RESEARCH ARTICLE

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Early-Onset Colorectal Cancer Survival among Unscreened Population -Multicenter Cohort Retrospective Analysis

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Abstract

Background: In Saudi Arabia and across the world, the incidence of early-onset colorectal cancer (< 50 years) has increased. The diagnosis of EOCRC, on the other hand, is frequently delayed. It is critical to implement a national screening program to identify those group of patients who might benefit from early diagnosis. **Method:** A retrospective search was conducted using data from the Ministry of National Guard Health Affairs' (MNG-HA) Cancer Registry. The population of 1440 CRC patients were eligible for the analyses. Patients' demographics including age at diagnosis, gender, and marital status, were all reported. The demographic and clinical characteristics were assessed across early-onset and late-onset groups using Chi-square and Fisher exact test where appropriate. **Results:** CRC patients, early-onset CRC (18-50 years) was reported in 23.26%, mainly with advance disease. Late-onset (>50 years) CRC individuals have worse survival rate and higher probability of dying compared to early-onset CRC individuals. After age at diagnosis classification into three categories (18-40 years), (41-50 years), and (>50 years) the Kaplan-Meier Survival curve show that early-onset (18-40 years) CRC individuals had significantly better survival than (41-50 years), and (>50 years) CRC patients. **Conclusions:** Comparing our data to another screened population using US SEER datasets, we discovered a substantial difference in survival rates, with the SEER population having a considerably greater chance of survival. There is very little research on the significance of screening for Saudi CRC patients, and this is an issue that needs to be looked into more. **Limitations:** A study's drawback is the lack of data for a variety of risk variables linked to colorectal cancer incidence, such as the KRAS mutation and environmental risk factors including BMI and smoking. More research with a nationally representative sample and comprehensive demographic and clinical data accessible is needed.

Keywords: Colorectal cancer- screening- early-onset- late-onset- survival

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Introduction

Colorectal cancer (CRC) is considered as second leading cause of cancer mortality worldwide and the third most prevalent cancer. Poor nutrition, alcohol consumption, smoking, and visceral fat are some of the risk factors for CRC. Males are more likely than females to experience greater rates of CRC mortality and morbidity. CRC is the most frequent malignancy among men and the third most common malignancy in women in Saudi Arabia, accounting for 2,047 new cases and 1,090 deaths in 2014. On the other hand, Obesity and low rates of physical exercise are related with the worst CRC outcomes in Saudi women (Alyabsi et al., 2021). Colorectal cancer survivors' quality of life was also harmed. Following cancer therapy, the most prevalent symptoms are fatigue, sleep loss, and urine frequency (Magaji et al., 2019).

The patient's age, the presence of comorbidities, sex, mode of presentation, tumor grading, and the timing of symptom onset are all factors that influence survival (Hansen et al., 2012). Furthermore, the laterality of colon cancer may affect survival outcomes (Beart et al., 1983; Benson et al., 2017; Jaruhathai et al., 2022; Lim et al., 2017).

Colorectal cancer (CRC) identified before the age of 50 is known as early-onset colorectal cancer (EOCRC). It is becoming more common all around the world (Siegel et al., 2019). Consequently, CRC research has switched to look at the molecular signature, incidence, clinical performance, risk factors, and pathological features of early-onset colorectal cancer comparing to late-onset colorectal cancer (CRC diagnosed beyond the age of 50). Because of a lack of patient and physician knowledge, EOCRC is often misdiagnosed as more benign illnesses.

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General incidence rate of CRC has reduced recently as a result of breakthrough in screening and treatment. However, the prevalence of EOCRC has increased significantly worldwide including Saudi Arabia (Agazzi et al., 2021; Alyabsi et al., 2021; Siegel et al., 2019). This is possibly related to misconceptions about colon function, colon cancer prevalence, and when patients should be tested for colon cancer (Alsulaim et al., 2021).

According to the 2018 update, American Cancer Society's Colorectal Cancer Screening for Adults at Average Risk, individuals aged 45 and older should begin screening with visual assessment and a high-sensitivity stool-based test, all positive non-colonoscopy results are followed by a colonoscopy (Rosato et al., 2013). The bowel cancer screening program (BCSP) of the National Health Service (NHS) in the United Kingdom and The Australian National Bowel Cancer Screening Program (NBCSP), have not modified their target range remains constant, proposing screening every two years for people aged between 50 and 74 (Archambault et al., 2021).

