RESEARCH ARTICLE

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Early Symptom Patterns by Tumor Laterality, Age at Onset, Stage, and Symptom-to-Treatment Initiation in Patients with Colorectal Cancer

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Abstract

Background: In Indonesia incidence of colorectal cancer (CRC) remains high. Information about early symptoms that can offer clinicians insights for timely diagnosis, prompt referral and quick treatment decisions is very limited. This study aims to examine the pattern of CRC early symptoms and its association with tumor laterality, age at onset, metastatic status, and symptom-to-treatment initiation (STI) duration and delay. **Method:** This cross-sectional study recruits 258 patients diagnosed with CRC between November 2022 and October 2023 from two distinct study databases. Patient baseline characteristics were also obtained from medical records and through interviews at baseline. Symptom-to-treatment initiation (STI) duration was defined as the number of days between the date of the symptom's onset and the date of the first treatment's initiation. Relative risk estimation for metastatic disease and the STI delay, based on tumor laterality and the age at onset group, were estimated using a log-binomial regression for each early symptom. **Result:** Experiencing abdominal mass as an early symptom is significantly associated with metastatic disease, specifically in right-sided CRC cases (relative risk/RR=2.08, 95% confidence interval/CI 1.29–3.37, p=0.003). In all study subjects, the median STI duration was 182 days (2–5,082 days), with more than half of the subjects experiencing an STI delay of >180 days. Experiencing rectal mass as an early symptom is significantly associated with a higher risk of STI delay >180 days in early onset CRC (RR=1.97, 95% CI 1.27–3.06, p=0.003) and left sided-CRC cases (RR=1.54, 95% CI 1.13–2.08, p=0.005). The non-specific early symptom of weight loss is associated with a higher risk of STI delay >180 days in right-sided CRC cases (RR=1.73, 95% CI 1.06–2.84, p=0.029). **Conclusion:** The findings underlined the importance of maintaining a high clinical suspicion, particularly in patients with rectal masses and unexplained weight loss, as they might experience STI delay.

Keywords: Colorectal cancer- symptom-to-treatment initiation- early symptoms- tumor laterality- metastatic disease

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Introduction

Colorectal cancer (CRC) is the third most prevalent malignancy and the second leading cause of cancer deaths worldwide, with the Asian population ranking first in terms of the incidence and mortality, compared to other populations [1]. In Indonesia, CRC ranks as the country's fourth most prevalent cancer incidence, with the fifth-largest in mortality rate in 2020 [2]. Data from our region, Yogyakarta province, shows that CRC incidence ranks second only after breast cancer [3], with an age-adjusted standardized rate (ASR) ranging from 7.03 to 9.20 per 100,000 population [4].

Currently, there is no specific national screening program in place for CRC in Indonesia. Consequently, only a limited number of patients are identified through

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this method, with the majority presenting symptomatically to primary care units. Various symptoms have been described in patients with CRC, with the predominant ones including rectal bleeding, bloody stools, diarrhea, constipation, abdominal or anal pain, and weight loss. However, these symptoms are frequently associated with benign conditions, making CRC among the most frequently missed diagnoses in primary care [5]. This necessitates the treating clinician to make decisions regarding the need for further investigation. There is currently no available test for use in primary care that exhibits an adequate discriminatory basis for referring patients for colorectal cancer assessment. Numerous studies have examined the utility of early symptom patterns and their predictive capabilities in relation to various clinical outcomes [6–8]. Early symptoms can offer valuable insights into the assessment of tumor laterality, consequently aiding in the selection of the most suitable first-line investigative approach. Previous studies have also explored the association between the early symptoms and the clinical stage [8–10]. Early-onset CRC (EOCRC) cases, defined as individuals age ≤50 years, may exhibit distinct patterns of early symptoms when compared to their older counterparts or late-onset CRC (LOCRC) [11].

Multiple studies have explored the relationship between early symptoms and delays in the treatment course of CRC patients. Most of these studies examined a specific time frame of delay, whether it was on its presentation, diagnosis, or treatment [12–14]. Delays for patients with cancer exhibit a complex interaction, as delays at a specific time frame may interact and compound the other throughout the timeline. Assessing symptom-to-treatment initiation (STI) duration, which is the time from the onset of early symptoms to the treatment's commencement, provides a more comprehensive understanding of this complex interaction throughout the patient's treatment journey.

