Cross-sectional Study

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The analysis between clinicopathological aspect of early-onset vs. late-onset colorectal cancer and mortality rate: a cross-sectional study

Kiki Lukman, MD, MSc, PhD[a,*], Andi Mulyawan, MD[a], Annisa Dewi Nugrahani, MD[b], Reno Rudiman, MD, MSc, PhD[a], Etis Primastari, MD[c]

Introduction: Early-onset colorectal cancer (CRC) has different clinical and pathological characteristics compared with late-onset CRC. Mortality rate as a postoperative outcome is a patient's postoperative outcome considered based on the state of life or death. The objective of this research is to analyse the comparison between clinicopathological aspect of early-onset vs. late-onset CRC as well as their correlation with the mortality rate in Indonesia to support global data.

Material and methods: The authors performed a case-control study on 170 subjects with CRC from November 2021 to November 2022 in a Tertiary Hospital in Bandung. Data were extracted from electronic medical records CRC Registry. Bivariate and correlation analyses were used to analyse the difference between variables using IBM SPSS 24.0. *P* less than 0.05 was considered statistically significant.

Results: Anaemia and tumour location variables were significantly different in the early-onset group compared with the late-onset group ($P < 0.001$). It was also found that anaemia ($P < 0.001$), pathological features ($P < 0.001$), and tumour location ($P = 0.013$) had significantly low correlation with onset of CRC ($r = 0.325$; $r = 0.397$; $r = 0.342$, respectively).

Conclusion: There is no statistically significant correlation between the clinicopathological features of CRC in both onset and mortality rates in this study.

Keywords: clinicopathology, early-onset colorectal cancer, late-onset colorectal cancer, mortality rate

Introduction

Colorectal cancer (CRC) is the third most common and has the second highest mortality rate worldwide when compared with other types of cancer. CRC is classified into two types based on the patient's age at the time of diagnosis: early-onset colorectal cancer (EOCRC) and late-onset colorectal cancer (LOCRC)[1]. According to the Amsterdam criteria, EOCRC refers to subjects diagnosed after the age of 50, whereas LOCRC refers to subjects diagnosed before the age of 50. While the majority of CRC cases are in older people, the incidence of EOCRC tends to increase globally[1,2].

HIGHLIGHTS

- Early-onset colorectal cancer has different clinicopathological characteristics compared with late-onset colorectal cancer
- Mortality rate is a postoperative outcome based on the condition of life or death
- Data regarding clinicopathological aspect of colorectal cancer and mortality rate are lacking

EOCRC has distinct clinical characteristics when compared to LOCRC. The majority of early-onset patients exhibit red flags such as unexplained anaemia, rectal bleeding, and changes in bowel habits[3]. LOCRC has a more diverse range of symptoms including rectal bleeding/haematochezia, melena, constipation, nausea, diarrhoea, abdominal pain, presence of an abdominal mass, anaemia, unexplained fatigue, and weight loss. In LOCRC, patients seek medical attention earlier since their symptoms are more distressing. Thus, LOCRC is typically diagnosed at an early stage[3–5]. The main reason for delayed diagnosis is mainly exclusion of people under the age of 45 from the screening programs target unless presence of family history of colorectal cancer. In many cases, EOCRC is diagnosed with metachronous cancer, indicating more advanced stages such as stage III and stage IV. EOCRC is more likely to cause metastases during the course of the disease compared to LOCRC[6–8].

When compared to LOCRC, EOCRC has different histopathological characteristics. EOCRC does not have precursor adenomatous lesions and more signet ring cells are found, whereas late-onset has fewer signet ring cells and can have a rare subtype of signet ring adenocarcinoma. A study in Indonesia discovered that the histopathological features of CRC differed

Departments of [a]Surgery, [b]Obstetrics and Gynaecology and [c]Anatomical Pathology, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia

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**Corresponding author. Address: Department of Surgery, Faculty of Medicine, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia; Pasteur No. 38, Bandung, West Java, Indonesia 40161. Tel: (+6222) 2551111; fax: (+6222) 2032216. E-mail address: kiki.lukman@unpad.ac.id (K. Lukman).*

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from previous studies conducted elsewhere. In Dr. Hasan Sadikin General Hospital Bandung, the most frequent histopathological features of subjects aged younger than 40 years were well-differentiated, moderately differentiated, poorly differentiated adenocarcinoma, and signet ring cells[6]. The majority of the histopathological features, namely adenocarcinoma (89.8%), were similar to those of LOCRC[9].

