

Survival Rate and Prognostic Factors for Colorectal Cancer in Sabah, Borneo, Malaysia: A Retrospective Cohort of a Population-Based Study

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Abstract

Background: Colorectal cancer is a major public health problem with significant number of cases and death in the population. This study aimed to determine the 5-year overall survival rate and the prognostic factors for colorectal cancer patients in Sabah. **Methods:** This was a retrospective cohort study conducted using secondary data from Malaysian National Cancer Registry (MNCR) database. A 5-year overall survival and the median survival time were determined with Kaplan-Meier survival curve. Cox regression analysis was done to determine the prognostic factors on survival. **Results:** A total of 1,152 patients were included in this study. The majority of the patients had colon cancer and presented at late stage (stage III and IV) as compared to early stage (stage I and II). From the analysis, the 5-year overall survival for colorectal cancer was 23.2% (95% CI: 21.8, 24.6) and the median survival time was 16 months (95% CI: 14.3, 17.7). Higher survivals are seen in males (23.6%, 95% CI: 20.4, 24.7), aged 50-74 years old (24.2%, 95% CI: 22.4, 26.0), Chinese (25.5%, 95% CI: 23.0, 28.0), lived in Keningau (25.6%, 95% CI: 20.8, 30.4), colon as primary tumor site (24.5%, 95% CI: 22.5, 26.4), diagnosed with stage I (55.6%, 95% CI: 48.7, 62.5) and received surgery with chemotherapy or radiotherapy (31.3%, 95% CI: 27.8, 34.8). The significant prognostic factor was the stage at diagnosis. Patients with stage IV colorectal cancer (HR: 11.18; 95% CI: 3.48, 35.93) had eleven times risk of dying as compared to stage I. **Conclusion:** The survival rate for colorectal cancer patients in Sabah was comparatively lower than other states in Malaysia and in some Asian countries. Those patients who presented at later stage had poorer survival. Health promotion and community-based screening program should be emphasized in addition to encouraging early diagnosis to improve survival.

Keywords: Colorectal cancer- survival- prognostic factors- Malaysia- Sabah

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Introduction

Colorectal cancer was the third most common cancer diagnosed globally. The estimated number of cases in 2018 was 1,026,215 in males and 823,303 in females, which made it 10.2% from total cancer cases diagnosed. Colorectal cancer mortality also ranked second after lung cancer (World Health Organization, 2020). Even though there is a high number of diagnosed cases and death, the 5-year survival rate was still high in Korea and Australia, which was more than 70%, meanwhile in Singapore, Japan, Italy, Belgium and some other countries was 60-69%. Countries that had less than 50% of survival were

Thailand, India, Ecuador and a few others (Allemani et al., 2018).

As Asia recorded the highest new cases compared to other regions (International Agency for Research on Cancer, 2019), colorectal cancer is also among the top cancer diagnosed in Malaysia. There were 13.5% of new colorectal cases diagnosed in 2012-2016, and colorectal cancer cases was the second most commonly diagnosed after female breast cancer. The incidence also was higher among males (Ministry of Health, 2019).

The overall mortality rate for colorectal cancer in Malaysia was 9.8 per 100,000 populations, with males had higher mortality rate than females (Abu Hassan et

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al., 2016). A multiple-hospital-based study had found that the 5-year survival rate was 48.7% for cases diagnosed in 2008-2009 (Abu Hassan et al., 2016). Meanwhile, another study which involved all states' cancer registries had found 40.8% for 5-year overall survival rate for cases diagnosed in 2007-2011 (Ministry of Health Malaysia, 2018). Both findings were lower than other developed countries (Allemanni et al., 2018).

Clinical characteristics such as stage and treatment (Abu Hassan, Mohd Suan, et al., 2016; Ghazali et al., 2010; Laohavinij et al., 2010; Lim et al., 2020; Magaji et al., 2017; McKay et al., 2014), demographic characteristics such as age and sex (Laohavinij et al., 2010; Lim et al., 2020; Magaji et al., 2017; McKay et al., 2014; Rasouli et al., 2017; Van Eeghen et al., 2015) and co-morbidities (Van Eeghen et al., 2015) were found to be some of the prognostic factors.