In the Indonesian context, information on early symptoms is very limited despite the fact that CRC is one of the major cancers in the country. In general, only a few studies have examined the pattern and impact of patients' early symptoms upon various clinicopathological characteristics [8]. Therefore, this study aims to analyze the patterns of patients' early symptoms with the patients' demographic and clinicopathologic characteristics and their impact on the STI delay. This information may give clinicians in primary care and referral hospitals insights into referral, diagnostic and treatment decisions, and tailoring therapies.

Materials and Methods

Study participants and design. This study is done cross-sectionally employing secondary data derived from two distinct databases with consecutive sampling method. The first database evaluates the survival of patients diagnosed with CRC between 2016 and 2019. The second database pertains to a study examining the presentation delay in patients diagnosed with CRC between November 2022 and October 2023. All the subjects were enrolled in Dr Sardjito General Hospital, Yogyakarta, a top referral hospital in Yogyakarta province, Indonesia. Most of the patients were referred from district hospitals in the region or the surrounding areas, either for diagnostic or treatment work up.

In the first database patient's age and pathologic data were obtained from electronic health medical records. Clinical data regarding their symptoms and symptom onset were obtained by the treating physician upon patient's admission to the hospital. In the second database face-to-face interviews with a trained research team using semi-structured questionnaires captured information on the early symptoms and the age data. This study obtained pathologic data from the medical records. The present study abstracted data from both studies in October 2023 and encompassed individuals aged 18 years or older.

Data collection and variable definition. We obtained secondary data on primary tumor laterality, age, clinical stage, early symptoms, date of the onset of the symptoms, and date of treatment initiation. The age was defined as the subject's age at diagnosis and further dichotomized into EOCRC (individuals aged ≤50 years) and LOCRC (individuals aged >50 years) [11]. The clinical stage was defined as the clinical presenting stage at diagnosis based on the 8th edition of the AJCC cancer staging system [15] and was categorized into non-metastatic disease (stage I-III) and metastatic disease (stage IV). Information about the stage was not always clear in non-metastatic patients, thus they were classified in one group. Primary tumor laterality was defined as the site of the primary colorectal tumor and categorized into right-sided CRC (tumor residing from caecum to the splenic flexure, including the transverse colon) and left-sided CRC (tumor residing at the descending colon, sigmoid colon, rectum and anal canal) [16].

The early symptom(s) was defined as the symptom that was first experienced at the onset of the disease before presenting to health facility, including the presence of bloody stools/rectal bleeding, change in bowel habits (diarrhea and/or constipation), abdominal mass, rectal mass, bloating/tenesmus, weight loss, abdominal pain, rectal pain, and fatigue. The selection of the early symptoms' category was adapted from the warning signs in the Bowel/Colorectal Cancer Awareness Measure (CAM) questionnaire [17]. Each subject can report more than one early symptom. These symptoms were recorded without considering their severity, frequency, or importance.

The endpoint of this study was the STI duration and delay. STI duration was defined as the number of days between the date of the symptom's onset and the date of the first treatment's initiation. The date of the symptom's onset was self-reported by each subject. In cases where the subjects could not recall the exact date, they were asked to provide at least a month or year. When only a single month was provided, the estimated date was set as the 15th of that month. For month ranges, the midpoint between the 15th of the two months was considered the estimated date. If patients could only provide a year, the estimated date was set as June 30th of that year [18]. The date of the treatment's initiation was retrieved from the medical records.

In the first database, since the data regarding the dates

of the onset of the symptoms date were provided from the history-taking by the treating physicians upon admission, many patients provided the date with the duration (number of weeks, months, or years) from the date of the history-taking. We applied the same method to the data available data, to enable an exact date estimation. In the second database, the data had already been collected using the method above during the interviews.

Statistical analyses

Each subject's baseline characteristics were presented with the frequency and proportion of categorical variables, and its mean and standard deviation or median for numerical variables. The median duration of the STI delay was determined as the cutoff for the categorization of this endpoint variable. Chi-square/Fisher's exact test was conducted to explore the early symptoms' proportional differences based on tumor laterality and age at onset. Relative risk estimation for metastatic disease and the STI delay, for the whole subject and based on tumor laterality and the age at onset group, were estimated using a log-binomial regression for each early symptom. The Mann-Whitney test was conducted to examine the STI duration difference for each early symptom based on tumor laterality and age at onset category. P-values of <0.05 were considered as statistically significant. All the statistical analyses were conducted using STATA software version 17 (Stata Corp., College Station, TX).

