Clinicopathologic Characteristics Influencing Overall Survival of Patients With Early- Versus Average-Onset Colorectal Cancer at a Tertiary Care Center in Indonesia

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ABSTRACT

PURPOSE There has been a global increase in early-onset colorectal cancer (EOCRC), yet there has been very limited exploration of its impact in Indonesia. This study aimed to determine the clinicopathologic characteristics and the overall survival (OS) of EOCRC compared with those of average-onset colorectal cancer (AOCRC).

METHODS Medical records were retrospectively reviewed from all patients presenting with colorectal cancer (CRC) at Dr Sardjito General Hospital (Yogyakarta, Indonesia) between 2016 and 2019. Sociodemographic, clinicopathologic, and treatment variables were extracted. *t* Tests were used to compare characteristics of EOCRC and AOCRC patient groups. The Cox proportional hazards regression model was used to analyze age and other potential prognostic factors.

RESULTS The total population (N = 1,276) comprised EOCRC (n = 149; 11.7%) and AOCRC (n = 1,127; 88.3%) patients. EOCRC patients were more likely to have a higher education level, be single, have out-of-pocket insurance, be underweight, and have signet ring histology (all *P* values <.05), compared with AOCRC patients. EOCRC and AOCRC groups had a comparable estimated 5-year OS of 34.2% and 36.9%, respectively. In multivariable analyses, performance status (Eastern Cooperative Oncology Group), hemoglobin level, cancer stage, and treatment intention were independent prognostic factors for OS (all *P* values <.05).

CONCLUSION To our knowledge, this first major study of EOCRC in Indonesia highlights its role in the overall burden of CRC and its connection with social determinants of health. Patients with EOCRC are more commonly underweight and generally have a higher proportion of signet ring histology than AOCRC, yet OS in both groups is similar. Future research is required to identify risk factors to inform the content and focus of public health education activities, alongside delineating the biology and causes of early and average onset of the disease.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Colorectal cancer (CRC) is the third most diagnosed malignancy and is responsible for the second-highest number of deaths worldwide.[1] In Indonesia, CRC is the fourth most commonly diagnosed cancer, with an age-standardized annual incidence rate of 12.4/100,000 individuals and mortality rate of 6.7/100,000 individuals.[2] CRC is generally observed as a disease of the elderly, with more than 90% of cases affecting individuals 50 years or older.[3-6] However, an increasing incidence of early-onset CRC (EOCRC), commonly defined as the onset of disease in patients younger than 40 years, is occurring worldwide.[7-9] Differences in clinicopathologic features and prognosis have been reported in EOCRC when compared with average-onset CRC (AOCRC). Compared with AOCRC, EOCRC exhibits a higher prevalence of mucin-producing tumors[5,10-14] and signet ring cell tumors (which tend to have a poorer prognosis)[4,5,13,15-17] and, overall, more poorly differentiated histologic grade.[5,10,12,13,17-20] EOCRCs are also reported to present at a more advanced stage than AOCRC[5,6,19,21-24] although internationally outcome data are mixed, with studies reporting similar or worse survival[8,9,16,18,19,25,26] and improved survival.[4,7,13,22,27]

A previous multinational cohort study has identified that the incidence of CRC is increasing in the East Asia regions.[28] Only

CONTEXT

Key Objective

What are the clinicopathologic features and the overall survival for patients with early-onset colorectal cancer (EOCRC) when compared with average-onset colorectal cancer (AOCRC) in Indonesia, an Asian lower-middle–income country that has a remarkable rapid development transition?

Knowledge Generated

We identified significant differences in sociodemographic, clinicopathologic, and treatment factors, with patients with EOCRC more likely to have higher education attainment, be single, have out-of-pocket insurance, be underweight, and have signet ring histology, compared with patients with AOCRC. While age was not a prognostic factor, Eastern Cooperative Oncology Group status, pretreatment hemoglobin level, disease stage, and treatment intention had impact on the patients' survival.

Relevance

The significant proportion of EOCRC contributes to the total cancer burden in the country and urges an increased early diagnosis attempt and further study to identify the underlying risk factors and possible molecular characteristics.

a few comprehensive data sets have described the incidence, clinicopathologic characteristics, and prognosis of CRC in the Southeast Asia regions[29-38] and specifically in the Indonesian population.[17,39] The clinicopathologic features and outcomes of EOCRC in Indonesia are even less clear.[39] In Yogyakarta Province (current population: 4,073,907),[40] there is the highest frequency of cancer in Indonesia,[41] with CRC being the third most common malignancy in both sexes.[42] There is very limited evidence related to the characteristics and survival of patients with CRC from the province,[43,44] with no exploration of EOCRC. Evidence is required to guide a service response to increasing cases of cancer and understand how best to support people with EOCRC. Therefore, this study aims to compare sociodemographic and clinicopathologic characteristics of EOCRCs compared with AOCRCs and analyze the survival and prognostic features of patients with CRC treated at a tertiary hospital in Yogyakarta. In doing so, it seeks to contextualize the broader trends of CRC epidemiology, characteristics, and survival within the Southeast Asia region, which can be valuable for neighboring countries facing similar challenges in terms of health care infrastructure and epidemiologic factors.

METHODS

Study Setting and Population

This study was retrospectively performed. We collected data on 1,276 consecutive patients of CRC attending Dr Sardjito General Hospital Yogyakarta, Indonesia, and who were diagnosed between January 2016 and December 2019. Patient data, tumor pathology, and type of first-line treatment were obtained from the hospital-based cancer registry. Further data were obtained from patient medical records, including insurance type, education, marital status, type of hospital where the surgery was performed, clinical data (performance status and pretreatment laboratory parameters), details of treatment intention, and data on the patient's last visit. Data extraction from patients' medical records was performed by trained research assistants between August 2020 and January 2021.