In Sabah, the second largest state in Malaysia (Jeffrey et al., 2016), colorectal cancer was the most common cancer diagnosed (Sabah State Health Department, 2015). As previously mentioned, the cases were also more common among males (Sabah State Health Department, 2015). The incidence of colorectal cancer was 14.3 and 11.2 per 100,000 populations in males and females respectively (Sabah State Health Department, 2015), which was similar to the report produced by Malaysian National Cancer Registry (MNCR) for the country (Malaysia, 2019). The Chinese had the highest incidence of colorectal cancer followed by the Bajau and the Murut (Sabah State Health Department, 2015). However, this information was not observed in other studies in Malaysia (Abu Hassan et al., 2016; Ghazali et al., 2010; Lim et al., 2020; Magaji et al., 2017; Malaysia, 2019; Shah et al., 2014). As for the stage of the disease, more patients were noted to be presented late, which led to advanced stage of diagnosis (Malaysia, 2019).

Colorectal cancer in developing nations, such as Malaysia, continues to be a major public health issue. With the increasing post-treatment survival rate, information on the pattern of quality of life and its related factors are critical in guiding the treatment options. Typical symptoms such as fatigue, sleep loss, frequency in urination and constipation are among the symptoms occurring post cancer treatment (Magaji et al., 2019).

In Malaysia, several studies had been done to look for the prognostic factors in colorectal cancer survival, which were mainly pertaining to hospital-based database in Peninsular Malaysia (Abu Hassan et al., 2016; Ghazali et al., 2010; Lim et al., 2020; Magaji et al., 2017). With the scarcity of the information on Sabah, this study aimed to estimate the 5-year overall survival rate for colorectal cancer patients who were the residents of Sabah and who were being diagnosed from January 2007 until December 2013. In addition, we aimed to determine the prognostic factors that would affect the 5-year overall survival among these patients.

Materials and Methods

Study design and patient's selection

This was a retrospective cohort study which was

conducted using the secondary data from MNCR database, a population-based cancer registry that headed all states' population-based cancer registries, including Sabah. The MNCR was led by National Cancer Registry Department located in Institut Kanser Negara, Federal Territory of Putrajaya, Malaysia (Ministry of Health Malaysia, 2016). The data stood by 26th April 2020 consist of Malaysian citizens and they were residents of Sabah who had been diagnosed with colorectal cancer from 1st January 2007 until 31st December 2013. The MNCR maintained its high validity, accuracy and comparability of data as mentioned elsewhere (Malaysia, 2019)

The inclusion criteria was the diagnosis of colorectal cancer (ICD-03: C18-C20) based on histological or cytological confirmation, or clinical investigations if the former confirmation methods were not done. Patients who were diagnosed at autopsy, or through death certificate, who had later incident dates than the dates of deaths, who had incomplete demographic information, and who had no follow up information were excluded from the study.

Sample size was calculated using time-to-event formula (In and Lee, 2018). The level of significance, α and power, $1-\beta$, were set at 0.05 and 0.84 respectively. The hazard ratio was 1.41 (Magaji et al., 2017). The calculated sample was 547 patients after anticipating for 10% of missing values and 4.1% of loss to follow up (Ghazali et al., 2010).

Variables

The data extracted from the MNCR database were the demographic and clinical data, such as age at diagnosis, sex, ethnicity, address, date of diagnosis, International Classification of Diseases and Related Health Problems 10th Revision, version 2010 (ICD-10) Codes (C18-C20), stage at diagnosis, treatment, primary tumor site and date of deaths or date of last follow up. Age was further categorized into < 50 years old, 50-74 years old and \geq 75 years old. Patients' addresses were grouped into seven administrative divisions (Sabah Lands and Survey Department, 2019). As Sabah consists of consists of Kadazan Dusun, Bajau, Chinese, Malay, Murut, Indian, Other Bumiputera and others ethnicities, the study categorized them as Kadazan Dusun, Bajau, Chinese and Others. The proportions of Malays and Indians were low in Sabah, hence categorized into Others, even though they were among the major ethnicities in Malaysia. Primary tumor site was divided into colon (C18.0-C18.9) and rectum (C19-C20) (Morris et al., 2011). TNM staging was extracted according to primary tumor (T), regional lymph nodes (N) and distant metastasis (M) staging classification (Piñeros et al., 2019). Treatment modalities were grouped into four categories, which were surgery only, surgery with chemotherapy or radiotherapy, surgery with chemotherapy and radiotherapy, and chemotherapy and/or radiotherapy (Abu Hassan et al., 2016).