Results

Patient characteristics

The subjects' baseline characteristics are presented in Table 1. From 1,277 eligible subjects from the first database, 1,168 subject data were excluded due to incomplete or missing data. From 202 eligible subjects from the second database, 53 subjects were excluded due to incomplete or missing data. Finally, 258 subjects were included in the analysis, which all met the inclusion criteria. The mean age of the subjects included in the analysis was 55.1 ± 11.4 years. A total of 68 (26.4%) subjects presented with right-sided CRC, and 190 (73.6%) subjects presented with left-sided CRC. Most subjects (145, 56.2%) presented with a non-metastatic disease. The median STI duration was 182 days (2–5,082 days). Accordingly, the treatment initiation delay category was rounded and categorized into ≤180 days and >180 days. Most subjects (131, 50.8%) presented with a STI delay of >180 days. The majority of subjects presented with at least more than one symptom (153, 59.3%) and only a few patients that presented asymptomatically (3, 1.16%).

The proportion of early symptoms based on tumor laterality and age at onset of CRC

The proportion of types of early symptoms for right- and left-sided CRC is presented in Table 2. Right-sided CRC has a statistically significant higher proportion for abdominal mass (p=0.049), bloating/tenesmus (p=0.035), and abdominal pain (p=0.001). Left-sided CRC has a statistically significant higher proportion for bloody stools/rectal bleeding (p<0.001), change in

Table 1. Baseline Characteristics of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Variables	Frequency (%) / Mean ± SD / Median (Min-Max)
Age (years)	55.1 ± 11.4
≤50 years (EOCRC)	84 (32.6)
>50 years (LOCRC)	174 (67.4)
Tumor Laterality	
Right-sided CRC	68 (26.4)
Left-sided CRC	190 (73.6)
Stage at Presentation	
Non-metastatic disease	145 (56.2)
Metastatic disease	113 (43.8)
Syptom-to-treatment Initiation Delay (days)	182 (2–5,082)
≤180 days	127 (49.2)
>180 days	131 (50.8)
Bloody stool/rectal bleeding	
No	159 (61.6)
Yes	99 (38.4)
Change in bowel habits (diarrhea/constipation)	
No	106 (41.1)
Yes	152 (58.9)
Abdominal mass	
No	238 (92.2)
Yes	20 (7.8)
Rectal mass	
No	241 (93.4)
Yes	17 (6.6)
Bloating/tenesmus	
No	224 (86.8)
Yes	34 (13.2)
Weight loss	
No	222 (86.0)
Yes	36 (14.0)
Abdominal pain	
No	157 (60.8)
Yes	101 (39.2)
Rectal pain	
No	240 (93.0)
Yes	18 (7.0)
Fatigue	
No	247 (95.7)
Yes	11 (4.3)
Number of early symptoms	2 (0–5)
0	3 (1.2)
1	102 (39.5)
>1	153 (59.3)

Abbreviations: SD,standard deviation; Min,minimum; Max,maximum; EOCRC,early-onset CRC; LOCRC,late-onset CRC; CRC,colorectal cancer

Table 2. The Proportion of Early Symptoms based on Tumor Laterality and Age Onset of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Early symptom	Tumor Laterality		p-value	Age Onset		p-value
	Right-sided CRC	Left-sided CRC		EOCRC	LOCRC	
	n (%)	n (%)		n (%)	n (%)	
Bloody stool/rectal bleeding	11 (16.2)	88 (46.3)	<0.001*	32 (38.1)	67 (38.5)	0.949
Change in bowel habits	30 (44.1)	122 (64.2)	0.004*	47 (55.9)	105 (60.3)	0.502
Abdominal mass	9 (13.2)	11 (5.8)	0.049*	8 (9.5)	12 (6.9)	0.460
Rectal mass	0 (0)	17 (8.9)	0.008*	6 (7.1)	11 (6.3)	0.803
Bloating/tenesmus	14 (20.6)	20 (10.5)	0.035*	11 (13.1)	23 (13.2)	0.978
Weight loss	8 (11.8)	28 (14.7)	0.544	14 (16.7)	22 (12.6)	0.382
Abdominal pain	38 (55.9)	63 (33.2)	0.001*	31 (36.9)	70 (40.2)	0.608
Rectal pain	1 (1.5)	17 (8.9)	0.049*	6 (7.1)	12 (6.9)	0.942
Fatigue	3 (4.4)	8 (4.2)	1,000	4 (4.8)	7 (4.0)	0.752

