WJCC

# World Journal of **Clinical** Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2021 November 16; 9(32): 9804-9814

DOI: 10.12998/wjcc.v9.i32.9804

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

# **Retrospective Study** Colorectal cancer patients in a tertiary hospital in Indonesia: Prevalence of the younger population and associated factors

Dadang Makmun, Marcellus Simadibrata, Murdani Abdullah, Ari F Syam, Hamzah Shatri, Achmad Fauzi, Kaka Renaldi, Hasan Maulahela, Amanda P Utari, Rabbinu R Pribadi, Virly N Muzellina, Saskia A Nursyirwan

**ORCID number:** Dadang Makmun 0000-0001-9558-6638; Marcellus Simadibrata 0000-0003-1131-5836; Murdani Abdullah 0000-0002-8801-0283; Ari F Syam 0000-0003-0041-3553; Hamzah Shatri 0000-0003-1393-9669; Achmad Fauzi 0000-0003-1736-2238; Kaka Renaldi 0000-0002-1092-9644: Hasan Maulahela 0000-0002-0396-4433; Amanda P Utari 0000-0002-7775-894X; Rabbinu R Pribadi 0000-0001-8450-4887; Virly N Muzellina 0000-0003-4949-7145; Saskia A Nursyirwan 0000-0003-0166-7651.

Author contributions: Makmun D designed and performed the research, conducted the analysis, and wrote the manuscript; Simadibrata M supervised the report and provided clinical advice; Shatri H contributed to the statistical analysis; and Makmun D, Simadibrata M, Abdullah M, Syam AF, Fauzi A, Renaldi K, Maulahela H, Utari AP, Pribadi RR, Muzellina VN and Nursyirwan SA performed the colonoscopy examination and provided clinical advice.

#### Institutional review board

statement: This study was reviewed and approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (Protocol No. 19-06-0751).

Dadang Makmun, Marcellus Simadibrata, Murdani Abdullah, Ari F Syam, Achmad Fauzi, Kaka Renaldi, Hasan Maulahela, Amanda P Utari, Rabbinu R Pribadi, Virly N Muzellina, Saskia A Nursyirwan, Division of Gastroenterology, Pancreatobiliary & Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo National General Hospital, Jakarta 10430, Indonesia

Hamzah Shatri, Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo National General Hospital, Jakarta 10430, Indonesia

Corresponding author: Dadang Makmun, FACG, MD, PhD, Attending Doctor, Professor, Division of Gastroenterology, Pancreatobiliary & Digestive Endoscopy, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo National General Hospital, Jl. Pangeran Diponegoro No. 71, Jakarta 10430, Indonesia. hdmakmun@yahoo.com

# Abstract

# BACKGROUND

An increasing trend in colorectal cancer (CRC) occurring at younger ages has been observed worldwide, even though incidence is declining in the general population. Most currently available guidelines still recommend CRC screening for older populations, despite an alarming rise in early-onset CRC incidence. Risk stratification is necessary to further determine the population most at risk for early-onset CRC. However, epidemiological data on related clinical characteristics and potential risk factors, especially in developing countries, have not been widely reported.

#### AIM

To investigate the prevalence, demographics, clinicopathologic features, and associated factors of young-onset CRC patients in a tertiary hospital in Indonesia.

#### **METHODS**

Patients undergoing colonoscopy examination between 2008 and 2019, yielding a diagnosis of CRC were identified from medical records. The subjects were classified into two groups according to their age at diagnosis, namely early-onset (18-49 years old) and late-onset (≥ 50-years-old). Demographic data, characteristics, and risk factors of both onset age groups were evaluated using the chi-



#### Informed consent statement: As

this was a retrospective study and only existing data from medical records were collected, patients were not required to give informed consent to the study. However, all patients agreed by written consent to the medical treatment provided in the healthcare setting.

Conflict-of-interest statement: The authors declare having no conflicts of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: htt p://creativecommons.org/License s/by-nc/4.0/

Specialty type: Medicine, research and experimental

Country/Territory of origin: Indonesia

#### Peer-review report's scientific quality classification

Grade A (Excellent): 0 Grade B (Very good): B Grade C (Good): C, C Grade D (Fair): 0 Grade E (Poor): E

Received: June 21, 2021 Peer-review started: June 21, 2021 First decision: July 18, 2021 Revised: August 15, 2021 Accepted: September 22, 2021 Article in press: September 22, 2021 Published online: November 16, 2021

P-Reviewer: Azar I, Emran TB, Gao W, Hisada H S-Editor: Wang JJ L-Editor: A

square and Fisher's exact test.

# RESULTS

Among 495 CRC patients confirmed by histopathology, 205 (41.4%) were classified as early-onset and 290 (58.6%) as late-onset. Most subjects in the earlyonset CRC group were male (53.7%), with 89.8% displaying adenocarcinoma histopathology. A majority (78%) of the early-onset CRC patients had left-sided tumors, with the rectum (41%) and rectosigmoid (17.6%) being the most common sites. Abdominal pain was the most frequent symptom in the early-onset CRC patients (55.6%), which was significantly higher than that in the late-onset CRC patients (43.8%, P < 0.05). Early-onset CRC cases were more likely to be underweight (34.6% vs 20.0%, P < 0.001) compared to late-onset CRC cases. The proportion of subjects with suspected hereditary nonpolyposis colorectal cancer (HNPCC) was also higher in the early-onset CRC group than in the late-onset age group (9.3% vs 4.1%, P < 0.05). However, no difference was observed in the parental or family histories of CRC cases.

# CONCLUSION

Early-onset CRC patients were more likely to have abdominal pain, underweight status, and HNPCC suspicion than late-onset CRC patients.