Key Variables

Data were collected on sociodemographic information, clinical characteristics, and treatment (see Appendix Table A1). Sociodemographic variables included age (dichotomized as early-onset for patients younger than <40 years and average-onset for patients 40 years and older; see Appendix 1 for the cutoff rationale),[8,9,45] sex (male *v* female), educational attainment (<junior high school or ≥junior high school), marital status (single, married, and widowed), insurance type (subsidized national health insurance, private or nonsubsidized national health insurance, and out-of-pocket payment), and type of center that performed surgery (tertiary hospital and nontertiary hospital). Clinical data included performance status on the basis of Eastern Cooperative Oncology Group (ECOG) scale (0-1, 2, and 3-4), BMI using WHO BMI cutoff for Asian populations (<18.5; underweight, 18.5-22.9; normal, 23-24.9; overweight, and ≥25; obese), pretreatment hemoglobin level (<10 and ≥10 g/dL), and pretreatment serum albumin level (<3.5 and ≥3.5 g/dL). Tumor location was categorized into two: right-sided colon (caecum, ascending colon, hepatic flexure, and transverse colon) and left-sided colon (splenic flexure, descending colon, sigmoid colon, rectosigmoid colon, and rectum). Tumor histopathologic parameters were determined according to the WHO classification and included histologic grade (1, 2, and 3-4), tumor morphology (adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma), T-stage (1, 2, 3, 4, and X if it was not determined or

unknown), N status (0, 1, 2, and X if it was not determined or unknown), and M status (0, 1, and X if it was not determined or unknown). Clinical disease stage was determined according to the seventh edition of the TNM classification of the American Joint Committee of Cancer for diagnoses made in 2016-2017,[46] and those from 2018 to 2019 were aligned with the eighth edition.[47] Treatment setting was categorized as adjuvant (including surgery only, surgery plus adjuvant and neoadjuvant chemotherapy, with or without radiation) and palliative (including surgery on unresectable tumors and chemotherapy with or without radiation, palliative surgery only, and palliative chemotherapy only).

Overall survival (OS) was calculated as the difference in months between the date of diagnosis and the date of death from any cause. If the patient had not been seen in the outpatient clinic for more than 6 months, we contacted the patient or family by telephone or mail correspondence. In 11 individuals who had died where the family only provided the year of death, we set June 30 of the corresponding year as the date of death. Where a patient or their family was not contactable, survival status was determined by the last visit to the hospital with the patient censored at this point.

Ethics Approval

The joint ethics committee from the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr Sardjito Hospital, Yogyakarta, approved the study (reference number KE/FK/0549/EC/2020). All patients provided written informed consent on admission to use their prospective database and files for research purposes. All collected data were anonymized.

Statistical Analysis

Distributions of variables were compared using *t* tests (binary variables) and chi-squared tests (variables with more than two categories). Kaplan-Meier curves were constructed to graphically compare the OS, and comparisons between groups of interest were performed using log-rank tests. Multivariable analyses of OS were performed using Cox proportional hazards regression and parametric lognormal regression. Multiple imputation was performed using chained equations. All statistical analyses were performed using Stata version 17 (StataCorp LLC, College Station, TX).

RESULTS

CRC Characteristics

In total, data from 1,276 patients ranging from age 9 to 93 years were collected and analyzed. Up to April 2022, the median follow-up time was 19 (0-74) months. The demographic and clinicopathologic characteristics of the patients are summarized in Table 1.

TABLE 1. Baseline Characteristics of Patients With Colorectal Cancer (N = 1,276)

Variable	Frequency (No.)	Percentage
Age, years		
<40	149	11.7
≥40	1,127	88.3
Sex		
Male	688	53.9
Female	588	46.1
Education		
<Junior high school	401	31.4
≥Junior high school	692	54.3
Unknown	183	14.3
Marital		
Single	52	4.1
Married	1,109	86.9
Widower/widow	92	7.2
Unknown	23	1.8
Insurance		
National health insurance (subsidised)	309	24.2
Private insurance or national health insurance (nonsubsidised)	848	66.5
Out-of-pocket	86	6.7
Unknown	33	2.6
Type of diagnostic center		
Tertiary hospital	625	49
Nontertiary hospital	400	31.3
Unknown	251	19.7
ECOG scale		
0-1	716	56.1
2	203	15.9
3-4	116	9.1
Unknown	241	18.9
BMI, kg/m^2		
<18.5	363	28.4
18.5-22.9	529	41.5
23-24.9	132	10.3
≥25	116	9.1
Unknown	136	10.6
Hemoglobin level, g/dL		
<10	253	19.8
≥10	856	67.1
Unknown	167	13.1
Serum albumin, g/dL		
<3.5	398	31.2
≥3.5	307	23.6
Unknown	577	45.2
Tumor location		
Right	268	21
Left	947	74.2
Unknown	61	4.8

(continued on following page)

TABLE 1. Baseline Characteristics of Patients With Colorectal Cancer (N = 1,276) (continued)

Variable	Frequency (No.)	Percentage
Histologic grading		
1	511	40
2	342	26.8
3-4	124	9.7
Unknown	299	23.4
Pathologic morphology		
Adenocarcinoma	1,114	87.3
Mucinous carcinoma	53	4.2
Signet ring cell carcinoma	25	2
Other	84	6.6
T status		
1	21	1.6
2	111	8.7
3	644	50.5
4	231	18.1
X	269	21.1
N status		
0	411	32.2
1	287	22.5
2	95	7.4
X	483	37.9
Metastatic status (M status)		
0 (nonmetastatic)	351	27.5
1 (metastatic)	440	34.5
X	485	38
TNM stage		
I	29	2.3
II	176	13.8
III	127	10
IV	441	34.5
Unknown	503	39.4
Treatment intention		
Adjuvant	151	11.8
Palliative	380	29.8
Not determined	162	12.7
Unknown	583	45.7

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Overall, the median age was 56 years and the CRC cohort was fairly evenly split between males and females (53.9% males *v* 46.1% females). A complete record was not available for every patient, but analysis of the available data showed that most cancers (87.3%) were adenocarcinoma and were located on the left side of the colon (74.2%). Histologic grade (not available in 23.4% of the cohort) showed mostly low/intermediate (grade 1/2, 66.8%), but tumors were often quite advanced at presentation (T3/4 in 68.6% of patients). Lymph node involvement was seen in 29.9% of patients, whereas distant metastasis (M1), where recorded, was seen in 34.5% of patients. Clinically, patients had good ECOG performance (716; 56.1%), normal BMI (529; 41.5%), baseline hemoglobin level ≥10 g/dL (856; 67.1%), and low serum albumin (<3.5 g/dL in 31.2%). Data were not known on the initial treatment strategy in 45.7%, and, where data were available, 29.8% had planned palliative treatment. In terms of sociodemographic data, a level of educational attainment of at least junior high school was seen in 54.3% and 86.9% of patients were married. Sixty-six percent was private or nonsubsidized national health insurance, and first diagnosis was made in a tertiary hospital in 49.0%.

Comparison of EOCRC with AOCRC

Comparative data of EOCRC and AOCRC are shown in Table 2 (binary variables, *t* tests) and Table 3 (categorical variables, chi-squared tests). Missingness was exhibited in all variables: the number of valid observations for each variable is given alongside the relevant test statistic and associated *P* value.

For binary variables, differences between EOCRC and AOCRC groups were exhibited at conventional levels of significance only in education (dichotomized by lower than or at least a level of junior high school, $P < .001$) and diagnostic center type (tertiary *v* nontertiary, $P = .067$).

For chi-squared tests, differences between EOCRC and AOCRC groups were exhibited at conventional levels of significance in several variables: marital status ($P < .001$), insurance type ($P = .008$), BMI ($P = .023$), and pathology morphology ($P < .001$).