*, p-value<0.05; Abbreviations: CRC, colorectal cancer; EOCRC, early-onset colorectal cancer; LOCRC, late-onset CRC

Table 3. The Relative Risk of Metastatic Disease based on the Initial Early Symptom and Tumor Laterality of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Early Symptom	All Cases (n=258)			Right-sided CRC (n=68)			Left-sided CRC (n=190)		
	Metastatic Disease (%)	RR (95% CI)	p-value	Metastatic Disease (%)	RR (95% CI)	p-value	Metastatic Disease (%)	RR (95% CI)	p-value
Bloody stool/rectal bleeding	42.4	0.95 (0.71–1.27)	0.727	54.5	1.35 (0.72–2.52)	0.345	40.9	0.87 (0.63–1.20)	0.398
Change in bowel habits	44.7	1.05 (0.79–1.40)	0.717	40.0	0.89 (0.51–1.57)	0.697	45.9	1.11 (0.79–1.57)	0.535
Abdominal mass	65.0	1.55 (1.08–2.20)	0.016*	77.8	2.08 (1.29–3.37)	0.003*	54.5	1.25 (0.71–2.20)	0.436
Rectal mass	29.4	0.66 (0.31–1.39)	0.271	-	-	-	29.4	0.64 (0.30–1.37)	0.253
Bloating/tenesmus	44.1	1.01 (0.67–1.51)	0.968	42.9	1.01 (0.51–1.98)	0.986	45.0	1.02 (0.61–1.70)	0.940
Weight loss	44.4	1.02 (0.69–1.51)	0.933	50.0	1.20 (0.56–2.55)	0.636	42.9	0.96 (0.61–1.53)	0.877
Abdominal pain	44.5	1.03 (0.78–1.36)	0.844	42.1	0.97 (0.56–1.69)	0.919	46.0	1.06 (0.76–1.48)	0.720
Rectal pain	44.4	1.01 (0.59–1.74)	0.954	-	-	-	47.1	1.07 (0.63–1.82)	0.800
Fatigue	36.4	0.82 (0.37–1.82)	0.633	33.3	0.77 (0.15–3.93)	0.757	37.5	0.84 (0.34–2.09)	0.712

* p <0.05; Abbreviations: CRC, colorectal cancer; RR,relative risk; CI,confidence interval

bowel habits (p=0.004), rectal mass (p=0.008), and rectal pain (p=0.049). The weight loss and fatigue proportion did not significantly differ between right- and left-sided CRC. The proportion of types of early symptoms for EOCRC and LOCRC did not differ significantly.

Risk of metastatic disease based on tumor laterality and age at onset group for each early symptom

The relative risk estimation of metastatic disease based on tumor laterality for each early symptom is presented in Table 3. For all the cases accounted for, the

Table 4. The Relative Risk of Metastatic Disease based on the Initial Early Symptom and Age Onset of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Early Symptom	All Cases (n=258)			Early-onset CRC (n=84)			Late-onset CRC (n=174)		
	Metastatic Disease (%)	RR (95% CI)	p-value	Metastatic Disease (%)	RR (95% CI)	p-value	Metastatic Disease (%)	RR (95% CI)	p-value
Bloody stool/rectal bleeding	42.4	0.95 (0.71–1.27)	0.727	43.7	1.08 (0.65–1.81)	0.760	41.8	0.89 (0.63–1.27)	0.529
Change in bowel habits	44.7	1.05 (0.79–1.40)	0.717	40.4	0.93 (0.56–1.55)	0.794	46.7	1.11 (0.79–1.57)	0.551
Abdominal mass	65.0	1.55 (1.08–2.20)	0.016*	62.5	1.58 (0.86–2.90)	0.136	66.7	1.54 (0.99–2.39)	0.052
Rectal mass	29.4	0.66 (0.31–1.39)	0.271	50.0	1.22 (0.52–2.83)	0.646	18.2	0.39 (0.11–1.38)	0.144
Bloating/tenesmus	44.1	1.01 (0.67–1.51)	0.968	27.3	0.62 (0.23–1.69)	0.352	52.2	1.19 (0.77–1.84)	0.421
Weight loss	44.4	1.02 (0.69–1.51)	0.933	42.9	1.03 (0.53–2.01)	0.921	45.4	1.01 (0.62–1.66)	0.949
Abdominal pain	44.5	1.03 (0.78–1.36)	0.844	35.5	0.78 (0.45–1.37)	0.393	48.6	1.15 (0.82–1.60)	0.411
Rectal pain	44.4	1.01 (0.59–1.74)	0.954	33.3	0.79 (0.25–2.51)	0.687	50.0	1.12 (0.62–2.03)	0.696
Fatigue	36.4	0.82 (0.37–1.82)	0.633	25.0	0.59 (0.10–3.27)	0.545	42.9	0.95 (0.40–2.28)	0.916