The objective of this research is to emphasize the alteration in survival rates CRC early-onset and CRC late-onset, as well as to compare survival rates by stage between screened CRC populations utilizing (SEER) and unscreened CRC populations (MNG-HA).

Materials and Methods

Study design, Setting, and Population

This current study adapted a retrospective cohort design utilizing the data for the Ministry of National Guard Health Affairs' (MNG-HA) Cancer Registry in the major two cities in Saudi Arabia, Riyadh and Jeddah city from 1/1/2009 to 31/12/2017 with follow-up time started at the date of CRC diagnosis in the registry and ended on the date of death, date of last contact or when study ended on December 31, 2017. The registries, stored information regarding demographic, clinical characteristics such as type of cancers, stage, and grade at the first diagnosis. The registries stored the data for treated patients at King Abdulaziz Medical City (KAMC) in Riyadh and Jeddah city. In each visit, patients' data were structured to store follow-up information, the date of last contact, and other information required to estimate patient survival. Inclusion criteria included patients aged ≥18 years diagnosed with colorectal cancer using International Classification of Diseases (ICD) (ICD-10 C18– C20) who treated at MNG-HA hospitals from January first, 2009, to December 31, 2017. Total patients who included in the study was 1,560. About 120 (7.6) patients were excluded from the study because of missing of required information such as unknown admission or contact dates. The total eligible patients for the analysis were 1440.

Patient and Tumor Characteristics

Demographic information such as age at diagnosis, gender, and marital status were retrieved from the cancer registries. Patient demographics including age at diagnosis, gender, and marital status, were all extracted from electronic health records. When classifying age at diagnosis groups, we accounted for the time of the study and the existing colorectal cancer screening guidelines (Burt et al., 2010). The recommended age for screening is 50, so we defined early-onset CRC as CRC diagnosed at age 50 or younger. The compared group (late-onset) included patients diagnosed with CRC at ages 51 years or older (Cheng et al., 2021). We further classify age at diagnosis into three groups (18-40, 41-50, and >50) (Chen et al., 2014; Lee et al., 2013; Young, 2006).

Statistical Analysis

We used Chi-square when we have sufficient observation in each cell and Fisher exact test when we have fewer than 5 observation per cell to examine the demographic and clinical characteristics across early-onset and late-onset groups. To build the multivariate model, we used purposeful variable backward selection technique to include only variables with $P< 0.05$. We used the Kaplan-Meier product limit method and the log-rank test to estimate the survival rates. Cox proportional hazards regression adjusted models were used to estimate the hazard ratio associated with early onset of CRC. To validate our finding, and to minimize potential confounder bias, we performed a sensitivity analysis with multiple and different age groups for each testing model. We used SAS statistical software version 9.4 (SAS Institute Inc. Cary, NC) to perform the analysis.

Results

The cohort included 1,440 individuals diagnosed with CRC, 826 (57.36%) males and 614 (42.64%) females, Table 1 represent patients' demographical and clinical characteristics. Among EOCRC, the proportions of diagnosed CRC males and female were approximately similar (50.75% vs 49.25%), while among late-onset patients, the proportions of males were 20% higher than females. When comparing between individuals with EOCRC to those with late onset CRC, incidence in male were more likely to increase at late onset (50.75% vs 59.37%; $P < .005$). EOCRC individuals were more likely to go through chemotherapy and/or surgical treatment (60%, and 55.85%; $P < 0.01$) compared to late-onset (44.52%, and 48.55%; $P <0.0001$).

The overall median survival for early-onset CRC individuals was significantly higher than late onset CRC individuals ($P = 0.03$) (Table 1). The median survival on the Kaplan-Meier Survival curve was substantially lower among people with late-onset CRC (69 months) (95% CI, 67-73 months) in comparison to early-onset CRC individuals 113 months (95% CI, 77-115 months) (Figure 1). However, when the early onset cohort was further sup-grouped into (18-40 years) and (41-50 years), the Kaplan-Meier Survival curve show that early-onset (18-40 years) CRC individuals had significantly higher survival than early-onset (41-50 years), and late onset (>50 years) ($P =0 .03$) (Figure 2).