Unrecorded staging and treatment information were matched by MNCR with the Malaysian National Cancer Patient Registry of Colorectal Cancer, Malaysia, which collects relevant data on colorectal cancer from participating hospitals (Abu Hassan et al., 2016). MNCR followed up all of the patients and updated the vital status

of the patients that was cross-checked using identification card numbers and names with hospital discharges' lists from Health Informatic Centre and death lists from National Registration Department. Hence, the vital status was classified as dead, alive or loss to follow up. For those who were alive after the closure date of the study and loss to follow up were censored in the analysis.

Statistical analysis

Analysis was done using IBM SPSS version 26.0. A 5-year overall survival and median survival time were determined with Kaplan-Meier survival curve. Cox regression analysis was done to determine the prognostic factors on survival. Variables with p-value < 0.25 in univariable analysis were included in multivariable analysis (Hosmer and Lemeshow, 2000). A stepwise forward and backward selection methods were used. A p-value of less than 0.05 was considered statistically significant and reported with 95% confidence interval. Log minus log plot of the predictor variables were used to test the proportional hazards' assumption against time. Goodness of fit was based on the chi-squared test comparing the -2 Log Likelihoods after each step of forward and backward selection method. The model was fit if the p-value was less than 0.05. Demographic data for all patients were complete. Patients with missing staging and treatment information were excluded from regression analysis.

Results

Patients characteristics

A total of 1,152 patients met the criteria of the study where 60.2% were males and 39.8% were females. Most of the patients aged between 50-74 years old (61%); meanwhile, age group of <50 years old and ≥75 years old were 22.8% and 16.1% respectively. Mean age at diagnosis was 59 years old (SD 14.4). Ethnicity distribution was the

highest among Chinese (34.3%), followed by Kadazan Dusun (17.9%) and Bajau (11.3%). The majority of the patients were the residents of West Coast (South) Division (42.1%) followed by Sandakan (15.9%), Tawau (15.0%), West Coast (North) (9.6%), Keningau (8.6%), Beaufort (4.9%) and Lahad Datu Division (3.0%). Only 0.9% of the patients had incomplete address information.

The clinical characteristics of colorectal cancer patients are shown in Table 1. The majority of the patients had colon cancer and presented at late stage (stage III and IV) as compared to early stage (stage I and II). However, only half of the patients recorded on treatment received.

Overall survival

The 5-year overall survival for colorectal cancer was 23.2% (95% CI: 21.8, 24.6), and the median survival time was 16 months (95% CI: 14.3, 17.7). The 5-year overall survival for each demographic and clinical characteristics are shown in Table 2. Higher survivals are seen in males (23.6%, 95% CI: 20.4, 24.7), aged 50-74 years old (24.2%, 95% CI: 22.4, 26.0), Chinese (25.5%, 95% CI: 23.0, 28.0), lived in Keningau (25.6%, 95% CI: 20.8, 30.4), colon as primary tumor site (24.5%, 95% CI: 22.5, 26.4), diagnosed with stage I (55.6%, 95% CI: 48.7, 62.5) and received surgery with chemotherapy or radiotherapy (31.3%, 95% CI: 27.8, 34.8).

Prognostic factors of colorectal cancer survival

Unknown cases, which the treatment modalities and stage at diagnosis were not recorded as they were non-mandatory in the notification process, were excluded from the analysis. Cox regression analysis revealed the significant variables which were age, ethnicity, primary tumor site, stage and treatment (Table 3). Meanwhile, a Kaplan-Meier Survival Curve for 5-year Overall Survival Rate for Colorectal Cancer, Sabah, 2007-2013 showed half of the survival rate was reached in just 16 months (Figure 1). Making further analysis with multivariable