* p <0.05; Abbreviations: CRC, colorectal cancer; RR, relative risk; CI, =confidence interval

Table 5. The Relative Risk of Symptom-to-Treatment Delay of >180 Days based on the Initial Early Symptom and Tumor Laterality of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Early Symptom	All Cases (n=258)			Right-sided CRC (n=68)			Left-sided CRC (n=190)		
	Delay >180 Days (%)	RR (95% CI)	p-value	Delay >180 Days (%)	RR (95% CI)	p-value	Delay >180 Days (%)	RR (95% CI)	p-value
Bloody stool/rectal bleeding	51.5	1.02 (0.80–1.31)	0.851	36.4	0.74 (0.32–1.69)	0.475	53.4	1.05 (0.80–1.37)	0.738
Change in bowel habits	46.0	0.80 (0.63–1.01)	0.066	40.0	0.76 (0.45–1.29)	0.312	47.5	0.79 (0.60–1.03)	0.082
Abdominal mass	45.0	0.88 (0.53–1.45)	0.610	55.6	1.21 (0.64–2.32)	0.557	36.4	0.68 (0.31–1.51)	0.351
Rectal mass	76.5	1.56 (1.16–2.09)	0.003*	-	-	-	76.5	1.54 (1.13–2.08)	0.005*
Bloating/tenesmus	52.9	1.05 (0.74–1.48)	0.782	42.9	0.89 (0.46–1.73)	0.732	60.0	1.17 (0.80–1.73)	0.420
Weight loss	55.6	1.11 (0.81–1.53)	0.519	75.0	1.73 (1.06–2.84)	0.029*	50.0	0.95 (0.64–1.42)	0.813
Abdominal pain	52.5	1.06 (0.83–1.35)	0.660	52.6	1.31 (0.77–2.24)	0.312	52.4	1.01 (0.75–1.34)	0.957
Rectal pain	50.0	0.98 (0.61–1.59)	0.946	-	-	-	52.9	1.02 (0.63–1.63)	0.942
Fatigue	45.4	0.89 (0.46–1.72)	0.731	66.7	1.44 (0.62–3.35)	0.392	37.5	0.71 (0.29–1.76)	0.460

* p <0.05; Abbreviations: CRC, colorectal cancer; RR, relative risk; CI, confidence interval

Table 6. The Relative Risk of Symptom-to-Treatment Initiation Delay of >180 Days based on the Initial Early Symptom and Age Onset of Patients with Colorectal Cancer in Yogyakarta between 2022-2023 (n=258)