Table 4 presents hazard ratio (HR) estimates from Cox regressions for both complete patients (n = 164) and multiply imputed data (n = 865) in our full cohort. Table 5 presents time ratio (TR) estimates from lognormal regression for complete patients and multiply imputed data. Because of small numbers in categories other than adenocarcinoma in the complete patient analyses, cancer type is omitted because of collinearity; this limitation does not exist in the multiply imputed data set.

Semiparametric multivariable analyses showed that ECOG status, hemoglobin level, and treatment intention were independent prognostic factors for OS (*P* values <.05). In the fully parametric models, ECOG index, hemoglobin level, stage, and treatment intention were independent prognostic factors for OS (*P* values <.05). For both multivariable analyses, ECOG 3-4 was associated with an increased hazard (HR, 1.803 [95% CI, 1.205 to 2.699]; $P = .005$) and a worse OS (TR, 0.506 [95% CI, 0.318 to 0.808]; $P = .005$) compared with ECOG 0-1. The hemoglobin level of ≥10 g/dL was associated with a reduced hazard (HR, 0.664 [95% CI, 0.497 to 0.887]; $P = .006$) and better survival (TR, 1.618 [95% CI, 1.151 to 2.273]; $P = .006$). Multiparametric models showed that stage 4 disease was associated with a worse survival than stage 1 (TR, 0.412

TABLE 2. Comparison of EOCRC With AOCRC Using *t* Tests

		AOCRC		EOCRC				
Variable	No.	No. where = 1	Proportion	No. where category = 1	Proportion	Diff	*t*	*P*
Sex (male = 0)	1,276	85	0.535	603	0.570	0.035	−0.815	.415
Education (0 = under patient junior high school)	1,093	119	0.602	573	0.844	0.242	−5.642	<.001
Diagnostic center (nontertiary = 0)	1,025	68	0.620	557	0.535	−0.085	1.836	.067
Hemoglobin (0 = under 10)	1,108	99	0.771	756	0.773	0.002	−0.051	.959
Serum albumin (0 = under 3.5)	699	33	0.434	268	0.407	−0.026	0.448	.654
Tumor location (0 = left)	1,215	36	0.216	232	0.252	0.035	−0.957	.339

Abbreviations: AOCRC, average-onset colorectal cancer; EOCRC, early-onset colorectal cancer.

[95% CI, 0.171 to 0.994]; $P = .049$). Furthermore, compared with the adjuvant treatment scheme, palliative intention was associated with an increased risk of mortality (HR, 1.976 [95% CI, 1.298 to 3.008]; $P = .002$) and a reduced OS (TR, 0.533 [95% CI, 0.326 to 0.871]; $P = .014$; Tables 4 and 5).

Overall Survival and Prognostic Features in the Whole Cohort

In the whole cohort, the observed median OS was 30 months with an estimated 5-year OS of 36.7%. Figure 1 presents, for our multiple imputation model, both a Kaplan-Meier survival curve and the modeled survival according to our lognormal model, with the generally good agreement suggesting that this parametric choice is appropriate.

EOCRC and AOCRC groups had a comparable median survival (30 months; Fig 2A), with an estimated 5-year OS of 34.2% and 36.9%, respectively. In multiple imputation analysis, EOCRC does not show a clear impact on survival compared with AOCRC, with a 7.6% reduction in hazard and a 15.3% increase in survival time.

In the multiple imputation analysis, a slight improvement in survival was estimated for men, reflected by a 6.4% reduction in hazard and an 8.8% increase in survival time (Fig 2B). However, the lack of statistical significance in these findings suggests that our analysis was not adequately powered to detect differences in survival of the magnitude suggested by our point estimates.

There was an observed worsening in survival with higher ECOG scores, particularly for ECOG 3-4 in imputed data, indicated by an 80.3% increase in hazard and a 49.4% reduction in survival time (Fig 2C). This trend was consistent in both models, but only ECOG 3-4 in imputed data demonstrates a statistically significant worsening in survival at the 1% level. The log-rank test suggests an overall significant difference at the 1% level.

Worsened survival was suggested for individuals with a BMI < 18.5, compared with the 18.5-22.9 group, with a 26.9% increase in the hazard and a 21.5% reduction in survival time (Fig 2D). This trend is consistent for BMI < 18.5 across both models but only reaches statistical significance at the 10% level.

Hemoglobin levels ≥10 are significantly (1% level) associated with improved survival in analyses on imputed data, as shown by a 33.6% reduction in hazard and a 61.8% increase in survival time (Fig 2E). This trend was also suggested in complete patient analysis, although at weaker levels of significance.

In the multiple imputation analysis, higher serum albumin levels (≥3.5) were linked with a 16.4% reduction in hazard and a 36.6% increase in survival time, suggesting improved survival, though not reaching statistical significance at conventional levels (Fig 2F). The complete patient analysis, showing significant improvement in survival, also supports this relationship.

Analysis of multiply imputed data for tumor location shows an 11.7% increase in hazard and a 0.9% increase in survival time for right-sided tumors, indicating no statistically significant impact (Fig 2G). Similarly, a tumor histologic grading of 2 (compared with 1) in the multiple imputation analysis does not show a statistically significant relationship in terms of changes in either hazard or survival time.

Advancing cancer stages are associated with generally worsened survival although this is only statistically significant ($P < .10$) for stage IV, with more than a doubling of the hazard in the Cox model and more than halving of survival in the lognormal model in our multiple imputation analysis (Fig 2H). The inability to detect statistical significance beyond the 10% level for these large point estimates suggests an underpowered analysis.

In the multiple imputation analysis, signet ring cell carcinoma shows an 83.5% increase in hazard and a 46.4% reduction in survival time, suggesting worse outcomes (Fig 2I). This is significant at the 10% level in the Cox model.