Key Words: Colorectal cancer; Early onset; Epidemiology; Associated factors; Tertiary hospital; Indonesia

©The Author(s) 2021. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core Tip:** This is the first study to evaluate clinicodemographics of early-onset colorectal cancer (CRC) patients and associated factors in Indonesia during a 12-year period from 2008-2019. We observed a slight increase in patients with early-onset CRC during the period of 2014-2019 compared to the period of 2008-2013. A larger proportion of patients with early-onset CRC were underweight, presented with abdominal pain, and suspected of suffering from hereditary nonpolyposis colorectal cancer.

Citation: Makmun D, Simadibrata M, Abdullah M, Syam AF, Shatri H, Fauzi A, Renaldi K, Maulahela H, Utari AP, Pribadi RR, Muzellina VN, Nursyirwan SA. Colorectal cancer patients in a tertiary hospital in Indonesia: Prevalence of the younger population and associated factors. World J Clin Cases 2021; 9(32): 9804-9814

URL: https://www.wjgnet.com/2307-8960/full/v9/i32/9804.htm DOI: https://dx.doi.org/10.12998/wjcc.v9.i32.9804

# INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignancy, after lung, breast and prostate cancers, and the third leading cause of cancer mortality worldwide[1]. A tertiary hospital-based survey in Indonesia revealed that CRC accounted for 73.7% of all gastrointestinal malignancies in 2002-2011[2]. In recent decades, a reduced incidence of CRC has been observed in some developed countries, such as the United States and Japan, mostly due to adequate participation of their populations in CRC screening programs recommended for individuals over 50 years of age[1,3]. The aim of CRC screening is to find and remove adenomatous polyps and to identify early stages of CRC. However, a steady rise in the incidence of CRC and an increasing incidence of CRC among younger individuals represent a burden in populations in developing countries, where health care infrastructures are limited, and screening and early detection are still lacking[4,5].

The main cause of the rising incidence of early-onset CRC has not been clearly identified. Several studies have suggested that this phenomenon might be related to an increasing occurrence of modifiable risk factors, such as sedentary activity, obesity, intestinal microbiomes, socioeconomic factors, and the westernization of diet and lifestyle, including smoking and a high-calorie, low-fiber diet[6-9]. Additional evi-



P-Editor: Yuan YY



dence has suggested that such nonmodifiable risk factors as genetics, race/ethnicity, diabetes mellitus, and family history of cancer also play a role[6,9,10].

Early-onset CRC was found to be associated with more advanced disease and a poorer clinical outcome than CRC in the older population[11,12]. Poor tumor differentiation, a high risk of distant metastasis, and treatment failure are characteristics commonly found in early-onset CRC, as it has been widely reported that these patients display more aggressive tumor biology and molecular and pathological features[13, 14]. The predominant symptoms of CRC in young adults are gastrointestinal bleeding, abdominal pain, and changes in bowel habits, including diarrhea and constipation, which are often incorrectly considered symptoms of benign anorectal diseases such as hemorrhoids or anal fissure. Hence, many early-onset CRC cases are diagnosed later in the disease course and present with an advanced stage at diagnosis[12,13,15].

As the surge in CRC incidence among younger individuals is of concern, screening and early detection for high-risk groups are important. However, clinical data regarding the characteristics and risk factors for early-onset CRC in Indonesia are lacking, and the currently available guidelines are still mainly focused on the older population. This study aimed to determine the clinical demographics of early-onset CRC in Indonesia, including its prevalence, clinical manifestations, histopathological features, and risk factors associated with the development of CRC in young individuals.

# MATERIALS AND METHODS

#### Study design

We conducted a retrospective cross-sectional study based on the medical records of patients who underwent a colonoscopy examination at Cipto Mangunkusumo National General Hospital (Jakarta, Indonesia), a tertiary academic hospital in Jakarta, during the period from January 2008 to December 2019. The protocol was approved by the Research Ethical Committee, Faculty of Medicine Universitas Indonesia, Cipto Mangunkusumo National General Hospital.

#### Patient selection

The study included patients aged ≥ 18 years with a diagnosis of CRC based on colonoscopy and histopathological examination. Consecutive sampling was used as the recruitment strategy in this study. Early-onset CRC patients were defined as those diagnosed within the age range of 18-49 years (early-onset age group), while late-onset CRC patients were defined as those diagnosed at age  $\geq$  50 years (late-onset age group). Patients with CRC due to secondary causes as well as those with missing variables were excluded from the study. All patients received health care at the study institution.

#### Data collection

Data on patient demographics, characteristics, clinical history, and risk factors were collected secondarily from medical records. Demographic variables included patient age and sex, while the characteristics evaluated in this study comprised clinical manifestations, tumor sites and histopathological features. The risk factors assessed in this study encompassed parental and family history of CRC, body mass index (BMI), smoking habit, possibility of familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC), as well as comorbidities such as diabetes mellitus and hypertension.

#### Statistical analysis

We used the chi-square and Fisher's exact tests to evaluate the categorical variables in the two onset age groups. A two-sided P value of < 0.05 was set for statistical significance. All results are presented in percentage proportion. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) Statistics software, version 23.0 (IBM Corp, Armonk, NewYork, United States).

# RESULTS

Among all the patients who underwent a colonoscopy examination during the 12-year period, from January 2008 to December 2019, at the Gastrointestinal Endoscopy Center



of the Cipto Mangunkusumo National General Hospital, 495 were diagnosed with CRC, as confirmed by histopathological analysis. The age of diagnosis ranged from 18years-old to 92-years-old, with a mean age of 52.7-years-old, and 54.9% of CRC cases were male. Based on their age at diagnosis, 205 patients (41.4%) were classified into the early-onset age group, while 290 (58.6%) were classified into the late-onset age group. Most patients were diagnosed between the ages of 50-years-old and 59-years-old (27.3%), followed by those between the ages of 40-years-old and 49-years-old (23.6%). A slight increase of early-onset CRC patients was observed from in the period of 2008-2013, at 41.2%, and the period of 2014-2019, at 41.5%. Descriptive demographic data for all subjects are provided in Table 1.