Early Symptom	All Cases (n=258)			Early-onset CRC (n=84)			Late-onset CRC (n=174)		
	Delay >180 Days (%)	RR (95% CI)	p-value	Delay >180 Days (%)	RR (95% CI)	p-value	Delay >180 Days (%)	RR (95% CI)	p-value
Bloody stool/rectal bleeding	51.5	1.02 (0.80–1.31)	0.851	43.7	0.95 (0.58–1.55)	0.831	55.2	1.05 (0.80–1.40)	0.708
Change in bowel habits	46.0	0.80 (0.63–1.01)	0.066	44.7	0.97 (0.61–1.56)	0.908	46.7	0.73 (0.56–0.96)	0.024*
Abdominal mass	45.0	0.88 (0.53–1.45)	0.610	12.5	0.26 (0.04–1.63)	0.149	66.7	1.27 (0.83–1.94)	0.271
Rectal mass	76.5	1.56 (1.16–2.09)	0.003*	83.3	1.97 (1.27–3.06)	0.003*	72.7	1.39 (0.94–2.06)	0.095
Bloating/tenesmus	52.9	1.05 (0.74–1.48)	0.782	54.5	1.24 (0.68–2.26)	0.474	52.2	0.97 (0.64–1.48)	0.897
Weight loss	55.6	1.11 (0.81–1.53)	0.519	57.1	1.33 (0.79–2.26)	0.286	54.5	1.02 (0.68–1.54)	0.911
Abdominal pain	52.5	1.06 (0.83–1.35)	0.660	51.6	1.24 (0.78–1.98)	0.361	52.9	0.98 (0.74–1.30)	0.898
Rectal pain	50.0	0.98 (0.61–1.59)	0.946	50.0	1.11 (0.48–2.57)	0.800	50.0	0.93 (0.52–1.67)	0.810
Fatigue	45.4	0.89 (0.46–1.72)	0.731	100.0	-	-	14.3	0.26 (0.04–1.60)	0.146

* p <0.05; Abbreviations: CRC, colorectal cancer; RR, relative risk; CI, confidence interval

presence of abdominal mass as an early symptom was significantly associated with a higher risk of metastatic disease (RR=1.55, 95% CI 1.08–2.20, p-value=0.016). In the subgroup analysis of subjects with right-sided CRC, the presence of abdominal mass as an early symptom was significantly associated with a higher risk of metastatic disease (RR=2.08, 95% CI 1.29–3.37, p-value=0.003). In subjects with left-sided CRC, none of the early symptoms has reached statistical significance for metastatic disease. The relative risk estimation of metastatic disease based on age at onset of CRC for each early symptom is presented in Table 4. For both EOCRC and LOCRC subgroup analysis, none of the early symptoms had reached statistical significance for metastatic disease.

Symptom-to-treatment initiation delay and duration based on tumor laterality and age at onset group for each early symptom

The relative risk estimation of STI delay (>180 days) based on tumor laterality for each early symptom, is presented in Table 5. For all the cases accounted for, the presence of rectal mass as an early symptom was significantly associated with a higher risk of >180 days of STI delay (RR=1.56, 95% CI 1.16–2.09, p-value=0.003). In the subgroup analysis of subjects with right-sided CRC, the presence of weight loss as an early symptom was significantly associated with a higher risk of STI delay >180 days (RR=1.73, 95% CI 1.06–2.84, p-value=0.029). In the subgroup analysis of subjects with left-sided CRC, the presence of rectal mass as an early symptom was significantly associated with a higher risk of STI delay >180 days (RR=1.54, 95% CI 1.13–2.08, p-value=0.005).

The relative risk estimation of STI delay (>180 days) based on age at onset of CRC for each early symptom, is presented in Table 6. In subjects with EOCRC, the presence of rectal mass as an early symptom was significantly associated with a higher risk of STI delay >180 days (RR=1.97, 95% CI 1.27–3.06, p-value=0.003). In subjects with LOCRC, the presence of a change in bowel habits as an early symptom was significantly associated with a lower risk of STI delay >180 days (RR=0.73, 95% CI 0.56–0.96, p-value=0.024).

The STI for each early symptom based on tumor laterality, is presented in Supplementary Table 1. For the right-sided CRC, none of the early symptoms has achieved a statistically significant difference in the analysis. For the left-sided CRC, subjects who reported the presence of change in bowel habits as an early symptom were significantly associated with a shorter STI (median 168.5 days vs. 250 days; p=0.030). Furthermore, subjects who reported the presence of a rectal mass as an early symptom were significantly associated with a longer duration of STI delay (median 403 days vs. 174 days; p=0.006).

The STI for each early symptom based on age at onset, is presented in Supplementary Table 2. For the EOCRC, subjects who reported the presence of an abdominal mass, they had a statistically significant shorter STI (median 63.5 days vs. 176 days; p=0.011). For the LOCRC subjects, there was a statistically significant shorter STI in the subjects who reported the presence of a change in bowel habits (median 165 days vs. 242 days, p=0.004) and fatigue (median 97 days vs. 194 days, p=0.021).