Late-onset CRC individuals had higher probability of dying compared to early-onset CRC individuals (23.28% vs 28.33%; $P < 0.01$) during the follow-up period (Table 1). In the multivariate Cox regression both unadjusted

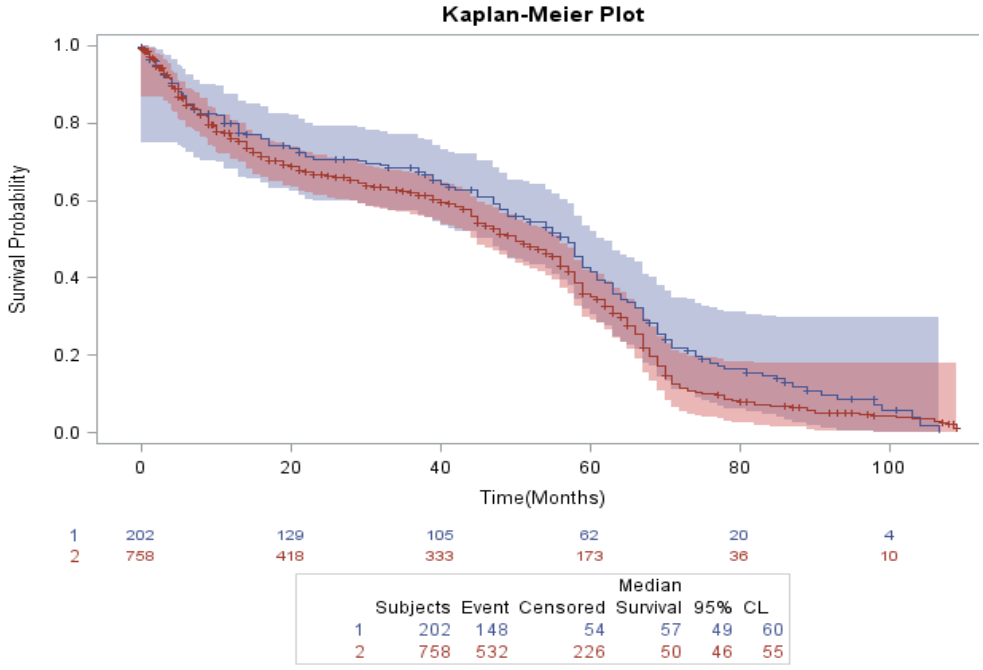

Figure 1. Kaplan-Meier Mortality Estimates for Early-Onset (18-50) and Late-Onset (>50) Colorectal Cancer (CRC)

and adjusted models, showed a statistically significant difference in survival between EOCRC vs late-onset CRC (HR, 0.82; 95% CI, 0.68-0.98; P 0.03), (HR, 0.78; 95% CI, 0.64-0.96; P 0.01) (Table 2). EOCRC patients was associated with lower mortality as compared to late-onset CRC individuals. Similarly, after age at diagnosis classification into three categories, both unadjusted and adjusted models showed that patients who aged between 18-40 years, relative to late-onset onset (>50years), showed statistically significant improved survival (HR, 0.81; 95% CI, 0.64-0.99; P 0.03), (HR, 0.77; 95% CI, 0.61-0.97; P 0.01).

In terms of overall survival rate, the MNG-HA and SEER cohorts were compared. EOCRC patients had a better overall survival rate than late-onset CRC patients across all stages in both populations (Table 3). Among localized and regional stages, the survival rate was significantly varied between MNG-HA and SEER. Survival rate among SEER population was 30% to 40 % significantly higher than MNG-HA for localized stages (93.7 vs 58.97) and (92.4 vs 47.75), and 10% to15% higher among regional stages (78.5 vs 65.27), and (76.55

