, this will need to be reviewed as new data emerges.[57]

There are several limitations to this study. Results drawn from a single-centre study may not reflect the entire Malaysian population, and the retrieval of patients' data using the International Classification of Diseases coding system might have been subject to misclassification. Incomplete medical records also limited the completeness of the data. Moreover, we did not compare the differences in risk factors and socioeconomic determinants between patients with young- and late-onset CRC owing to incomplete data.

In conclusion, CRC in young adults is unique in terms of ethnic predilection and tumour biology, but age alone does not affect survival outcomes. Diagnosis at an early stage would improve survival, in general, among patients with CRC. However, a significant minority of patients in our study population had young-onset CRC. Hence, clinicians need to be suspicious when young adults present with altered bowel habit or per-rectal bleeding, even in the absence of predisposing factors.

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