Discussion

To our knowledge, this is the first study in Indonesia that examined CRC patients' early symptoms and their association with tumor laterality, age, stage, and STI duration. The study identified the three most common early symptoms, namely change in bowel habits, abdominal pain, and rectal bleeding or bloody stools. The median duration of STI was 182 days, with 193 days for right-sided CRC and 170 days for left-sided CRC. These findings are very informative for the healthcare system in Indonesia. By 2022, 90.73% of the Indonesian population had enrolled in the National Health Insurance program [19]. As per the regulatory requirement, individuals covered by the insurance are required to initially report their symptoms to a primary care facility before being referred to a secondary or tertiary hospital for in-depth investigation as indicated. Data regarding the early symptoms of CRC and its association with tumor laterality, the stage at presentation, and STI duration offer valuable insights to clinicians for referral decisions, particularly those in primary care units. It also provides clear details for policymakers to enhance the referral system in Indonesia, contributing to more effective and timely healthcare interventions for CRC.

The observed pattern of early symptoms in the present study is comparable when only considering EOCRC patients in this study and aligns with prior studies' findings [20,21]. As indicated in a previous systematic review, rectal bleeding is not an exclusive symptom among young patients with CRC. In whole CRC cases, the initial occurrence of rectal bleeding yields a positive predictive value (PPV) of 5.0% for CRC. When appearing alongside a change in bowel habits or when mixed with stools, the PPV increases to 10.5% and 11.0%, respectively [22]. Guidelines provided by the American Academy of Family Physicians recommend considering colonoscopy in individuals with unexplained gastrointestinal bleeding, iron deficiency anemia, or unexplained significant diarrhea [23]. Although there is no provision for colonoscopy coverage by the national health insurance for screening CRC cases in Indonesia, our data makes a strong case to prepare for a proper screening's implementation in the future.

We found that bloody stools/rectal bleeding, a change in bowel habits, rectal mass, and rectal pain are significantly higher in left-sided CRC, which supported previous studies [24,25]. Tumor laterality is an emerging prognostic and predictive factor for CRC outcomes, with patients with right-sided CRC having a poorer chemotherapy response, overall survival, and progression-free survival [26,27]. The presence of early symptoms associated with right-sided CRC can warrant the clinicians in primary care units considering the urgency for referral and further investigation. Similar early symptom patterns in our EOCRC and LOCRC cases supported previous findings [28].

Our study demonstrated that the median duration of STI was 182 (2–5082) days, with 193 (2–1746) days for right-sided CRC and 170 (3–5082) days for left-sided CRC. This duration was longer compared to previous studies from the Netherlands, which was 138 (2-1995) days [13], or Spain, which was 155 (84.0-283.5) days [12], and China (82.37 days for colon cancer and 114.44 days for rectal cancer) [14]. The duration and delay of STI exhibited a complex interaction with various factors that may affect its duration. Various plausible causes may affect the STI duration. Patients might delay their presentation due to the stigma of the social impact of CRC, low awareness of CRC symptoms, and trying traditional/complementary/alternative medicine before presentation [29]. Patient presentation delays can also originate from fear and denial of the diagnosis, exacerbated by societal and family perceptions of cancer [30]. Previous studies of cancer patients in Indonesia have also highlighted that a significant proportion of patients experienced misdiagnosis and time-consuming referrals, followed by long queues due to the limited healthcare capacity [31,32]. Furthermore, indirect medical costs not covered by the National Health Insurance, such as transportation and accommodation, are also perceived as barriers to seeking timely diagnostic workups and treatment [33]. Regarding the fact that the longer diagnostic interval may impact on the patients' survival [34–36], it is essential to strengthen public awareness of CRC symptoms, stimulate individuals to visit their health facility upon the symptom's presentation earlier, and improve the health referral system to accommodate a faster diagnostic and treatment initiation process.

We also demonstrated that left-sided CRC and LOCRC patients with early symptoms of a change in bowel habits have a shorter STI duration. Especially in LOCRC, it is also associated with a lower risk of experiencing an STI delay of >180 days. This finding contrasts with a previous study that indicated a change in bowel habits as a non-specific symptom, specifically increased the presentation duration [37]. This finding might be due to in our subjects, we observed that older patients often presented with poor performance status and, therefore, are more prone to complications from constipation or diarrhea symptoms, such as dehydration and poor nutritional status.