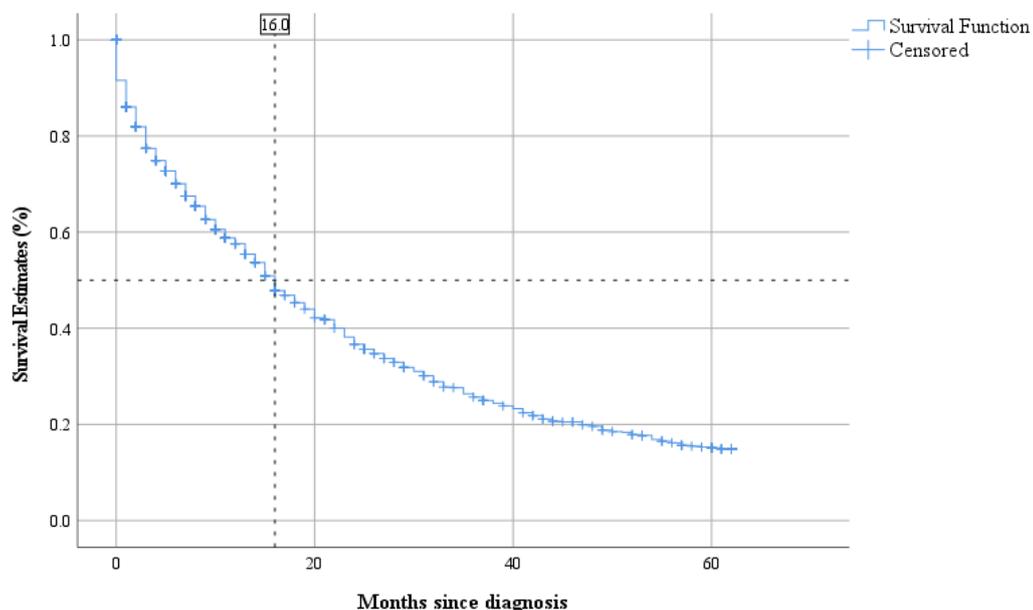


Figure 1. Kaplan-Meier Survival Curve for 5-Year Overall Survival Rate for Colorectal Cancer, Sabah, 2007-2013

Table 1. Clinical Characteristic of Colorectal Cancer Patients, Sabah, 2007-2013

Clinical Characteristics	n	%
Total	1152	
TNM staging		
Stage I	26	2.3
Stage II	105	9.1
Stage III	126	10.9
Stage IV	163	14.1
Unknown	732	63.5
Primary tumor site		
Colon	712	61.8
Rectum	440	38.2
Treatment		
Surgery + Chemotherapy/ Radiotherapy	194	16.8
Surgery + Chemotherapy + Radiotherapy	61	5.3
Surgery only	195	16.9
Chemotherapy and/or Radiotherapy	128	11.1
Unknown	574	49.8

n, number of cases

Cox regression, the significant prognostic factor was the stage at diagnosis (Table 4) after adjusted for treatment and age group. Patients with stage IV colorectal cancer (HR: 11.71; 95% CI: 3.66, 37.52) had eleven times risk of dying as compared to stage I. The proportional hazard assumption was met in this Cox proportional hazard regression model as the curves remained parallel with each other. The model with stage at diagnosis as the prognostic factor fits significantly as the p-value from the Likelihood-ratio test was less than 0.001.

Discussion

The 5-year overall survival for colorectal cancer in this study was 23.2% with median survival time at 16 months, which was lower compared to other studies. The staging at diagnosis was the only significant prognostic factor for colorectal cancer in Sabah. A higher overall survival was noted in some of the Asian countries such as Thailand and Philippines, which were 44.0% and 40.2% respectively (Kittrongsiri et al., 2020; Laudico et al., 2010). Singapore estimated the overall survival for colorectal cancer was 51.0% for males and 52.8% for females (Ministry of Health Singapore, 2017). Other studies in Malaysia also showed higher survivals compared to this study (Abu Hassan et al., 2016; Ghazali et al., 2010; Lim et al., 2020; Ministry of Health Malaysia, 2018). The difference could probably due to the population-based analysis that reflects on the general diagnosis and treatment of colorectal cancer in a population; meanwhile, the hospital-based analysis mainly reflects on the treatment effect of colorectal cancer in the involved departments (Chen et al., 2017; Chen et al., 2018; Xu et al., 2016).

Another reason for a lower overall survival in this study could be due to the unavailability of population-based colorectal screening program which was yet to be implemented during the study period (Chandran et al.,