Surgery is the primary modality for early-stage cancer with curative goals for both onsets. Many factors influence surgical success rates, including clinical conditions, histopathological features, patient comorbidities, and postoperative complications. Subjects with comorbidities are more likely to die after surgery[1,10]. The postoperative mortality rate is a patient's postoperative outcome based on the condition of life or death[11]. There have only been studies that compared the clinicopathological characteristics of EOCRC vs. LOCRC[12,13], but there is a lack of data that examines the relationship between these clinicopathological aspects and postoperative outcomes such as mortality rates, particularly in developing countries like Indonesia. Therefore, this study aimed to analyse the comparison of clinicopathological features between EOCRC and LOCRC as well as the correlation between CRC onset and mortality rate in Dr. Hasan Sadikin Hospital, Bandung as local data that can be used to support global data.

Materials and methods

Design of the study and subject recruitment

This was a cross-sectional study designed to examine the comparison between the clinicopathological aspect of EOCRC vs. LOCRC as well as their correlation with the mortality rate in CRC subjects as the primary outcomes. The work has been reported in line with the STROCCS guideline[14] with Research Registry UIN researchregistry8748. The data used were secondary data extracted from the medical records of subjects at CRC Registry, Dr. Hasan Sadikin General Hospital Bandung, starting from November 2021 to November 2022 until the minimum number of samples was fulfilled using a consecutive sampling method.

(1) CRC subjects who had been diagnosed clinically, radiologically, and pathologically at Dr. Hasan Sadikin General Hospital Bandung and (2) the subjects that had definitive therapies only at Dr. Hasan Sadikin General Hospital Bandung were included in this study. The subjects with incomplete medical record data were excluded from this study.

Ethical aspect and research approval

The data collection from CRC Registry was categorized as low risk as it was conducted using electronic medical record data. After receiving approval and recommendations from the Ethics Committee Review Board of Hasan Sadikin General Hospital—Faculty of Medicine, Universitas Padjadjaran, all procedures were performed in accordance with applicable guidelines and regulations, with reference number LB.02.01/X.6.5/328/2022.

Data analysis

Comparison analysis would be carried out using the independent *t*-test, χ^2, Fisher's Exact, Mann–Whitney, and Kolmogorov–Smirnov test depending on the distribution of data. Correlation analysis would be utilized as the analysis between variables. A *P* value of less than 0.05 was considered statistically significant.

Results

Subject characteristics

As shown in Table 1, this study involved 170 subjects aged 20–89 years with a mean age of 52.35 ± 14.31 years. In this study,

Table 1
Subject characteristics.

Variables	Total subjects ($n = 170$)	Percentage (%)
Age (years)		
Mean ± SD	52.35 ± 14.31	
Median (Min–Max)	51.5 (20–89)	
Sex		
Male	73	42.94
Female	97	57.06
Clinical features		
Hematochezia	83	48.82
Melena	1	0.59
Abdominal pain	40	23.53
Constipation	134	78.82
Abdominal mass	3	1.76
Diarrhoea	24	14.12
Anaemia	59	34.71
Pathological features		
Adenocarcinoma	124	72.94
Mucinous adenocarcinoma	4	2.35
Signet ring cells	20	11.76
Others	22	12.94
Stages		
Stage 0	1	0.59
Stage I	17	10.00
Stage IIA	6	3.53
Stage IIB	14	8.24
Stage IIC	0	0.00
Stage IIIA	32	18.82
Stage IIIB	36	21.18
Stage IIIC	3	1.76
Stage IV	61	35.88
Tumour locations		
Iliocecal	1	0.59
Caecum	0	0.00
Ascenden colon	21	12.35
Transverse colon	10	5.88
Descenden colon	14	8.24
Sigmoid colon	23	13.53
Rectosigmoid	17	10.00
Rectum	75	44.12
Anorectal	1	0.59
Colon	1	0.59
Cervical	1	0.59
Combination	6	3.53
Outcome		
Life	159	93.53
Death	11	6.47
Onset		
Early	72	42.35
Late	98	57.65

In descriptive data, nominal-categoric data (age) is presented in the form of mean ± SD and median (min–max) while the others are presented in the form of percentages.
Max, maximum; Min, minimum.

there were more female subjects (57.06%) than male subjects (42.94%). Of all subjects, the majority of subjects (134 subjects) complained of difficult bowel movements or constipation (78.82%). In addition, in general, subjects also experienced hematochezia (48.82%), anaemia based on clinical symptoms and laboratory results (34.71%), abdominal pain (23.53%), and diarrhoea in 14.12% patients.