#### Histopathological features

The early- and late-onset age groups shared similar histopathological features, with the largest proportion identified with adenocarcinoma (in both: 92.3%), followed by carcinoma nonepithelial (6.3%) and carcinoid (1.4%). While adenocarcinoma was observed in 89.8% of the early-onset age group and 94.1% of the late-onset age group, only 3.4% and 1.0% of cases, respectively, displayed carcinoid histopathology, as can be seen in Table 2.

#### Tumor locations

Among all CRC cases, most patients presented with malignant tumors on the left side (77.4%), with 43.6% of the tumors being located in the rectum and 14.9% in the rectosigmoid. A similar proportion of rectal cancer was observed between the two onset age groups, with 41% of cases in the early-onset age group and 45.5% of cases in the late-onset age group. Tumors located at the rectosigmoid were observed in 17.6% and 13.1% of patients in the early- and late-onset age groups, respectively. The ascending colon was the most common site for right-sided tumors, accounting for 13.2% of cases in the early-onset age group and 11.7% of cases in the late-onset age group. Data on the anatomical site of tumors are presented in Table 3.

#### Clinical manifestations

Differences were observed in the clinical manifestations of the two onset age groups. Abdominal pain was the most common symptom in the early-onset age group, which was experienced by 114 subjects (55.6%), while only 43.8% of the late-onset age group experienced abdominal pain. In contrast, hematochezia was the second most common clinical manifestation in the early-onset age group (48.3%) and the most common symptom in the late-onset age group, affecting 150 subjects (51.7%). Data on the clinical manifestations presenting in CRC patients are presented in Table 4.

#### Risk factors associated with CRC

The majority of subjects were categorized as overweight and obese. However, subjects in the early-onset age group were more likely to be underweight, with 71 patients (34.6%) having a low BMI. In contrast, only 58 patients (20.0%) in the late-onset age group were underweight, while 131 patients (45.2%) in this category were overweight and obese. The reverse trend occurred in the early-onset age group, with 63 patients (30.7%) categorized as overweight and obese.

A significant difference was also observed with regard to the suspicion of inherited CRC syndrome, with 19 subjects (9.3%) in the early-onset age group and only 12 subjects (4.1%) in the late-onset age group identified. However, no difference between the two onset age groups was observed for suspicion of FAP, parental history, or other family history of CRC.

Comorbid diseases were more prevalent in the late-onset age group, with 53 subjects (18.3%) and 75 subjects (25.2%) diagnosed with diabetes mellitus and hypertension, respectively. In contrast, only 8 patients (3.9%) had diabetes mellitus and 7 (3.4%) had hypertension in the early-onset age group. Comparison of associated risk factors among early- and late-onset CRC patients is presented in Table 5.

# DISCUSSION

An increasing incidence of early-onset CRC is a widely observed global phenomenon, with studies from various centers reporting similar results. A systematic review by Saad El Din *et al*<sup>[16]</sup> revealed that North America and Australia were the two regions with the highest increase in young-onset CRC incidence. A European study by Vuik et al[17] reported annual increases in the incidence of CRC of 7.9% for those aged 20-29



Table 1 Demographics of colorectal cancer patients in 2008-2019			
Variables	< 50-years-old, <i>n</i> (%)	≥ 50-years-old, <i>n</i> (%)	Total subjects, <i>n</i> (%)
Study population			495 (100)
Age at diagnosis			
< 50-years-old	205 (41.4)		
8-29	26 (5.3)		
30-39	62 (12.5)		
40-49	117 (23.6)		
$\geq$ 50-years-old		290 (58.6)	
50-59		135 (27.3)	
60-69		95 (19.2)	
70-79		52 (10.5)	
80-89		8 (1.6)	
Sex			
Male	110 (53.7)	162 (55.9)	272 (54.9)
Female	95 (46.3)	128 (44.1)	223 (45.1)
Time period			
2008-2013	47 (41.2)	67 (58.8)	114 (23.0)
2014-2019	158 (41.5)	223 (58.5)	381 (76.9)

Table 2 Histopathological features of early-onset and late-onset colorectal cancer patients in 2008-2019			
Histopathological feature	< 50-years-old, <i>n</i> (%)	≥ 50-years-old, <i>n</i> (%)	Total, <i>n</i> (%)
Adenocarcinoma	184 (89.8)	273 (94.1)	457 (92.3)
Nonepithelial	6 (6.9)	25 (6.1)	31 (6.3)
Carcinoid	3 (3.4)	4 (1.0)	7 (1.4)

years, 4.9% for those aged 30-39 years, and 1.6% for those aged 40-49 between 2004 and 2016. A study by Sung et al[18], which involved several Asian countries, including Taiwan, Korea, Japan and Hong Kong, reported a significant increase in early-onset CRC between 1995 and 2014, with most cases classified as rectal cancer and mostly occurring in men. Similar results were observed in a study in Indonesia by Makmun et al[2], which found that the incidence of CRC in patients aged < 30 years increased from 4.4% in 2002-2006 to 9% in 2007-2011. All these reports align with similar initial findings, whereby the proportion of CRC diagnosed at a younger age was higher, although not significantly, in the period 2014-2019 compared with 2008-2013, with the highest increase in incidence among the population aged 30-39 years.