Undetermined and palliative treatment pathways were also associated with large and statistically significant increases in hazard (75.3% and 97.6%, respectively) and reductions in survival time (43% and 46.7%, respectively) compared with

TABLE 3. Comparison of EOCRC With AOCRC Using Chi Squared Tests

	AOCRC		EOCRC					
Variable	No.	Percentage	No.	Percentage	Total	No.	χ^2	*P*
Marital status								
Married	992	89.86	117	78.52	1,109			
Single	23	2.08	29	19.46	52			
Widower/widow	89	8.06	3	2.01	92	1,253	103.997	<.001
Insurance								
National health insurance (subsidised)	277	25.27	32	21.77	309			
Private or national health insurance (nonsubsidised)	752	68.61	96	65.31	848			
Out-of-pocket	67	6.11	19	12.93	86	1,243	9.542	.008
ECOG								
ECOG 0-1	631	68.66	85	73.28	716			
ECOG 2	182	19.80	21	18.10	203			
ECOG 3-4	106	11.53	10	8.62	116	1,035	1.249	.536
BMI								
18.5-22.9	472	46.73	57	43.85	529			
23-24.9	123	12.18	9	6.92	132			
<18.5	308	30.50	55	42.31	363			
≥25	107	10.59	9	6.92	116	1,140	9.526	.023
Pathology morphology								
Adenocarcinoma	996	94.77	118	83.69	1,114			
Mucinous carcinoma	45	4.28	8	5.67	53			
Signet ring cell carcinoma	10	0.95	15	10.64	25	1,192	57.796	<.001
T								
1	18	2	3	2.75	21			
2	99	11.02	12	11.01	111			
3	577	64.25	67	61.47	644			
4	204	22.72	27	24.77	231	1,007	0.557	.906
N								
0	367	52.58	44	46.32	411			
1	248	35.53	39	41.05	287			
2	83	11.89	12	12.63	95	793	1.376	.503
M								
0	317	45.03	34	39.08	351			
1	387	54.97	53	60.92	440	791	1.11	.292
TNM stage								
I	27	3.94	2	2.27	29			
II	155	22.63	21	23.86	176			
III	115	16.79	12	13.64	127			
IV	388	56.64	53	60.23	441	773	1.278	.734
Treatment intention								
Adjuvant	137	22.24	14	18.18	151			
Not determined	144	23.38	18	23.38	162			
Palliative	335	54.38	45	58.44	380	693	0.723	.697

Abbreviations: AOCRC, average-onset colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EOCRC, early-onset colorectal cancer.

the adjuvant baseline category (Fig 2J). This trend is consistent and significant across both models and data sets, underscoring the impact of the treatment type on survival.

DISCUSSION

To our knowledge, this study presents the largest study population of Indonesian patients with CRC with EOCRC

TABLE 4. Multivariate Analyses for Survival in Colorectal Cancer, Cox Regression

	Complete Patient				Multiple Imputation			
Variable	Hazard Ratio	*P*	Lower CI	Upper CI	Hazard Ratio	*P*	Lower CI	Upper CI
Age, years								
≥40								
<40	1.181	.678	0.539	2.588	0.924	.638	0.665	1.284
Sex								
Female (omitted)								
Male	0.802	.425	0.467	1.379	0.936	.531	0.760	1.152
ECOG								
ECOG 0-1 (omitted)								
ECOG 2	1.434	.284	0.742	2.773	1.214	.213	0.893	1.650
ECOG 3-4	1.673	.313	0.615	4.548	1.803 [c]	.005	1.205	2.699
BMI								
18.5-22.9 (omitted)								
23-24.9	1.491	.311	0.688	3.230	0.950	.779	0.663	1.361
<18.5	1.825 [a]	.053	0.992	3.358	1.269 [a]	.066	0.984	1.636
≥25	0.587	.330	0.201	1.715	1	.998	0.703	1.423
Hemoglobin								
<10 (omitted)								
≥10	0.559 [a]	.066	0.301	1.039	0.664 [c]	.006	0.497	0.887
Serum albumin								
<3.5 (omitted)								
≥3.5	0.515 [b]	.015	0.302	0.879	0.831	.197	0.625	1.104
Tumor location								
Left (omitted)								
Right	1.937 [b]	.043	1.021	3.673	1.117	.425	0.851	1.465
Pathology morphology								
Adenocarcinoma (omitted)								
Mucinous carcinoma	Collinear				0.828	.474	0.494	1.388
Signet ring cell carcinoma	Not present				1.835 [a]	.082	0.926	3.639
Histologic grading								
1 (omitted)								
2	0.781	.353	0.463	1.316	1.103	.442	0.857	1.419
TNM stage								
I (omitted)								
II	1.481	.714	0.181	12.114	1.348	.469	0.599	3.032
III	0.761	.804	0.088	6.572	1.381	.457	0.587	3.244
IV	2.021	.507	0.253	16.116	2.188 [a]	.057	0.978	4.895
Treatment intention								
Adjuvant (omitted)								
Not determined	2.858 [a]	.079	0.886	9.219	1.753 [b]	.023	1.086	2.829
Palliative	3.171 [c]	.007	1.379	7.292	1.976 [c]	.002	1.298	3.008
Observations	164				865			

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]*P* < .10.
[b]*P* < .05.
[c]*P* < .01.

reported. Patients with EOCRC had a distinct socio-demographic character and poor histology. Comparable median survival between EOCRC and AOCRC groups was observed. Factors significantly associated with OS included performance status, hemoglobin level, cancer stage, and treatment intention. We recognize that hereditary syndromes

TABLE 5. Multivariate Analyses for Survival in Colorectal Cancer, Lognormal Parametric Regression

	Complete Patient				Multiple Imputation			
Variable	Time Ratio	*P*	Lower CI	Upper CI	Time Ratio	*P*	Lower CI	Upper CI
Age, years								
≥40								
<40	1.040	.910	0.531	2.037	1.153	.453	0.795	1.673
Sex								
Female (omitted)								
Male	1.162	.496	0.754	1.791	1.088	.474	0.864	1.369
ECOG								
ECOG 0-1 (omitted)								
ECOG 2	0.658	.127	0.384	1.126	0.825	.270	0.585	1.163
ECOG 3-4	0.472 [a]	.078	0.204	1.089	0.506 [c]	.005	0.318	0.808
BMI								
18.5-22.9 (omitted)								
23-24.9	0.922	.796	0.500	1.703	1.157	.468	0.780	1.717
<18.5	0.662 [a]	.091	0.410	1.067	0.785 [a]	.094	0.592	1.042
≥25	1.472	.307	0.701	3.091	0.967	.868	0.654	1.430
Hemoglobin								
<10 (omitted)								
≥10	1.661 [a]	.071	0.957	2.881	1.618 [c]	.006	1.151	2.273
Serum albumin								
<3.5 (omitted)								
≥3.5	1.709 [b]	.017	1.101	2.653	1.366 [a]	.059	0.988	1.889
Tumor location								
Left (omitted)								
Right	0.667	.144	0.388	1.148	1.004	.978	0.742	1.360
Pathology morphology								
Adenocarcinoma (omitted)								
Mucinous carcinoma	Collinear				1.419	.229	0.803	2.509
Signet ring cell carcinoma	Not present				0.536	.148	0.230	1.249
Histologic grading								
1 (omitted)								
2	1.088	.686	0.722	1.639	0.853	.265	0.643	1.131
TNM stage								
I (omitted)								
II	0.537	.455	0.105	2.746	0.713	.454	0.291	1.748
III	1.051	.953	0.200	5.538	0.708	.465	0.276	1.812
IV	0.366	.220	0.073	1.822	0.412 [b]	.049	0.171	0.994
Treatment intention								
Adjuvant (omitted)								
Not determined	0.396 [b]	.044	0.161	0.975	0.570 [b]	.043	0.331	0.981
Palliative	0.391 [c]	.004	0.206	0.742	0.533 [b]	.014	0.326	0.871
Observations	164				865			