Table 2. Five-Year Survival Rate of Colorectal Cancer, Sabah, 2007-2013

Variables	Survival rate (95% CI)
Sex (n=1152)	
Male	23.6 (20.4, 24.7)
Female	22.5 (21.8, 25.4)
Age (n=1152)	
< 50 years old	23.4 (20.6, 26.2)
50 to 74 years old	24.2 (22.4, 26.0)
≥75 years old	18.8 (15.4, 22.3)
Ethnicity (n=1152)	
Chinese	25.5 (23.0, 28.0)
Kadazan/Dusun	24.9 (21.5, 28.2)
Bajau	20.5 (16.5, 24.6)
Others	21.0 (18.8, 23.1)
Area of residency (n=1142) ^a	
Keningau Division	25.6 (20.8, 30.4)
West Coast (South) Division	23.7 (21.5, 26.0)
West Coast (North) Division	19.7 (15.7, 23.8)
Tawau Division	24.9 (21.3, 28.6)
Lahad Datu Division	18.6 (13.0, 24.2)
Beaufort Division	19.8 (13.8, 25.8)
Sandakan Division	22.1 (18.7, 25.4)
Primary tumor site (n=1152)	
Colon	24.5 (22.5, 26.4)
Rectum	21.5 (19.4, 23.5)
TNM staging (n=420) ^a	
Stage I	55.6 (48.7, 62.5)
Stage II	41.4 (36.1, 46.6)
Stage III	33.3 (29.4, 37.3)
Stage IV	20.3 (17.4, 23.1)
Treatment (n=578) ^a	
Surgery + Chemotherapy/Radiotherapy	31.3 (27.8, 34.8)
Surgery + Chemotherapy + Radiotherapy	30.6 (25.3, 35.9)
Surgery only	30.2 (26.2, 34.1)
Chemotherapy and/or Radiotherapy	22.2 (18.7, 25.7)

95% CI, 95% Confidence Interval; ^aMissing data were excluded from analysis

2020; Ministry of Health Malaysia, 2012). It was proven that the diagnosis through community-based screening program had led to early stage at diagnosis, which subsequently had better survival rate, as evidenced in this study and other studies (Abu Hassan et al., 2016; Aryaie et al., 2013; Ghazali et al., 2010; Kral et al., 2020; Lim et al., 2020; Magaji et al., 2017; Rasouli et al., 2017; Sazali et al., 2021). Screening strategies need to be revisited and may need newer approach such as using smart healthcare delivery to improve access via digital health integration. The process of screening and case referral for intervention may be improved further (Jeffree et al., 2020).

On the other hand, Sabah, as the second largest state in Malaysia with 73,904 km², had four referral centers for colorectal cancer with other 20 hospitals, 109 health clinics, eight private hospitals (Ministry of Health

Table 3. Univariable Cox Regression Analysis of Colorectal Cancer, Sabah, 2007-2013

Variables	Crude HR (95% CI)	p value*
Sex (n=1152)		
Male	1	0.536
Female	1.05 (0.91, 1.21)	
Age (n=1152)		
< 50 years old	1	0.015
50 to 74 years old	0.99 (0.83, 1.18)	
≥75 years old	1.31 (1.04, 1.64)	
Ethnicity (n=1152)		
Chinese	1	0.026
Kadazan/Dusun	1.02 (0.83, 1.26)	
Bajau	1.31 (1.02, 1.66)	
Others	1.24 (1.05, 1.47)	
Area of residency (n=1142) ^a		
Keningau Division	1	0.32
West Coast (South) Division	1.09 (0.84, 1.42)	
West Coast (North) Division	1.35 (0.98, 1.86)	
Tawau Division	1.05 (0.77, 1.42)	
Lahad Datu Division	1.35 (0.85, 2.13)	
Beaufort Division	1.34 (0.91, 1.98)	
Sandakan Division	1.19 (0.88, 1.60)	
Primary tumor site (n=1152)		
Colon	1	0.076
Rectum	1.14 (0.99, 1.32)	
TNM staging (n=420) ^a		
Stage I	1	<0.001
Stage II	3.56 (1.10, 11.55)	
Stage III	6.15 (1.93, 19.57)	
Stage IV	12.55 (4.0, 39.46)	
Treatment (n=578) ^a		
Surgery + Chemotherapy/Radiotherapy	1	0.004
Surgery + Chemotherapy + Radiotherapy	1.10 (0.77, 1.57)	
Surgery only	1.09 (0.83, 1.43)	
Chemotherapy and/or Radiotherapy	1.64 (1.24, 2.16)	

95% CI, 95% Confidence Interval; HR, hazard ratio; *p-value calculated based on Wald statistic; ^aMissing data were excluded from analysis

Malaysia, 2020) and one radiotherapy service (Jeffrey et al., 2016) to cover around 3.61 million populations (Department of Statistics Malaysia Official Portal, 2020). However, not all treatment modalities were available in one center. The lack of expertise and facilities could affect the survival estimate in a population (Magaji et al., 2017). Despite that, socioeconomic status played an important role in determining the time of presentation. Lower socioeconomic status was significantly associated with late presentation and having advanced stage at diagnosis (Kong et al., 2010; Magaji et al., 2017).