Based on demographic data, the present study revealed that CRC patients in our tertiary hospital were predominantly men in both the early- and late-onset age groups, although this difference was not statistically significant. Nonetheless, previous studies similarly demonstrated a slightly higher incidence of CRC among male patients in populations < 40-years-old[19,20]. The average age at diagnosis among all CRC patients in this study was 52.7 years. The mean age at diagnosis varies among studies, with a report from Saudi Arabia noting an average age of 57.9 years and a study in Australia reporting a mean age of 69 years[11,21]. A recent study from the United States documented an average age at diagnosis of 43 years for those categorized in the early-onset age group and 71 years in the late-onset age group [22].

Clinical and histopathological features among both the early- and late-onset age groups were found to be quite similar in this study, with adenocarcinoma being the most common histopathology. This finding is also consistent with several previous studies from other countries, in which adenocarcinoma accounted for 87% and 88.6% of CRC patients in Egypt and early-onset CRC in Saudi Arabia, respectively [7,11].



WJCC | https://www.wjgnet.com

Table 3 Anatomical sites of tumors presenting in early- and late-onset colorectal cancer patients in 2008-2019			
Tumor sites	< 50-years-old, <i>n</i> (%)	≥ 50-years-old, <i>n</i> (%)	Total, <i>n</i> (%)
Right side	45 (22.0)	67 (23.1)	112 (22.6)
Cecum	13 (6.3)	17 (5.9)	30 (6.1)
Ascending colon	27 (13.2)	34 (11.7)	61 (12.3)
Hepatic flexure	1 (1.1)	5 (1.2)	6 (1.2)
Transverse colon	4 (2.0)	11 (3.8)	15 (3.0)
Left side	160 (78.0)	223 (76.9)	383 (77.4)
Descending colon	17 (8.3)	9 (3.1)	26 (5.3)
Rectum	84 (41.0)	132 (45.5)	216 (43.6)
Sigmoid	13 (6.3)	42 (14.5)	55 (11.1)
Rectosigmoid	36 (17.6)	38 (13.1)	74 (14.9)
Anus	1 (1.1)	1 (0.2)	2 (0.4)
Anorectal	9 (4.4)	1 (0.3)	10 (2.0)

#### Table 4 Clinical manifestations of early- and late-onset colorectal cancer patients in 2008-2019

Clinical manifestation	< 50-years-old, <i>n</i> (%)	≥ 50-years-old, <i>n</i> (%)	Total, <i>n</i> (%)	Ρ
Diarrhea	46 (22.4)	83 (28.6)	129 (26.1)	0.123
Constipation	69 (33.7)	94 (32.4)	163 (32.9)	0.772
Abdominal pain <sup>a</sup>	114 (55.6)	127 (43.8)	241 (48.7)	0.011
Hematochezia	99 (48.3)	150 (51.7)	249 (50.3)	0.452
Weight loss	72 (35.1)	97 (33.4)	169 (34.1)	0.699

<sup>a</sup>Fisher's exact test, P < 0.05

Regarding the anatomical site, the current study identified that most early-onset CRC patients developed tumors on the left side of the colon, with the rectum being the most common site. Other studies have reported similar findings. One study conducted among young Nigerians and African-American populations with CRC observed that 75% of the patients were diagnosed with rectal cancer[23]. Two retrospective studies from Singapore and Brazil found that young CRC patients tended to present with leftsided tumors [24,25]. The latest study, presented herein, revealed that early-onset CRC patients presenting left-sided tumors were slightly more prevalent than late-onset CRC patients, although this difference was not significant. This finding is supported by a similar study from the Czech Republic that showed a shift in tumor location to the proximal colon among young compared with elderly patients, with tumors on the left side identified in 25.1% of young patients and in 22.3% of older patients, in which the rectum was the most common site of the tumors[26]. A meta-analysis conducted in North America among CRC patients aged < 50 years also showed that younger cases were less likely to present with right-sided primary tumors[27].

Regarding clinical symptoms, this study identified abdominal pain as the most common clinical manifestation in early-onset CRC patients; moreover, this symptom was significantly more prominent in the early-onset age group than in the late-onset age group. A similar study revealed that the presenting symptom of abdominal pain, among several other factors, was significantly associated with an increased risk of CRC in the early-onset age group vs the late-onset age group[28]. Abdominal pain among CRC patients is suggested to be related to the anatomical site of tumors, with left-sided tumors more likely to cause relative obstructive symptoms due to more solid stools and constricting lesions. The second most common symptom, hematochezia, was present in 48.3% of the early-onset CRC subjects. The presence of blood in the stool is known to be the most common initial symptom of tumors in the rectum. A study from Pakistan demonstrated that blood in the stool was the most prevalent early-onset CRC

Table 5 Clinical manifestations of early- and late-onset colorectal cancer patients in 2008-2019				
Variables	< 50-years-old, <i>n</i> (%)	≥ 50-years-old, <i>n</i> (%)	Total, <i>n</i> (%)	Р
Smoking	69 (33.7)	114 (39.3)	183 (37)	0.199
Parental history of CRC	8 (3.9)	4 (1.4)	12 (2.4)	0.072
Other family history of CRC	6 (2.9)	8 (2.8)	14 (2.8)	0.911
Suspicion of FAP	4 (2.0)	6 (2.1)	10 (2.0)	0.927
Suspicion of HNPCC <sup>a</sup>	19 (9.3)	12 (4.1)	31 (6.3)	< 0.05
BMI				
Underweight <sup>c</sup>	71 (34.6)	58 (20.0)	129 (26.1)	< 0.001
Normoweight	71 (34.6)	101 (34.8)	172 (34.7)	0.521
Overweight and obese <sup>b</sup>	63 (30.7)	131 (45.2)	194 (39.2)	< 0.005
Comorbidities				
Diabetes mellitus <sup>c</sup>	8 (3.9)	53 (18.3)	61 (12.3)	< 0.001
Hypertension <sup>c</sup>	7 (3.4)	73 (25.2)	80 (16.2)	< 0.001

<sup>a</sup>Chi-square test, P < 0.05.