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]*P* < .10.
[b]*P* < .05.
[c]*P* < .01.

are responsible for the pathogenicity of around 15%-20% of patients with EOCRC (eg, Lynch Syndrome, polyposis syndrome, including familial adenomatous polyposis, *MUTYH*-associated polyposis, and juvenile polyposis).[16,48] We further screened Lynch Syndrome in selected patients of this group using a panel test that included microsatellite

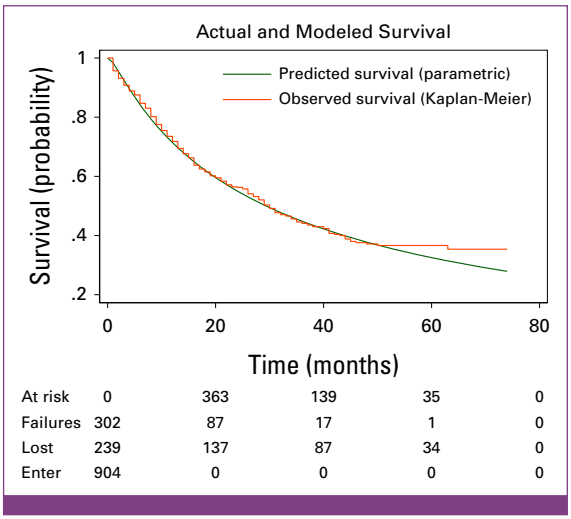

FIG 1. Multiple imputation model including both a Kaplan-Meier survival curve and the modeled survival according to our lognormal model.

instability, *BRAF* V600E mutation, and *MLH-1* promoter methylation. Our study revealed a potentially higher frequency (13.85%) of Lynch Syndrome among the local patients with CRC,[49] which may partially contribute to our reported higher prevalence of EOCRC as compared with that in Western settings.[7,9,13,16]

This study provides insights into the age of CRC onset in the study setting. Compared with international literature using the age cutoff of <40 years, the prevalence of young onset in our setting is higher than that reported in the United States, Canada, France, Italy, and Australia (1.4%-6.0%),[7,9,16,50] the Netherlands (3.0%),[13] and Japan (3.5%).[8] Our data are similar to those reported in Tunisia (14.2%)[51] and Turkey (18.0%),[25] but lower than those in India (31.3%).[18] In other South East Asia regions, the rates are highly variable comparing, for example, Singapore (5.0%)[38] and Cambodia (29.8%).[34] In terms of differences between EOCRC and AOCRC, this study highlights the important role of social determinants of health in South East Asia. Characteristics related to EOCRC in the study sample included higher education attainment and a lower likelihood of being married. Although higher education is typically an indicator of better awareness of cancer symptoms,[39] there is no difference in stage at diagnosis between patients with EOCRC and AOCRC. Higher education attainment might relate to the increased rate of EOCRC patients diagnosed in our tertiary hospital and the use of out-of-pocket money. These indicate that younger patients come from higher economic status and wish to avoid delays in the referral processes of government facilities.[40] The lower rate of marriage may reflect the younger age of the population. Our data also showed that younger patients were more likely to be underweight than the older. This is consistent with other studies,[41] and low patient weight may reflect a difference in disease biology. Our findings differ from reports in neighboring countries where, for example, female sex in Malaysia[30] and Thailand[35] and ethnicity in Malaysia[29-31] were predominant aspects for EOCRC.

The estimated 5-year OS of 36.7% in our cohort of EOCRC is lower than reports using a similar cutoff age, such as Singapore (56.6%),[38] China (48.9%),[52] and Scotland (57.0%).[53] A recent study from Ethiopia showed a similar 5-year OS (29.0%) for patients 29 years and younger, but a higher rate (45.0%) for those age 30-39 years.[54] There is a common perception that EOCRC would have a worse prognosis than AOCRC.[15,45,55-57] We did not find any difference between the two groups, and this issue remains unclear as several publications have reported similar survival[20,31,35,38] or improved outcomes in EOCRC.[8,16,18,19,25-27] Our findings differ from existing studies in Indonesia that showed increased CRC survival in older compared with younger groups.[39] Various prognostic factors aligned with study findings have been observed in surrounding countries including advanced stage and treatment.[31,33,37] Other reports showed that signet ring histology and diagnostic period affected the survival.[33,35,37] Yet, there remain limited comparative data from the Southeast Asia regions and neighboring countries.

While data are emerging related to incidence trends, clinicopathologic characteristics, and mortality risk associated with EOCRC and AOCRC, factors related to social determinants of health are rarely considered in the South East Asia regions.[29-31,35] Our intersectional approach contextualizes findings within this setting, highlighting various disparities unique within the region. For example, in Southeast Asia, including Indonesia, key factors influencing delivery and access to cancer care include (1) archipelagos and mountainous geographic landscapes; (2) concentration of health care resources and cancer treatment centers in large urban areas; (3) preferences for traditional healers, driven by deep-rooted cultural and religious practices;[58] and (4) rapid development and urbanisation,[59] along with water and air pollutants that are known geographical risk factors for CRC in Indonesia.[60] For Indonesia, these factors are further exacerbated by nonuniform and comprehensive CRC screening and low CRC screening participation,[61] limited coverage of screening methods by health insurance, and low awareness regarding CRC symptoms, risk factors, and screening modalities.[62] This is problematic given that our results warrant a need for heightened clinical suspicion for CRC in young individuals to ensure early diagnosis before presentation at advanced-stage disease. Screening might be considered from as early as 40 years, as recommended after modeling research[63] and accounting for genetic predisposition related to diet and lifestyle.[64] Advocating for screening services development needs to be accompanied by future research to determine lifestyle and other external risk factors for CRC locally to guide the content and focus of public health education activities.