Based on pathological features, 124 subjects (72.94%) had adenocarcinoma features and 20 subjects (26.67%) had signet ring cell carcinoma. Twenty-two subjects (12.94%) had other pathological features [benign (10), unspecified carcinoma (9), malignant melanoma (2), and mixed adeno-neuroendocrine carcinoma (1)]. Based on the clinical stage, the majority of subjects were in stage IV (35.88%) and stage IIIB (21.18%). As for the tumour locations, most of the patient's tumours (75 subjects) were located in the rectum (44.12%), then 23 subjects in the sigmoid colon (13.53%), 21 subjects in the ascending colon (12.35%), 17 subjects (10.00%) in the rectosigmoid, 14 subjects in the descending colon (8.24%), 10 subjects (5.88%) in the transverse colon, six subjects (3.53%) had mixed tumour locations. Of the 170 subjects, 159 survived (93.53%) survived after surgery and 11 subjects died (6.47%). The study subjects also consisted of 72 EOCRC subjects and 98 LOCRC subjects.

Comparative analysis of clinicopathological features between onset

A comparative analysis (bivariate analysis) was performed as shown in Table 2. It was found that anaemia and tumour location were significantly different in the early-onset group compared with the late-onset group ($P < 0.001$) while the other variables were not.

Correlation analysis between variables

It was found that anaemia ($P < 0.001$), histopathological features ($P < 0.001$), and tumour location ($P = 0.013$) had significantly low correlation (respectively $r = 0.325$; $r = 0.397$; respectively). $r = 0.342$ respectively) for EOCRC and LOCRC as shown in Table 3. There is no statistically significant correlation between the clinicopathological features of CRC in both onset and mortality rates in this study.

Discussion

In this study, EOCRC had the most tumour locations in the rectum and proximal colon while LOCRC had the most tumour locations in the distal colon. This study demonstrated significantly more clinical anaemia in EOCRC patients with predominant tumour locations in the proximal colon relative to the distal colon and rectum. These findings confirm the results of several previous studies[5,15]. The faecal occult blood test screening has been reported to have high sensitivity for detecting tumours of the colon and rectum, indicating that both colon and rectal cancers frequently bleed into the lumen. Although the distinction between proximal and distal colorectal cancer may be mechanically related to bleeding, other effects such as immunological mechanisms must also be considered as well[5,15,16].

Proximal colon tumours frequently exhibit distinct genetic features (in particular, the BRAF V600E mutation and mismatch repair (MMR) deficiency/mismatch repair deficiency), which result from the development of serrated precursor lesions via the serrated route of colorectal carcinogenesis[15,17]. Anaemia is very common in patients with MMR-deficient tumours (72.5%), and both microcytic and normocytic anaemia were more common in the MMR-deficient subgroup. MMR-deficient tumours, on the other hand, were mostly found in the proximal colon. Furthermore, in multiple linear regression, MMR deficiency was not a significant predictor of blood haemoglobin levels. Further studies are needed to accurately analyse blood haemoglobin levels in MMR deficiency cases at various tumour sites.

Blood haemoglobin levels in colorectal cancer are inversely related to systemic inflammation. High serum IL-8, and low serum albumin, are mainly associated with normocytic anaemia. IL-8 is a proinflammatory chemokine associated with the promotion of neutrophil chemotaxis and degranulation. Serum IL-8 levels are elevated in many malignancies and IL-8 is thought to be an important contributor to cancer-associated inflammation. Serum albumin levels reflect systemic inflammation since albumin synthesis decreases in response to IL-6. These findings support the notion that, in particular, normocytic anaemia in colorectal cancer is associated with systemic inflammation. These associations may also have therapeutic significance, as modulation of the inflammatory response has shown some potencies of inflammatory anaemia treatment[5,15,17].