<sup>b</sup>Fisher's exact test, P < 0.005

<sup>c</sup>Fisher's exact test, P < 0.001.

BMI: Body mass index; CRC: Colorectal cancer; FAP: Familial adenomatous polyposis; HNPCC: Hereditary nonpolyposis colorectal cancer.

presentation, along with abdominal pain, especially in those with left-sided tumors [15]. Thus, rectal bleeding in younger age groups is a red-flag symptom and should prompt early investigation.

The main cause of this global increase in early-onset CRC incidence has not yet been clearly identified, but several internal and external factors are suggested to play a role in the development of this phenomenon. Most studies have identified several potential risk factors, such as the westernization of diet and lifestyle, which might explain the increasing incidence of early-onset CRC in regions that have more recently adopted Western lifestyles (i.e., high intake of alcohol and/or processed meat, high-calorie and low-fiber diet), less physical activity, obesity, smoking, family history of CRC, and hereditary syndromes, as well as chronic systemic diseases, including diabetes mellitus and hypertension[22,29-32].

This study revealed that although most subjects were generally categorized as overweight and obese, the majority of those classified into the early-onset age group had either low or normal BMI (both 34.6%). Moreover, we observed that the proportion of underweight patients was significantly higher in the early-onset age group than in the late-onset group, indicating that in this study, young CRC patients were more likely to be underweight, despite many recent studies suggesting obesity as one of the potential risk factors for early-onset CRC[32-34]. However, the association between BMI and early-onset CRC is still controversial, as other studies revealed that early-onset CRC patients were more likely to be underweight than normal controls and that patients with an increased BMI had a 31% reduction in the odds of developing early-onset CRC[29,35]. A possible explanation for these contradictory findings could be that almost 70% of patients with gastrointestinal cancer in Indonesia were diagnosed at an advanced stage, at which time the patients had already experienced weight loss<sup>[2]</sup>. A United States' study also provided supporting evidence that over one-third of early-onset CRC patients had already lost weight due to the cancer[35]. Moreover, it is evident from several studies that early-onset CRC cases tend to present with a more advanced and aggressive disease course[36,37], which may explain why the magnitude of symptoms, especially weight loss, was more substantial in early-onset CRC subjects. One study that is consistent with these findings demonstrated that weight loss among early-onset CRC subjects generally began 5 years prior to baseline colonoscopy and that early-onset CRC cases were 2-fold more likely to lose  $\geq$  5 kg of body weight than controls over this period[35].

In contrast to currently available data, this study did not find any significant difference in family history of CRC between the early- and late-onset age groups. This differs from the findings reported by Chen et al[38], in which the absolute prevalence

WJCC | https://www.wjgnet.com

of family history in young-onset CRC patients (25%) was significantly higher than that in late-onset CRC patients (17%). The current study showed that only 3.9% of all earlyonset CRC patients had a parental history of CRC and that 2.9% had other-family histories of CRC. This low percentage agrees with Riaz *et al*[15]'s data from Pakistan, which indicated that most of the early-onset CRC patients had no family history of CRC. Moreover, the pattern of early-onset CRC cases in Asia may differ from that occurring in the West, where approximately 26% of early-onset CRC patients were reported to have at least one first-degree relative with a history of CRC[39].

The association between genetic risk factors and younger-age onset of CRC has been extensively studied, as 9%-26% of patients with early-onset CRC carry pathogenic germline cancer prediction genes[38,40]. In another study with a lower age of CRC onset cutoff (< 35 years), hereditary cancer syndromes were identified in 35% of the CRC patients[41]. Confirmed or probable cases of hereditary cancer syndromes were also reported as significantly more prevalent among patients with early-onset CRC than among patients in older populations (7% *vs* 1%)[38]. Hereditary cancer syndromes in early-onset CRC were mainly attributed to Lynch syndrome or HNPCC, with a prevalence ranging from 4% to 20%[42,43]. This study demonstrated a similar result, whereby among all early-onset CRC patients, 9.3% were suspected to have HNPCC, and this proportion was significantly higher than that in the late-onset age group (4.1%).

This is the first study in Indonesia to evaluate the current incidence of early-onset CRC and to provide new insights into the prevalence, sociodemographics, clinical characteristics, and potential risk factors for early-onset CRC. Nevertheless, as a preliminary study of these circumstances, several limitations exist, especially with respect to interpretation of the findings. This study may not be representative of the real conditions in Indonesia, since it was conducted in a single tertiary health center and using a retrospective cross-sectional study design. Moreover, cohort studies involving larger sample sizes are needed to better assess the association between early-onset CRC and probable risk factors.

#### CONCLUSION

This study is the first to demonstrate the current clinicodemographic of early-onset CRC cases in Indonesia. The prevalence of early-onset CRC in Indonesia is increasing, similar to the prevalence trends seen worldwide. In this study, most patients with early-onset CRC had left-sided tumors, particularly in the rectum, and adenocarcinoma histopathology. Compared with late-onset CRC patients, early-onset CRC patients were more likely to be underweight and to present with abdominal pain and suspicion of HNPCC. Further studies involving a larger sample size are required to better assess the association of potential risk factors and early-onset CRC, to redefine the most appropriate cutoff age and the populations at-risk for CRC who will most benefit from screening. Nevertheless, based on these findings, it is proposed that CRC screening should be initiated at an earlier age.