The strength of this study includes the involvement of a comprehensive data set of consecutive patients attending a large, tertiary hospital, addressing a gap in the evidence base

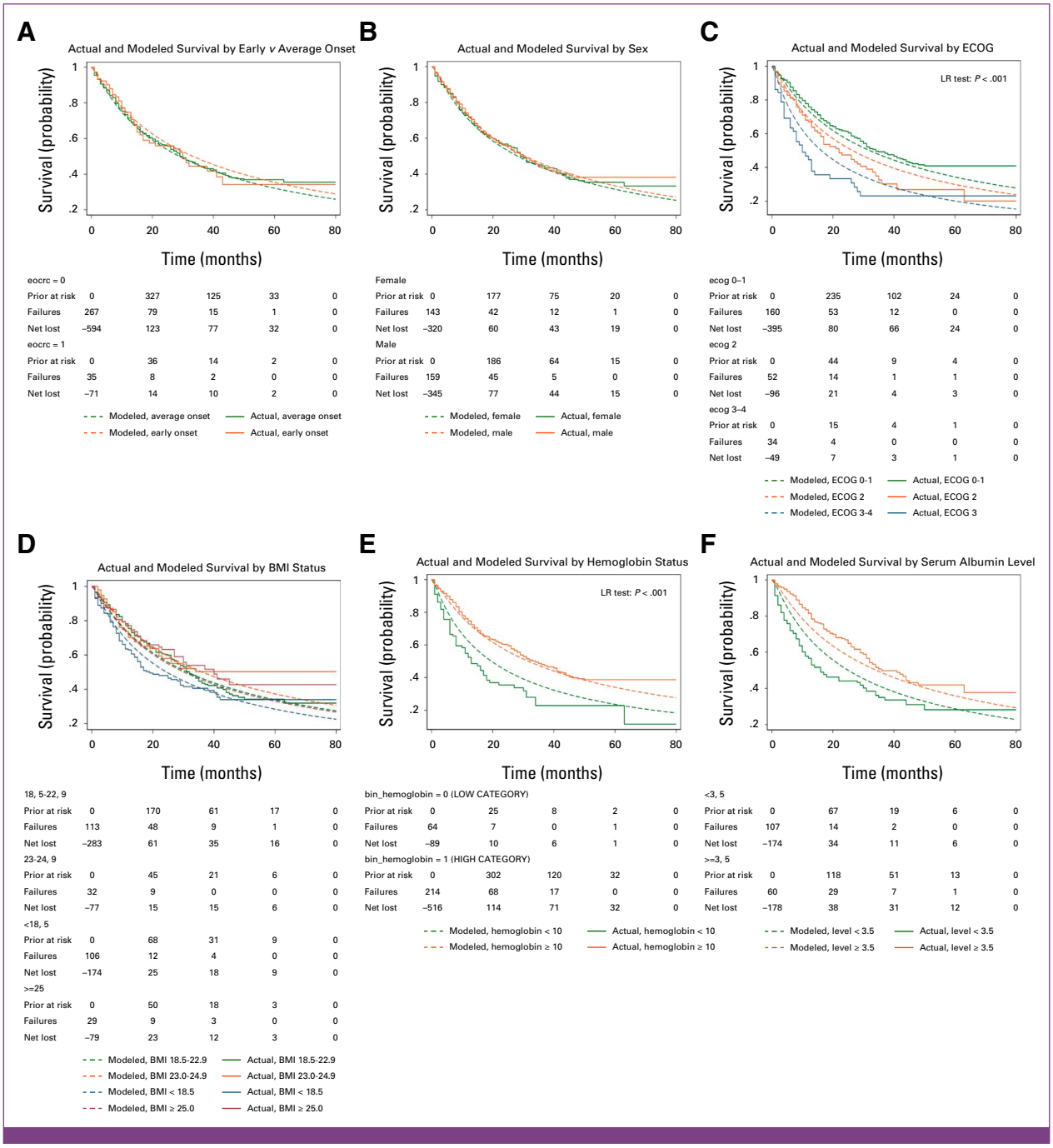

FIG 2. Multiple imputation analysis by (A) early-onset versus average-onset CRC, (B) male versus female, (C) ECOG, (D) BMI, (E) hemoglobin status, (F) serum albumin, (G) tumor location left versus right, (H) TNM stage, (I) pathology morphology, and (J) treatment intention. CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EORC, early-onset colorectal cancer; LR, log-rank. (continued on following page)

for cancer care in Indonesia and other low- and middle-income settings. The use of data that were obtained from the cancer registry and medical records has introduced study limitations. Given the retrospective nature of the analysis and the fact that the cancers were not reported in accordance with a template containing a minimum data set, complete data were not available for every patient. In some fields, the data were missing for a significant proportion of patients potentially confounding the interpretation.

In conclusion, our findings contribute to gaps in the literature about characteristics and survival of patients with CRC in low- and middle-income countries, and specifically for Indonesia and South East Asian regions. We highlight that

