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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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ABSTRACT

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

Methods: The study consisted of 206 patients with young-onset CRC (age < 50 years at diagnosis) and 1,921 patients with late-onset CRC (age ≥ 50 years at diagnosis) diagnosed during 2002–2016. 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%. Mean age for young-onset CRC was 39.5 ± 7.4 years, with male-to-female ratio of 1.2:1.0. There were more Malay patients with young-onset CRC than late-onset CRC (44.0% vs. 19.9%, p = 0.004). Most CRC were diagnosed at advanced stage in both groups. However, young-onset CRC showed more aggressive tumour characteristics, such as poorer differentiation and mucinous subtype. Despite such differences, 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 treatment modality 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, prognosis between both groups were equivalent.

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

INTRODUCTION

Colorectal cancer (CRC) currently ranks as 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 when compared to 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 due to rapid socioeconomic development leading to a more Western diet and lifestyle.[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 multiethnic Asian population, consisting predominantly of Malay, Chinese and Indian people. Identifying disparities in the ethnic distribution of young- and late-onset CRC would help 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 was a retrospective study 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 patients aged less than 50 years, as per previous studies that have considered young-onset patients to be those of prescreening 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, 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, diagnosed with CRC during the period 2009–2013 were 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.: 201761-5295).

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 percentages. 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. Statistical significance was considered 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%. Demographics and pathological characteristics of patients with young-onset CRC are shown in Table I. Mean age of patients with young-onset CRC was 39.5 ± 7.4 years, with male-to-female ratio of 1.2:1.0. A majority of patients with young-onset CRC were diagnosed at advanced stage (71.2%). Tumours were mostly left-sided (39.8%) or in the rectum (40.8%), and predominantly adenocarcinoma (91.1%). Most tumours were moderately differentiated (75.6%), but among the very young-onset CRC (age < 30 years), tumours were more likely to be poorly differentiated ($p = 0.003$).

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

Factor	No. (%)
Age (yr)*	39.5 ± 7.4
Gender	
Men	111 (53.9)
Women	95 (46.1)
Ethnicity	
Malay	76 (36.9)
Chinese	92 (44.7)
Indian	28 (13.5)
Other	10 (4.9)
TNM staging (n = 194)	
Stage I	16 (8.2)
Stage II	40 (20.6)
Stage III	76 (39.2)
Stage IV	62 (32.0)
Tumour site (n = 201)	
Left	80 (39.8)
Right	39 (19.4)
Rectum	82 (40.8)

Tumour histology (n = 192)	
Adenocarcinoma	175 (91.2)
Mucinous adenocarcinoma	11 (5.7)
Signet cell adenocarcinoma	6 (3.1)
Grade (n = 176)	
Well differentiated	11 (6.3)
Moderately differentiated	133 (75.6)
Poorly differentiated	32 (18.1)
Lymphovascular permeation (n = 140)	
Present	75 (53.6)
Absent	65 (46.4)
Perineural permeation (n = 113)	
Present	13 (11.5)
Absent	100 (88.5)
Clinical presentation (n = 178)	
Altered bowel habit	84 (47.2)
Per-rectal bleeding	60 (33.7)
Abdominal pain	56 (31.5)
Loss of weight	51 (28.7)
Intestinal obstruction	32 (18.0)
Anaemia	11 (6.2)
Tenesmus	10 (5.6)
Metastatic symptoms/local invasion	7 (3.9)
Interval between onset of symptoms and diagnosis of CRC (mth)*	4.4 ± 2.6
Predisposing factor (n = 142)	
None	108 (76.1)
Family history of malignancy	26 (18.3)
Previous history of other malignancy	4 (2.8)
Familial adenomatous polyposis	4 (2.8)
Comorbidity (n = 197)	
None	173 (87.8)
Diabetes mellitus	17 (8.6)
Hypertension	7 (3.6)
Treatment modality (n = 197)	
Surgery only	47 (23.9)
Surgery with chemotherapy	99 (50.3)
Surgery with concurrent chemoradiotherapy	42 (21.3)
Chemotherapy only	6 (3.0)
Radiotherapy only	3 (1.5)

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

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 among 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 in comparison with late-onset CRC ($p < 0.005$). A majority (81.7%) of young-onset CRC received combination therapy when compared to late-onset CRC (55.1%). However, this difference did not reach statistical significance.

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

Factor	**No. (%)**		**p-value**
	Young-onset CRC (n = 75)	**Late-onset CRC (n = 580)**	
Gender			0.292
Men	33 (44.0)	315 (54.3)	
Women	42 (56.0)	265 (45.7)	
Ethnicity			0.004
Malay	33 (44.0)	115 (19.9)	
Chinese	30 (40.0)	392 (67.6)	
Indian	7 (9.3)	66 (11.3)	
Other	5 (6.7)	7 (1.2)	
TNM staging	**n = 71**	**n = 483**	0.82
Stage I	3 (4.2)	46 (9.6)	
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 (6.6)	
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 (9.6)	
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 missing due to retrospective nature of study; subtotal shown separately in individual categories. ASA: American Society of Anesthesiologists physical status classification system; CRC: colorectal cancer

OS and DSS rates are shown in Fig. 1. There was no statistically significant difference in 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. Sub-analysis comparing individual disease stages between age groups showed no statistical significance 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 treatment modality as independent prognostic factors.