In both the EOCRC and LOCRC groups, the patient mortality rate increased in advanced stages (stage IV, IIIA, and IIIB). This is consistent with previous research. The 5-year survival rate for colorectal cancer ranges from 77% in stage I cases to only 2% in stage IV cases. The 5-year life expectancy in developed countries is over 60%, but it is only 50% in Iran. However, although not statistically significant ($P = 0.76$), 5-year survival for all cases of CRC increased from 42.7% to 44.6%[18]. Meanwhile, according to data from other Indonesian centres, 43% of the 142 CRC patients included in the study survived during the observation period (5 years). According to the findings, subjects aged 45 years had a higher 5-year survival rate (47.4% vs. 41.3%)[19]. The study, however, discovered no statistically significant relationship between age and survival. This finding contradicts the findings of Chao-Hsien and colleagues, who discovered that age was a predictor of survival and prognosis in colorectal cancer[19]. Early-stage cancer has a better prognosis, whereas advanced stage cancer develops very quickly and aggressively, reducing survival rates[5,15–19].

The main reason for delayed diagnosis of EOCRC is mainly exclusion of those below 45 years old from the screening programs target unless presence of family history of colorectal cancer as mentioned before. EOCRC is frequently characterized by DNA methylation loss, increased KRAS mutation rate, and familial syndrome. Some studies in Western Europe, North America, and Asia found that the majority of EOCRCs have hereditary microsatellite instability features and high microsatellite instability. EOCRC is a hereditary disease that is linked to Lynch syndrome or familial adenomatous polyposis[5,15–20]. In contrast, studies in Indonesia on immunohistochemical examination to see microsatellite instability and p53 expression among colorectal cancer patients aged older than 40 years with younger than or equal to 40 years showed that high p53 expression was associated with a low proportion of microsatellite instability status[21,22]. As a result, it is possible to conclude that the contributing factor is the sporadic carcinogenesis pathway, which is consistent with other studies showing that in EOCRC, there is a

Table 2.

Comparative analysis of clinicopathological features between onset.

	Early onset		Late onset		
Variabel	**Subjects ($n=72$)**	**Percentage (%)**	**Subjects ($n=98$)**	**Percentage (%)**	***P* value**
Sex					0.111
Male	36	50.00	37	37.76	
Female	36	50.00	61	62.24	
Clinical features					
Hematochezia	39	54.17	44	44.90	0.232
Melena	0	0.00	1	1.02	1.000
Abdominal pain	16	22.22	24	24.49	0.731
Constipation	55	76.39	79	80.61	0.505
Abdominal Mass	0	0.00	3	3.06	0.263
Diarrhoea	12	16.67	12	12.24	0.413
Anaemia	34	47.96	17	16.67	< 0.001*
Pathological features					0.061
Adenocarcinoma	44	61.11	80	81.63	
Mucinous adenocarcinoma	2	2.78	2	2.04	
Signet ring cells	20	27.78	0	0.00	
Others	6	8.33	16	16.33	
Stages					0.386
Stage 0	0	0.00	1	1.02	
Stage I	7	9.72	10	10.20	
Stage IIA	2	2.78	4	4.08	
Stage IIB	8	11.11	6	6.12	
Stage IIC	0	0.00	0	0.00	
Stage IIIA	8	11.11	24	24.49	
Stage IIIB	18	25.00	18	18.37	
Stage IIIC	1	1.39	2	2.04	
Stage IV	28	38.89	33	33.67	
Tumour locations					0.001*
Iliocecal	0	0.00	1	1.02	
Caecum	0	0.00	0	0.00	
Ascenden colon	13	18.06	8	8.16	
Transvers colon	6	8.33	4	4.08	
Descenden colon	11	15.28	3	3.06	
Sigmoid colon	12	16.67	11	11.22	
Rectosigmoid	5	6.94	12	12.24	
Rectum	22	30.56	53	54.08	
Anorectal	0	0.00	1	1.02	
Colon	0	0.00	1	1.02	
Cervical	0	0.00	0	0.00	
Combination	3	4.17	4	4.08	
Outcome					0.531
Life	66	91.67	93	94.90	
Death	6	8.33	5	5.10	

Comparative analysis between clinicopathology and onset was carried out using the independent *t*-test method for numerical variables, Fisher's Exact for nominal categories and Mann–Whitney for ordinal categories if the data were normally distributed. For data that were not normally distributed, analysis was carried out using the Kolmogorov–Smirnov.

*The data were stated to be significant if the *P* value < 0.05.

mutation of the p53 gene in more than 80% of cases, indicating that colorectal cancer is sporadic. The p53 gene, as well as several other genes such as APC, MCC, KRAS, and DCC, are not usually involved in carcinogenic events that lead to Lynch syndrome and are hereditary.