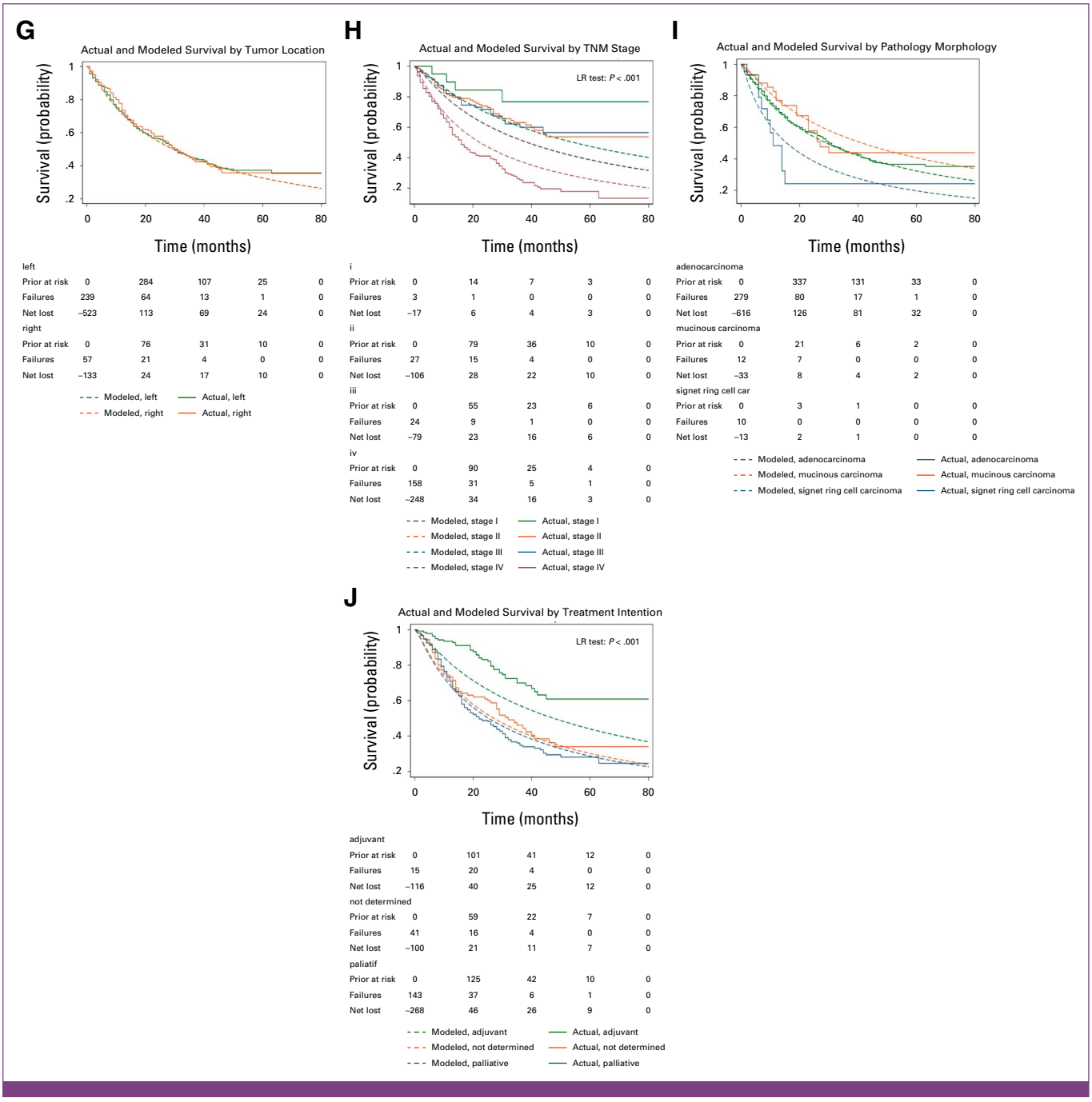

FIG 2. (Continued).

EOCRC forms a significant proportion of the total CRC disease burden in Indonesia. Despite the presence of adverse histologic features and an association with being underweight, the survival in patients with EOCRC is comparable with that in the AOCRC group. Increasing early diagnosis by improving cancer awareness (for both individuals in the community and health professionals) and improvement of the referral system may lead to more favorable outcomes in this under-researched and economically important group of patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX 1. RATIONALE FOR THE USE OF 40 YEARS AS THE CUTOFF FOR EARLY-ONSET COLORECTAL CANCER

The rationale for using age 40 years as the cutoff in our analysis was driven by three factors: (1) the data set used in the analysis, (2) comprehensive epidemiologic data, and (3) the wider comparative literature. Below, we outline details surrounding each of these factors.

1. Our team analyzed colorectal cancer (CRC) data from the regional population–based cancer registry using joinpoint analyses (see Appendix Figs A1 and A2). We found that the highest percentage change of CRC incidence was observed in patients between age 35 and 39 years. In addition, when comparing cutoffs <40 years and <50 years, the joinpoint analyses demonstrated that the annual percentage change is higher in the age group of <40 years than that of age <50 years.
2. We looked at a comprehensive epidemiologic data set for comparison (the SEER registry [1973–2005]). Analysis of the data set identified an increasing annual percentage change of 2.2% of rectosigmoid cancer diagnosed in patients younger than 40 years.[66] The greatest percentage change in rectal cancer incidence was identified in patients between age 35 and 39 years. Indeed, distinct differences and unique clinicopathologic and genetic alterations in early-onset CRC in patients age 40 years have been supported in other studies.[67]
3. We acknowledge that the wider global literature does commonly use 50 years as a cutoff, and this coincides with the starting age of most screening programs in the general risk population. However, having derived insights from our data set, we also compared the use of age 40 years as a cutoff when reported across the wider literature. An earlier literature review[68] highlighted the widespread use of the 40 years cutoff, and multiple subsequent studies have also used this cutoff.[8,9,13,16,18,37,38,69]

TABLE A1. Summary of Variables Developed for the Analysis

Variable Category	Variable	Level
Sociodemographic information	Age	Dichotomised as early-onset for cases younger than 40 years or average-onset for cases 40 years and older. These were aligned with previous classifications[8,9,45] and based on our findings in recent publication.[65] Patients with EOCRC in our local hospital represented 11.7%, whereas AOCRC cases constituted 88.3% of data observed. If age <50 years had been used as a criterion for EOCRC, as used by previous reports,[4-6,24] the EOCRC group would constitute 27.6% of the whole cohort
	Sex	Male or female
	Educational attainment	<Junior high school or ≥junior high school
	Marital status	Single, married, or widowed
	Insurance type	Subsidised national health insurance, private or nonsubsidised national health insurance, and out-of-pocket payment
Clinical data	Performance status	Using the ECOG scale (0-1, 2, or 3-4)
	BMI	Using the WHO BMI cutoff for Asian populations (<18.5 as underweight, 18.5-22.9 as normal, 23-24.9 as overweight, and ≥25 as obese)
	Pretreatment hemoglobin level	<10 or ≥10 g/dL
	Pretreatment serum albumin level	<3.5 or ≥3.5 g/dL
	Tumor location was categorized into two	Right-sided colon (caecum, ascending colon, hepatic flexure, and transverse colon) or left-sided colon (splenic flexure, descending colon, sigmoid colon, rectosigmoid colon, and rectum)
	Tumor histopathologic parameters	Determined according to the WHO classification and included histologic grade (1, 2, or 3-4)
	Tumor morphology (adenocarcinoma, mucinous carcinoma, and signet ring cell carcinoma)	T-stage (1, 2, 3, 4, or X if it was not determined or unknown)
		N status (0, 1, 2, or X if it was not determined or unknown)
		M status (0, 1, or X if it was not determined or unknown)
	Clinical disease stage	Determined according to the seventh edition of the TNM classification of the AJCC for diagnoses made in 2016-2017[46] and those from 2018 to 2019 were aligned with the eighth edition[47]
Treatment	Type of center that performed surgery	Tertiary hospital or nontertiary hospital
	Treatment setting	Adjuvant (including surgery only, surgery plus adjuvant and neoadjuvant chemotherapy, with or without radiation) or palliative (including surgery on unresectable tumors and chemotherapy with or without radiation, palliative surgery only, and palliative chemotherapy only)

Abbreviations: AJCC, American Joint Committee of Cancer; AOCRC, average-onset colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EOCRC, early-onset colorectal cancer.