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*

DISCUSSION

The incidence of CRC among young adults is on the rise and has become a major public health problem.[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 experiential-guided. 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 multiracial 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. Proportions of young-onset CRC in developing countries were noted to be higher when compared to 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 preceding generations.[24] 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] Likewise, 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 CRC causation.[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, Chinese ethnicity had the highest CRC incidence (27.35), followed by Malay (18.95), and Indian (17.55).[39] Other institutional studies in Malaysia had similar findings.[40,41] These ethnic differences could be due to genetic factors, as similar patterns were observed in Singapore and Brunei.[18,42] The incidence disparity 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 people in the younger group. Although the exact causation has not been identified, an increasingly Westernised lifestyle among 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 future 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. Young-onset CRC 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 remains a dilemma for clinicians to investigate per-rectal bleeding among young adults thoroughly due 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 a majority of 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] 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 to detect early colorectal cancer, which has 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) were superior, when compared to monotherapy, for achieving better survival outcomes. Our study showed a trend for more young-onset CRC receiving combination therapy when compared with late-onset CRC. Although this finding did not achieve statistical significance, this could be attributed to type II error, due to the limited sample size.

In view of 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 cost-benefit of screening in Malaysia is unclear, at this stage, due to low yield compared to Western populations and limited resources.[54-56] Hence, in a resource-limited setting, guidance on identification of susceptible individuals, as well as 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 ICD (International Classification of Diseases) coding system might have been subject to misclassification. Incomplete medical records also limited the completeness of the data. We

also did not compare differences in risk factors and socioeconomic determinants between patients with young- and late-onset CRCs due to incomplete data.

In conclusion, CRC in young adults is unique in terms of ethnic predilection and tumour biology, but age alone does not impact on survival outcomes. Earlier stage at diagnosis 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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FIGURE

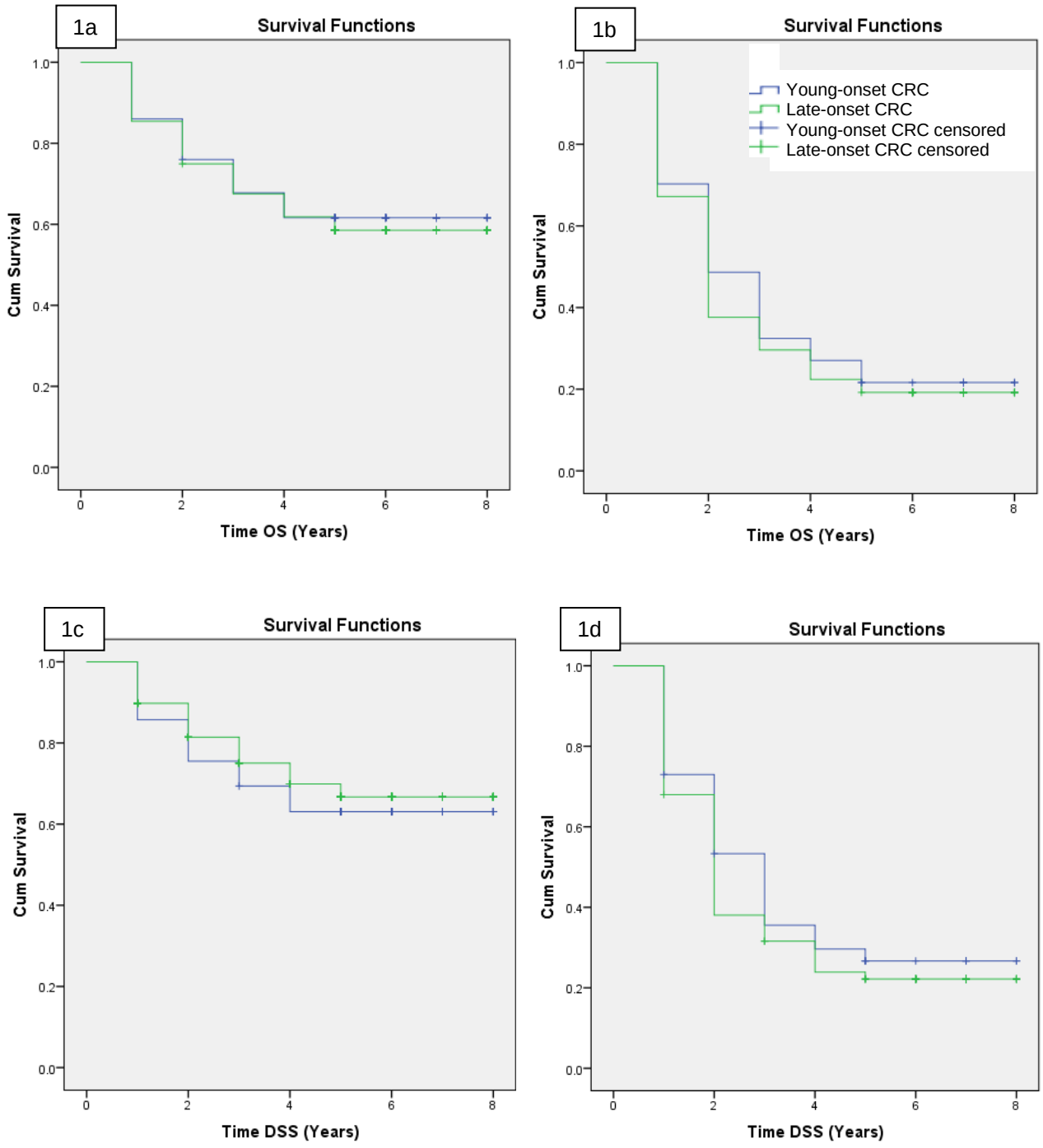

Fig. 1 Kaplan-Meier graphs show (a) OS in Stages I–III, (b) OS in Stage IV, (c) DSS in Stages I–III and (d) DSS in Stage IV. CRC: colorectal cancer; DSS: disease-specific survival; OS: overall survival