# **ARTICLE HIGHLIGHTS**

#### Research background

The incidence of early-onset colorectal cancer (CRC) has been increasing worldwide. Determining the population at-risk for early-onset CRC, who will most benefit from screening, is important.

#### **Research motivation**

The reports of clinical characteristics as well as potential risk factors associated with early-onset CRC, especially in developing countries, are still lacking.

#### Research objectives

The objective of this study was to evaluate the prevalence, demographics, clinicopathologic features, and associated factors of young-onset CRC patients in a tertiary hospital in Indonesia.

Zaishideng® WJCC | https://www.wjgnet.com

#### Research methods

In this study, patients who underwent colonoscopy examination between 2008 and 2019 and were diagnosed with CRC based on histopathological findings were identified from medical records. The subjects were classified into two groups, according to their age at diagnosis: Early onset (18-49 years old) and late onset ( $\geq$  50 years old). Demographic data, characteristics, and risk factors of both age groups were evaluated using the chi-square and Fisher's exact tests.

#### Research results

Among the total 495 patients assessed, 205 (41.4%) were classified as early-onset CRC. Most subjects in the early-onset age group were male (53.7%), had adenocarcinoma histopathology (89.8%), and presented with left-sided tumors (78%). Abdominal pain was the most frequent symptom in the early-onset age group (55.6%), a significantly higher proportion than that in late-onset age group (43.8%, P < 0.05). Early-onset CRC cases were more likely to be underweight compared to late-onset CRC cases (34.6% vs 20.0%, P < 0.001). The proportion of subjects suspected with hereditary nonpolyposis colorectal cancer (HNPCC) was also higher in the early-onset age group than in the late-onset age group (9.3% *vs* 4.1%, *P* < 0.05).

#### Research conclusions

Most patients with early-onset CRC were male, had left-sided tumors, and histopathologically displayed adenocarcinoma. A higher proportion of early-onset CRC cases presented with abdominal pain. The early-onset CRC patients were more likely to be underweight and suspected of having HNPCC compared with the late-onset CRC patients.

#### Research perspectives

Further multicenter research involving a larger sample size is required to better assess the clinical demographics of early-onset CRC patients and the potential risk factors associated with early-onset CRC; these data will help to redefine the most appropriate cutoff age and the populations at-risk for CRC who will most benefit from screening.

### ACKNOWLEDGEMENTS

The authors are grateful to the doctors and nurses at the Gastrointestinal Endoscopy Center of the Cipto Mangungkusumo National General Hospital and especially to Rizani Putri Iman, MD and Rani Ramadhani, MD for their essential support of this study.

#### REFERENCES

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: 1 GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
- 2 Makmun D, Simadibrata M, Abdullah M, Syam AF, Fauzi A, Renaldi K, et al. Changing trends in gastrointestinal malignancy in Indonesia: the Jakarta experience. J Cancer Res Ther 2014; 2: 160-168 [DOI: 10.14312/2052-4994.2014-24]
- 3 Abualkhair WH, Zhou M, Ahnen D, Yu Q, Wu XC, Karlitz JJ. Trends in Incidence of Early-Onset Colorectal Cancer in the United States Among Those Approaching Screening Age. JAMA Netw Open 2020; 3: e1920407 [PMID: 32003823 DOI: 10.1001/jamanetworkopen.2019.20407]
- Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol 2019; 14: 89-103 [PMID: 31616522 DOI: 10.5114/pg.2018.81072]
- 5 Araghi M, Soerjomataram I, Jenkins M, Brierley J, Morris E, Bray F, Arnold M. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer 2019; 144: 2992-3000 [PMID: 30536395 DOI: 10.1002/ijc.32055]
- Connell LC, Mota JM, Braghiroli MI, Hoff PM. The Rising Incidence of Younger Patients With 6 Colorectal Cancer: Questions About Screening, Biology, and Treatment. Curr Treat Options Oncol 2017; 18: 23 [PMID: 28391421 DOI: 10.1007/s11864-017-0463-3]
- Veruttipong D, Soliman AS, Gilbert SF, Blachley TS, Hablas A, Ramadan M, Rozek LS, Seifeldin IA. Age distribution, polyps and rectal cancer in the Egyptian population-based cancer registry. World J Gastroenterol 2012; 18: 3997-4003 [PMID: 22912550 DOI: 10.3748/wjg.v18.i30.3997]
- Naganna SM, Vidyavathi K, Kumar H, Bhaskaran A. Histomorphological characteristics of 8



colorectal carcinoma in the young and elderly: is there a difference? Indian J Pathol Oncol 2016; 3(2): 293-29 [DOI: 10.5958/2394-6792.2016.00056.9]