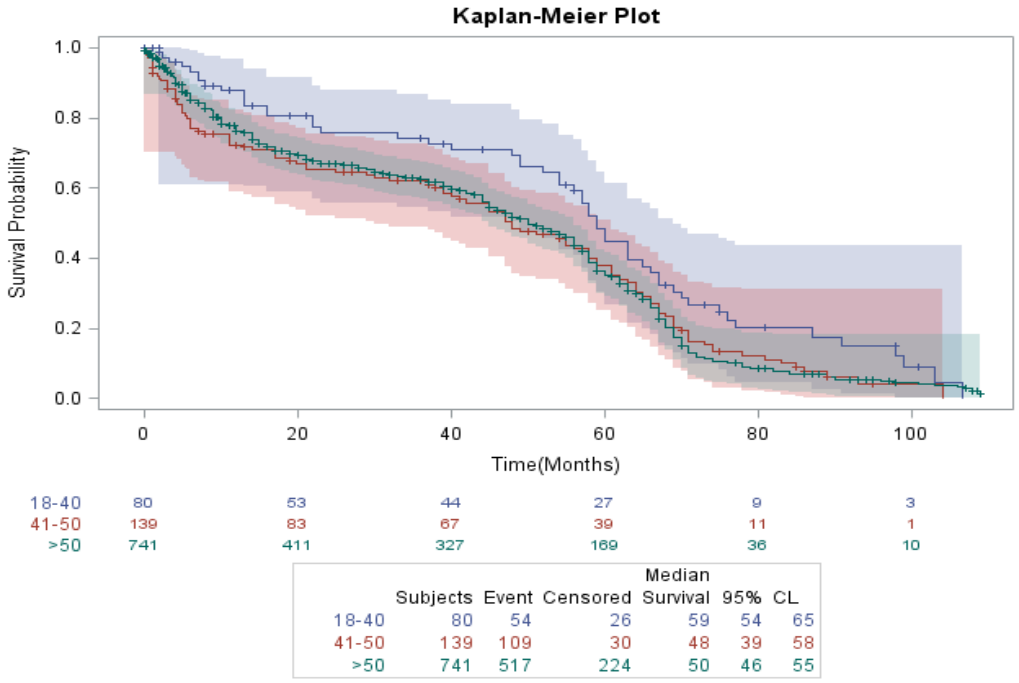

Figure 2. Kaplan-Meier Mortality Estimates for Early-Onset (18-40), (4-50), and Late-Onset (>50) Colorectal Cancer (CRC)

Table 1. Demographic, Clinical and Pathological Characteristics of Collateral Cancer Patients at MNG-HA Hospitals a (N=1440)

Patients Characteristics	Early-onset (18-50 years) N (%) a	Late-onset (51 or older) N (%)	*P* [b]
Total	335 (23.26)	1105 (76.74)	
5-year overall survival	67.53%	59.65%	0.03
Died	78 (23.28)	313 (28.33)	0.01
Gender			0.005
Male	170 (50.75)	656 (59.37)	
Female	165 (49.25)	449 (40.63)	
Marital status			
Married	239 (71.34)	865 (78.28)	0.008
Unmarried	96 (28.66)	240 (21.72)	
Stage at diagnosis			0.17
Distance metastasis	133 (39.7)	398 (36.02)	
Localized	39 (11.64)	182 (16.47)	
Regional	146 (43.58)	468 (42.35)	
Unknown	17 (5.07)	57 (5.16)	
Pathological Grading			0.87
Well differentiated	15 (4.47)	49 (4.43)	
Moderate differentiated	249 (74.32)	820 (74.2)	
Poor differentiated	27 (8.05)	100 (11.05)	
Others	44 (13.13)	136 (12.3)	
Tumor Morphology (Histotype)			0.34
Adenocarcinoma (AC), NOS	273 (81.49)	954 (86.33)	
Mucinous AC	30 (8.96)	73 (6.61)	
Mucin-producing AC	3 (0.9)	8 (0.72)	
Signet ring cell carcinoma	5 (1.49)	10 (0.90)	
AC in villous/tubuvillous adenoma	7 (2.09)	13 (1.18)	
Others [g]	17 (5.07)	47 (4.25)	
Tumor location			0.21
Left side	238 (71.04)	770 (69.68)	
Right side	57 (17.01)	228 (20.63)	
Unknown	40 (11.94)	107 (9.68)	
Chemotherapy			<0.0001
Yes	201 (60.00)	492 (44.52)	
No	134 (40.00)	613 (55.48)	
Surgical treatment			0.01
Yes	188 (55.85)	536 (48.55)	
No	148 (44.15)	568 (51.45)	
Radiotherapy			0.26
Yes	26 (7.76)	67 (6.06)	
No	309 (92.24)	1038 (93.94)	

[a],Sample size and percentage N(%); [b], P value of the chi-square, and fisher exact test where appropriate

Table 2. Hazard Ration ComparingA Early-Onset versus Late-Onset

Age at diagnosis	Model 1 [a]		Model 2 [b]	
	HR (95% CI) [d]	*P* [e]	HR (95% CI)	P
Early-onset vs late-onset				
<50 years	0.82 (0.68, 0.98)	0.03	0.78 (0.64, 0.96)	0.01
>50	Reference		Reference	
Early-onset vs late-onset				
<40	0.81 (0.64, 0.99)	0.04	0.77 (0.61, 0.97)	0.03
41-50	0.95 (0.77, 1.17)	0.66	0.99 (0.79, 1.24)	0.96
>50	Reference		Reference	

[a], Unadjusted; [b], Adjusted for demographics, clinical factors and treatment factors; [d], Hazard ratio (HR), confidence interval (CI); [e], P-value (P) Cox regression model

vs62.09) (Table 3).