These conditions can result in an earlier presentation and often to the emergency department, prompting clinicians to conduct quicker diagnostic and treatment procedures. Presenting with older age might indicate to clinicians the need to run investigations for possible CRC cases. Another possible explanation is that patients with left-sided CRC, who experience the early symptom of a change in bowel habits, might also experience other alarming symptoms, such as bloody stools, rectal bleeding, rectal pain, or rectal mass, which makes the investigation more directed, leading to shorter symptom-to-treatment duration.

Having an abdominal mass as an early symptom in EOCRC patients is associated with a shorter STI duration, which aligns with previous findings [14]. EOCRC patients may have different health information-seeking behavior, with higher utilization of information from online resources compared to LOCRC patients. Presenting with alarming symptoms such as an abdominal mass might drive this subpopulation to proactively seek information and treatment, while LOCRC patients are seeking and putting more reliance on healthcare providers first [38]. Having EOCRC patients presenting with abdominal masses might also drive clinicians to give more timely diagnostic procedures and aggressive treatment since young patients mostly do not have any other comorbidities and present with a better functional status. The presence of abdominal mass is also associated with the risk of metastatic disease in right-sided CRC patients since the presence of abdominal mass might indicate a further progression of colon cancer growth. The identification of symptoms associated with metastatic disease is critical. Prior local studies have shown a poor median overall survival of 13 months in this patient population, with an estimated 5-year overall survival rate of only 16.1% [39].

Patients experiencing weight loss as a presenting symptom in this study are associated with higher risk of STI delay >180 days, specifically in right-sided CRC cases, as also reported by other study in presentation delay [13]. Significant weight loss is usually realized after a considerable time, prolonging the presentation duration. Presenting with significant weight loss, as a non-specific symptom, is also associated with a missed diagnostic opportunity for CRC [40]. With significant weight loss, patients are also prone to have a poor nutritional and functional status, which might hinder treatment initiation. Experiencing fatigue as an early symptom, which is also a non-specific symptom, is surprisingly found to be associated with a shorter duration of STI, specifically in LOCRC cases. This has never been observed by other previous studies, and may be a unique attribute of the local cases.

We found that left-sided CRC patients, and also EOCRC cases as a general, who experienced early symptoms of rectal mass have a longer STI duration and a higher risk of STI delay of >180 days. Rectal mass is one of the anorectal complaints that are often misdiagnosed as hemorrhoids because of similar presentations [41]. Presenting at a younger age might be overlooked for further investigation. In countries with established provisions for CRC screening, patients presenting with a rectal mass, including hemorrhoids, can undergo CRC screening strategies that are less likely to cause a misdiagnosis [42]. Since no CRC screening strategies provision has been established in Indonesia, many patients presenting with rectal masses will undergo surgery. With the low index of suspicion and the possibility of mass recurrence and repeated surgery, the diagnostic and treatment duration for undergoing proper CRC management can be prolonged.

This study's strength lies in conducting subgroup analyses based on tumor laterality and age at the onset of CRC, exploring how these factors may influence outcomes, and providing insights for clinical practice. Nonetheless, several limitations warrant acknowledgment. As a single institution study conducted in a referral hospital, this study's results should only be generalized cautiously. The reliance on self-reported dates for symptom onsets for calculating onset-to-treatment duration and for the types of early symptoms experienced might be affected by recall bias. This limitation particularly affects the first database, which is solely derived from medical records. In the second database, the potential of this recall bias is mitigated through face-to-face interviews, with precision measures outlined in the methodology. There remains an inherent challenge of data heterogeneity arising from utilizing two databases, which affects data quality variability. Furthermore, different inclusion periods from the two databases might also affect the STI duration, compounded by the impact of the Coronavirus disease 2019 (COVID-19) pandemic during the inclusion of the second database.

In conclusion, the early symptoms of rectal mass and weight loss are associated with an increased risk of STI delay, while abdominal mass is associated with an increased risk of metastatic disease. The early symptoms can provide insights into the pattern of tumor laterality, the stage, and STI delay. Recognizing this pattern during a patient's presentation in primary care units or the referral hospitals can help patients receive timely diagnostic opportunities and appropriate treatment. Heightened consideration must be maintained, especially in patients with the presence of rectal masses and unexplained weight loss, since these patients might have a longer STI duration and experience delays possibly due to misdiagnosis. This finding also urges the provision of CRC screening regulations in Indonesia, which might help the early recognition of CRC cases and timely treatment.

Author Contribution Statement

All authors contributed equally in this study.

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