Based on the correlation analysis between variables, it was discovered that anaemia, histopathological features, and tumour location had a significant low correlation with the incidence of CRC onset. Taken together, these findings support the notion that normocytic anaemia in CRC, in particular, is associated with systemic inflammation. Anaemia is more common in EOCRC, where the tumour is located in the proximal tumour area. As previously stated, this condition is linked to genetic and molecular factors.

According to histopathology, up to 90% of CRC cases originate from the glandular mucosa and are classified as adenocarcinoma originating from colorectal mucosal epithelial cells[5,23]. Adenocarcinoma is distinguished by the development of glands. When compared with LOCRC, EOCRC does not have precursor adenomatous lesions and more signet ring cells are found, whereas late-onset has fewer signet ring cells and can have a rare subtype of signet ring adenocarcinoma. This is consistent with the findings of this study[6,9,21,22].

Signet ring cells are poorly differentiated when they have an infiltrative pattern or a collection of extracellular mucin[24]. In

Table 3
Correlation between variables and onset.

Variable	Correlation	r	*P* value
Sex	Phi	0.122	0.111
Hematochezia	Phi	−0.092	0.232
Melena	Phi	0.066	0.390
Abdominal pain	Phi	0.026	0.731
Constipation	Phi	0.051	0.505
Abdominal mass	Phi	0.115	0.134
Diarrhoea	Phi	−0.063	0.413
Anaemia	Phi	0.325	< 0.001*
Pathological features	Contingency coefficient	0.397	< 0.001*
Stages	Theta	0.075	0.386
Tumour locations	Contingency coefficient	0.342	0.013*
Mortality rate (outcome)	Phi	−0.065	0.397

r = correlation coefficient (r = 0.20–0.40: low correlation; r = 0.40–0.70: moderate correlation; r = 0.70–0.90: high correlation; 0.90–1.00: very high correlation).
**P* value was statistically significant if < 0.05.

other studies, EOCRC was found to have 50–95% gland formation and to be moderately differentiated[6,9]. Left colorectal cancer is more common than right colorectal cancer and has worse pathological features and prognosis. On the other hand, the majority of EOCRC cases are diagnosed in later stages. EOCRC patients have a lower survival rate than LOCRC patients. As in previous studies adenocarcinoma was the most common pathological feature in both groups in this study[5,23–25]. Other studies have also found a higher prevalence of poorly differentiated histological signet ring cells in young colorectal cancer patients. However, there is no statistically significant correlation between the clinicopathological features of CRC and both the onset and mortality rates in this study.

Conclusions

There was a statistically significant difference in clinicopathological features (anaemia and tumour location) between subjects EOCRC vs. LOCRC. There is no statistically significant correlation between the clinicopathological features of CRC in both onset and mortality rates in this study.

Limitations

Nevertheless, this study also has several limitations, including cross-sectional method derived from electronic medical records, thus only documented details were available for evaluation. Many relevant data such as details about adenoma, family history, emergency clinical features, and type of surgery were not adequately available. This study is also still monocentric. Nonetheless, this study provides relevant data regarding the clinicopathological features of EOCRC vs. LOCRC as well as their correlation with mortality rate and will add to existing world databases to create valid conclusions.

Ethical approval

Ethics Committee Review Board of Hasan Sadikin General Hospital—Faculty of Medicine, Universitas Padjadjaran waived the need for informed consent with reference number LB.02.01/X.6.5/328/2022. All methods were carried out in accordance with relevant guidelines and regulations.

Consent

Not Applicable. The authors declare that the personal data from any subjects involved in this study will not be shared based on subjects' confidentialities.

Source of funding

The study did not receive external funding.

Conflicts of interest disclosure

The authors declare that we have no conflicts of interest.

Author contribution

K.L., A.M., R.R., and E.P. did the conception of the study and revised the manuscript critically for important intellectual content. A.M. and A.D.N. did the acquisition of data, analysis and interpretation of the data, drafted the manuscript and revised the manuscript critically for important intellectual content.

Guarantors

The guarantors of this study is Kiki Lukman, M.D (first author) and Andi Mulyawan, M.D. (second author). We declare that this manuscript is not under consideration elsewhere and none of the paper's contents have been published previously. All authors have read and approved to the manuscript as written. The authors maintain no conflict of interest.

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