Discussion

In this study, we observed that EOCRC patients' overall median survival rate was markedly higher than late-onset CRC individuals. Prior research from the United States that supports our findings was recently published (Cheng et al., 2021). According to statistics, early-onset colon cancer accounts for 11% and 10% of all CRC cases in European and Western nations, respectively (Agazzi et al., 2021; Alyabsi et al., 2021). The findings of the current study demonstrated that early-onset cancer accounts for around 23% of all CRC cases. The alarming discovery in the current study revealed that nearly 23% of CRC patients in our community were young individuals identified at an advanced stage. Although, there are minimal Saudi studies investigating early-onset incidence, in alignment with our finding, a study conducted by Alyabsi et al., (2021) demonstrated that the early-onset CRC incidence in Saudi Arabia, increased (Alyabsi et al., 2021). Hence, an urgent monitoring system need to be implementing to lower the general incidence rates of CRC (Siegel et al., 2019).

Definitions of EOCRC is still heterogenous with some variation across countries in terms of screening protocols (Archambault et al., 2021; Rosato et al., 2013). A National Bowel Cancer Screening Program must be created in Saudi Arabia, with a focus on those aged 40 and over. This cutoff number was suggested based on our findings that CRC patients aged (41-50) and patients above 50 exhibit a similar pattern in the Kaplan-Meier Survival curve, with a considerably worse survival rate than patients aged less than 40. Cheng et al., (2021) prior findings are precisely in accord with the conclusions of this study. However,

Table 3. Five-Year Colorectal Cancer Survival by Stages in MNG-HA compared to US SEER

	All stages		Localized		Regional	
	Survival (%)	95% CI	Survival (%)	95% CI	Survival (%)	95% CI
Early-onset						
US SEER	63.6	(62.8, 63.5)	93.7	(93.2, 94.1)	78.5	(77.9, 79.05)
MNG-HA	67.53	(77, 115)	58.97	(57, 78)	65.27	(67, 114.83)
Late-onset						
US SEER	61.71	(64.5, 65.3)	92.4	(92.0, 92.8)	76.55	(86.7, 77.2)
MNG-HA	59.65	(67, 73)	47.75	(53, 63)	62.09	(67, 82)

one of the most significant non-modifiable contributors of EOCRC development is age between 40 and 50 years, as contrast to 40 years (Rosato et al., 2013). We have definitely revealed that patients under the age of 40 have a greater chance of surviving. The necessity of screening is emphasized here because over 75% of our population is diagnosed late in life, with a worse survival rate. EOCRC patients' may have distinct biological characteristics comparing to old CRC patients' which possibly result in a different prognosis.

It is essential to comprehend the age-related variability of CRC in order to inform treatment strategies and comprehend the distinctive biological differentiation within early-onset CRC. Advances in screening, monitoring, and therapy have reduced overall CRC death rates in developed countries as represented by US SEER. Despite the fact that certain high-income nations, like as Saudi Arabia, have a robust and free healthcare system with all treatment regimens available to all patients, the survival rate in local and regional CRC is lower than in the United States. This is owing to the absence of a CRC screening program. The paper's recommendation is to underline the need of screening for Saudi patients.

In conclusion, the current study revealed that nearly two times more young individuals CRC patients with advanced stage compared to the Western and the US countries. The absence of screening in Saudi Arabia added more burden to patients diagnosed with CRC. The finding of the current study is a call for health policy makers in the kingdom explaining the vivid need for CRC screening for individuals aged 40 years or older in Saudi Arabia. However, more studies in a national level population are need it to confirm these findings.

Author Contribution Statement

M.R: Conceptualization, Methodology, Software M.R, R.A Data curation, Writing- Original draft preparation. M.R, R.A, M.A, Visualization, Investigation. M.R, R.A Supervision.: M.R, D.A, T.A: Software, Validation.: M.R: Writing- Reviewing and Editing M.R, R.A, D.A, M.A, and T.A.

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Funding statement

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Ethics approval

Ethical approval was obtained from the Local Institutional Review Board of the Saudi National Guard Health Affairs, Jeddah (IRBC/1346/17). All patients' identifying variables were omitted before the analysis.

Data availability

The data that support the findings of this study are available from King Abdullah International Medical Research Centre (KAIMRC) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of King Abdullah International Medical Research Centre (KAIMRC)

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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