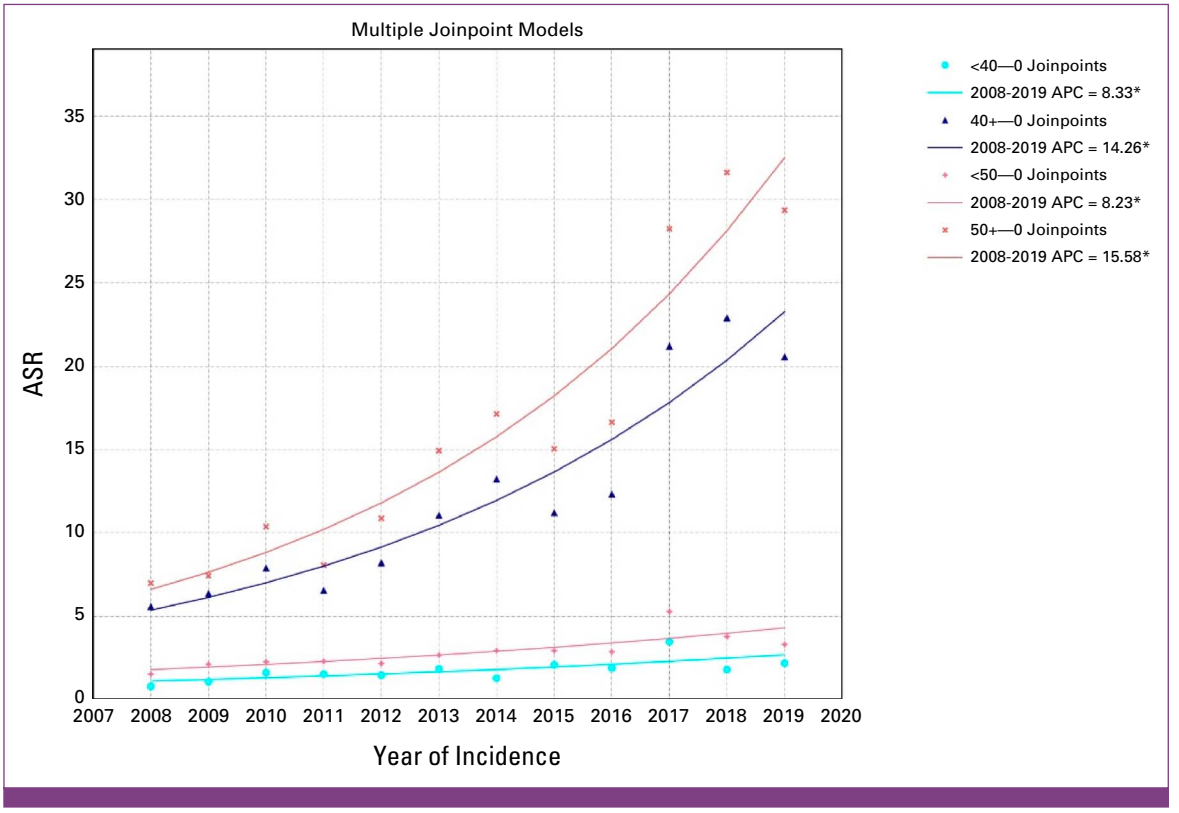

FIG A1. Joinpoint analysis showing APCs of CRC in Yogyakarta province diagnosed from 2008 to 2019 with group separation of <40 years (light blue line) versus ≥40 years (purple line) and <50 years (pink line) versus ≥50 years (red line). Courtesy of the Yogyakarta population–based cancer registry. The joinpoint analysis showed that APC of early-onset CRC, either using 40- or 50-year cutoff, significantly increased. However, the APC of the 40-year group (light blue line; APC, 8.33) is higher than that of the 50-year group (pink line; APC, 8.23), making it reasonable to use 40 years as the border for early-onset CRC. *Indicates significance. APC, annual percentage change; ASR, age-specific standardized rate; CRC, colorectal cancer.

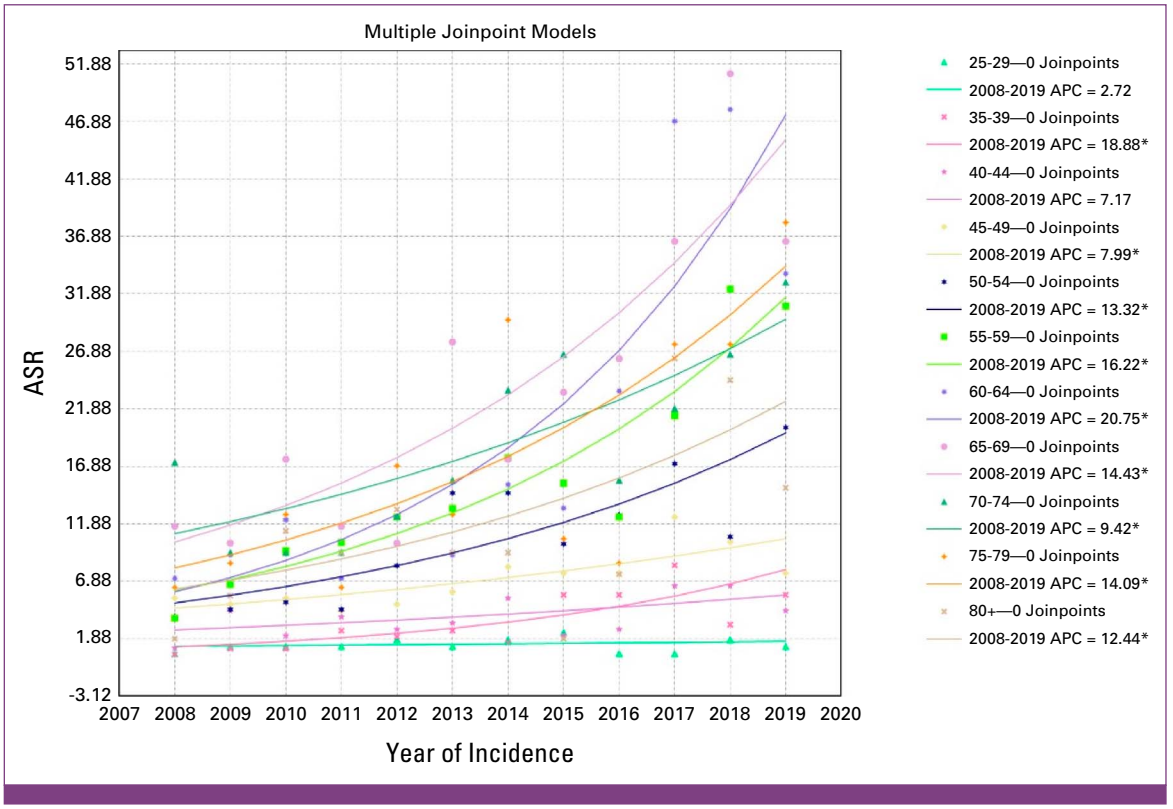

FIG A2. Joinpoint analysis showed APCs of CRC in Yogyakarta province diagnosed from 2008 to 2019 across different age groups with 5 years age increments. Courtesy of the Yogyakarta population–based cancer registry. The joinpoint analyses demonstrated that among early-onset cases, the highest percentage change in CRC incidence was identified in patients between age 35 and 39 years (APC, 18.88). This analysis also underlines a strong rationale for the use of <40 years as a cutoff value for early-onset CRC. *Indicates significance. APC, annual percentage change; ASR, age-specific standardized rate; CRC, colorectal cancer.