- 9 Carethers JM. The Increasing Incidence of Colorectal Cancers Diagnosed in Subjects Under Age 50 Among Races: CRaCking the Conundrum. Dig Dis Sci 2016; 61: 2767-2769 [PMID: 27480086 DOI: 10.1007/s10620-016-4268-1]
- Jones HG, Radwan R, Davies M, Evans M, Khot U, Chandrasekaran TV, Williams N, Murray A, 10 Jones W, Harris D, Bevnon J. Clinicopathological characteristics of colorectal cancer presenting under the age of 50. Int J Colorectal Dis 2015; 30: 483-489 [PMID: 25707594 DOI: 10.1007/s00384-015-2166-1]
- 11 Albasri A, Yosef H, Hussainy AS, Sultan SA, Alhujaily A. Histopathological features of colorectal cancer in Al-Madinah region of Saudi Arabia: 8 years experience. Asian Pac J Cancer Prev 2014; 15: 3133-3137 [PMID: 24815459 DOI: 10.7314/apjcp.2014.15.7.3133]
- 12 Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y, Chen H, Yi C, Zheng S, Yuan Y. Young patients (≤ 35 years old) with colorectal cancer have worse outcomes due to more advanced disease: a 30-year retrospective review. Medicine (Baltimore) 2014; 93: e135 [PMID: 25415667 DOI: 10.1097/MD.00000000000135
- Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. Mol Oncol 2019; 13: 109-131 [PMID: 30520562 DOI: 10.1002/1878-0261.124171
- 14 Mueller M, Schneider MA, Deplazes B, Cabalzar-Wondberg D, Rickenbacher A, Turina M. Colorectal cancer of the young displays distinct features of aggressive tumor biology: A single-center cohort study. World J Gastrointest Surg 2021; 13: 164-175 [PMID: 33643536 DOI: 10.4240/wjgs.v13.i2.164]
- 15 Riaz R, Masood N, Benish A. Red flag symptoms: detailed account of clinicopathological features in young-onset colorectal cancer. Intest Res 2017; 15: 203-207 [PMID: 28522950 DOI: 10.5217/ir.2017.15.2.203
- 16 Saad El Din K, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, De Vera MA. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. BMC Cancer 2020; 20: 288 [PMID: 32252672 DOI: 10.1186/s12885-020-06766-9]
- Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ, Zadnik V, Pellisé M, Esteban L, Kaminski MF, Suchanek S, Ngo O, Májek O, Leja M, Kuipers EJ, Spaander MC. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut 2019; 68: 1820-1826 [PMID: 31097539 DOI: 10.1136/gutjnl-2018-317592]
- Sung JJY, Chiu HM, Jung KW, Jun JK, Sekiguchi M, Matsuda T, Kyaw MH. Increasing Trend in 18 Young-Onset Colorectal Cancer in Asia: More Cancers in Men and More Rectal Cancers. Am J Gastroenterol 2019; 114: 322-329 [PMID: 30694865 DOI: 10.14309/ajg.00000000000133]
- 19 Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer 2007; 96: 828-831 [PMID: 17311019 DOI: 10.1038/sj.bjc.6603628]
- 20 Chambers AC, Dixon SW, White P, Williams AC, Thomas MG, Messenger DE. Demographic trends in the incidence of young-onset colorectal cancer: a population-based study. Br J Surg 2020; 107: 595-605 [PMID: 32149386 DOI: 10.1002/bjs.11486]
- Young JP, Win AK, Rosty C, Flight I, Roder D, Young GP, Frank O, Suthers GK, Hewett PJ, 21 Ruszkiewicz A, Hauben E, Adelstein BA, Parry S, Townsend A, Hardingham JE, Price TJ. Rising incidence of early-onset colorectal cancer in Australia over two decades: report and review. J Gastroenterol Hepatol 2015; 30: 6-13 [PMID: 25251195 DOI: 10.1111/jgh.12792]
- 22 Gausman V, Dornblaser D, Anand S, Hayes RB, O'Connell K, Du M, Liang PS. Risk Factors Associated With Early-Onset Colorectal Cancer. Clin Gastroenterol Hepatol 2020; 18: 2752-2759.e2 [PMID: 31622737 DOI: 10.1016/j.cgh.2019.10.009]
- Holowatyj AN, Maude AS, Musa HS, Adamu A, Ibrahim S, Abdullahi A, Manko M, Aminu SM, 23 Mohammed A, Idoko J, Ukwenya Y, Carpten J, Chandler PD, Hampel H, Faruk M. Patterns of Early-Onset Colorectal Cancer Among Nigerians and African Americans. JCO Glob Oncol 2020; 6: 1647-1655 [PMID: 33141623 DOI: 10.1200/GO.20.00272]
- 24 Goh SS, Loo EX, Lee DJ. Trends and Clinical Outcomes in Young-onset Colorectal Cancer Patients. Ann Acad Med Singap 2020; 49: 848-856 [PMID: 33381778 DOI: 10.47102/annals-acadmedsg.20207
- 25 Silva ACB, Vicentini MFB, Mendoza EZ, Fujiki FK, da Fonseca LG, Braghiroli MIFM, Hoff PM. Young-age onset colorectal cancer in Brazil: Analysis of incidence, clinical features, and outcomes in a tertiary cancer center. Curr Probl Cancer 2019; 43: 477-486 [PMID: 30826126 DOI: 10.1016/j.currproblcancer.2019.01.009
- 26 Kocián P, Svobodová I, Krejčí D, Blaha M, Gürlich R, Dušek L, Hoch J, Whitley A. Is colorectal cancer a more aggressive disease in young patients? Cancer Epidemiol 2019; 63: 101621 [PMID: 31634775 DOI: 10.1016/j.canep.2019.101621]
- 27 Griffiths CD, McKechnie T, Lee Y, Springer JE, Doumouras AG, Hong D, Eskicioglu C. Presentation and survival among patients with colorectal cancer before the age of screening: a systematic review and meta-analysis. Can J Surg 2021; 64: E91-E100 [PMID: 33599450 DOI: 10.1503/cjs.013019
- Syed AR, Thakkar P, Horne ZD, Abdul-Baki H, Kochhar G, Farah K, Thakkar S. Old vs new: Risk 28 factors predicting early onset colorectal cancer. World J Gastrointest Oncol 2019; 11: 1011-1020



[PMID: 31798781 DOI: 10.4251/wjgo.v11.i11.1011]

- Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, Giannakis M, Wu K, Cao Y, Ng K, Ogino S. 29 Rising incidence of early-onset colorectal cancer - a call to action. Nat Rev Clin Oncol 2021; 18: 230-243 [PMID: 33219329 DOI: 10.1038/s41571-020-00445-1]
- 30 Nguyen LH, Liu PH, Zheng X, Keum N, Zong X, Li X, Wu K, Fuchs CS, Ogino S, Ng K, Willett WC, Chan AT, Giovannucci EL, Cao Y. Sedentary Behaviors, TV Viewing Time, and Risk of Young-Onset Colorectal Cancer. JNCI Cancer Spectr 2018; 2: pky073 [PMID: 30740587 DOI: 10.1093/jncics/pky073]
- 31 Kim JY, Jung YS, Park JH, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI, Choi KY, Park DI. Different risk factors for advanced colorectal neoplasm in young adults. World J Gastroenterol 2016; 22: 3611-3620 [PMID: 27053853 DOI: 10.3748/wjg.v22.i13.3611]
- 32 Kim NH, Jung YS, Yang HJ, Park SK, Park JH, Park DI, Sohn CI. Prevalence of and Risk Factors for Colorectal Neoplasia in Asymptomatic Young Adults (20-39 Years Old). Clin Gastroenterol Hepatol 2019; 17: 115-122 [PMID: 30025922 DOI: 10.1016/j.cgh.2018.07.011]
- Sanford NN, Giovannucci EL, Ahn C, Dee EC, Mahal BA. Obesity and younger versus older onset 33 colorectal cancer in the United States, 1998-2017. J Gastrointest Oncol 2020; 11: 121-126 [PMID: 32175114 DOI: 10.21037/jgo.2019.12.07]
- 34 Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, He X, Fuchs CS, Ogino S, Willett WC, Chan AT, Giovannucci EL, Cao Y. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. JAMA Oncol 2019; 5: 37-44 [PMID: 30326010 DOI: 10.1001/jamaoncol.2018.4280]
- 35 Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, Provenzale D, Kaltenbach T, Gawron AJ, Martinez ME, Gupta S. Risk Factors for Early-Onset Colorectal Cancer. Gastroenterology 2020; 159: 492-501.e7 [PMID: 31926997 DOI: 10.1053/j.gastro.2020.01.004]
- 36 Burnett-Hartman AN, Powers JD, Chubak J, Corley DA, Ghai NR, McMullen CK, Pawloski PA, Sterrett AT, Feigelson HS. Treatment patterns and survival differ between early-onset and late-onset colorectal cancer patients: the patient outcomes to advance learning network. Cancer Causes Control 2019; 30: 747-755 [PMID: 31102084 DOI: 10.1007/s10552-019-01181-3]
- Rho YS, Gilabert M, Polom K, Aladashvili A, Kopeckova K, Megdanova V, Coleman N, Greally M, 37 Marrelli D, Roviello F, McDermott R, Petrova V, Mihaylova Z, Bortlicek Z, Prausova J, Batist G, Azoulay L, Kavan P. Comparing Clinical Characteristics and Outcomes of Young-onset and Lateonset Colorectal Cancer: An International Collaborative Study. Clin Colorectal Cancer 2017; 16: 334-342 [PMID: 28462853 DOI: 10.1016/j.clcc.2017.03.008]
- Chen FW, Sundaram V, Chew TA, Ladabaum U. Advanced-Stage Colorectal Cancer in Persons 38 Younger Than 50 Years Not Associated With Longer Duration of Symptoms or Time to Diagnosis. Clin Gastroenterol Hepatol 2017; 15: 728-737.e3 [PMID: 27856366 DOI: 10.1016/j.cgh.2016.10.038]
- Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J, Williams L, Hanson K, Gruber SB, 39 Rozek LS. Germline Genetic Features of Young Individuals With Colorectal Cancer. Gastroenterology 2018; 154: 897-905.e1 [PMID: 29146522 DOI: 10.1053/j.gastro.2017.11.004]
- Daca Alvarez M, Quintana I, Terradas M, Mur P, Balaguer F, Valle L. The Inherited and Familial 40 Component of Early-Onset Colorectal Cancer. Cells 2021; 10 [PMID: 33806975 DOI: 10.3390/cells10030710]
- Mork ME, You YN, Ying J, Bannon SA, Lynch PM, Rodriguez-Bigas MA, Vilar E. High Prevalence 41 of Hereditary Cancer Syndromes in Adolescents and Young Adults With Colorectal Cancer. J Clin Oncol 2015; 33: 3544-3549 [PMID: 26195711 DOI: 10.1200/JCO.2015.61.4503]
- Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K, Bacher J, Bigley C, Nelsen L, 42 Goodfellow PJ, Goldberg RM, Paskett E, Shields PG, Freudenheim JL, Stanich PP, Lattimer I, Arnold M, Liyanarachchi S, Kalady M, Heald B, Greenwood C, Paquette I, Prues M, Draper DJ, Lindeman C, Kuebler JP, Reynolds K, Brell JM, Shaper AA, Mahesh S, Buie N, Weeman K, Shine K, Haut M, Edwards J, Bastola S, Wickham K, Khanduja KS, Zacks R, Pritchard CC, Shirts BH, Jacobson A, Allen B, de la Chapelle A, Hampel H; Ohio Colorectal Cancer Prevention Initiative Study Group. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. JAMA Oncol 2017; 3: 464-471 [PMID: 27978560 DOI: 10.1001/jamaoncol.2016.5194]
- Stigliano V, Sanchez-Mete L, Martayan A, Anti M. Early-onset colorectal cancer: a sporadic or 43 inherited disease? World J Gastroenterol 2014; 20: 12420-12430 [PMID: 25253942 DOI: 10.3748/wjg.v20.i35.12420]

WJCC | https://www.wjgnet.com



# Published by Baishideng Publishing Group Inc 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA Telephone: +1-925-3991568 E-mail: bpgoffice@wjgnet.com Help Desk: https://www.f6publishing.com/helpdesk https://www.wjgnet.com