The significant prognostic factor for this study was the stage at diagnosis. The result was consistent with other studies (Abu Hassan et al., 2016; Aryaie et al., 2013; Gabriel et al., 2018; Joachim et al., 2019; Laohavinij et al., 2010; Lim et al., 2020; Magaji et al., 2017). In this study, patients with stage IV colorectal cancer had the highest risk of death as compared to stage II and III. A

Table 4. Prognostic Factor for Colorectal Cancer Survival, Sabah, 2007-2013 (n=355)

Variables	Adjusted HRa (95% CI)	p-value*
Stage at diagnosis		
Stage I	1	<0.001
Stage II	3.51 (1.07, 11.54)	
Stage III	6.49 (2.02, 20.90)	
Stage IV	11.71 (3.66, 37.52)	

HR, hazard ratio; CI, confidence interval; *p-value calculated based on Wald statistic; n, number of cases; ^aMultivariable Cox Regression analysis after adjusted for treatment and age group

study in Golestan, Iran, revealed a very much increased risk of death for colorectal cancer patients with distant metastasis, which was nearly 56 times higher risk (Aryaie et al., 2013). A study in America had quite a similar risk of death for stage IV colorectal cancer with our study (HR: 15.6), but their finding was for patients aged ≤ 50 years old. Other studies in Malaysia showed that they had lower risk of death from advanced stage of cancer as compared to this study (Ghazali et al., 2010; Lim et al., 2020). Another found the risk of death for patients with stage IV colorectal cancer to be twice as high. Even though the risk was lower, the 5-year overall survival did not differ much from our findings (Abu Hassan et al., 2016).

We did not find other variables (sex, age, ethnicity, area of residency, primary tumor site and treatment) as the significant prognostic factors for colorectal cancer survival in this study. These findings were contradicting with other studies which found that males (Joachim et al., 2019), age ≥ 65 years old (Rasouli et al., 2017) and treatment (Abu Hassan et al., 2016; Ghazali et al., 2010; Laohavinij et al., 2010; Magaji et al., 2017) were the prognostic factors for poor colorectal cancer survival.

On the other hand, patients who received surgical treatment was found to possess higher risk of dying with poorer survival rate (Abu Hassan et al., 2016; Laohavinij et al., 2010; Magaji et al., 2017). Unlike this study, we observed poorer survival among those who did not receive any surgical treatment (Ghazali et al., 2010). Having a combination of treatment with adjuvant therapy (chemotherapy and/or radiotherapy) would have improved survival (Abu Hassan et al., 2016). Better survival among Chinese patients were also observed elsewhere (Abu Hassan et al., 2016; Ministry of Health Malaysia, 2018). Patients with Chinese background ethnicity were found to default less (Rashid et al., 2009), and probably the cultural difference and attitude towards the illness (Du et al., 2002) had led to better survival among them.

There were some limitations to this study. This secondary data was highly dependent on the effort of passive notification by data providers and active case findings by the cancer registry staff. Further search of additional information could not be performed due to total lockdown during COVID-19 pandemic in the country.

For future studies, it is recommended to collect more clinical information to improve our understanding on the treatment and other important variables that were not analysed in this study.

In conclusion, the survival rate for colorectal cancer

patients in Sabah was comparatively lower than other studies in Malaysia and in some Asian countries. Stage at diagnosis was the only significant prognostic factor for colorectal cancer survival in Sabah. Patients who presented at later stage had poorer survival as compared to early stage. On that account, health promotion including cancer awareness should be delivered to the society to encourage early presentation and diagnosed at early stage. The usage of community-based screening program should be emphasized in addition to encouraging early diagnosis to improve survival.

Author Contribution Statement

Conception and analysis: PNA, RA; Data curation, methodology and drafting the article: PNA; Article review and editing: NOT, RA, SSSAR, FR, NG, MAAR, SNY; Project administration: PNA, SSSAR; Project resources: SSSAR; Project supervision: NOT, RA.

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Ethical considerations

This study obtained ethical clearance from Ethical Committee of Faculty of Medicine and Health Sciences, University Malaysia Sabah (UMS) (JKEtika 1/20(18)) and Medical Review and Ethical Committee, Ministry of Health Malaysia (NMRR-19-3789-52258 (IIR)).

Availability of Data

The datasets generated and/or analyzed during the study are not publicly available as they belonged to Malaysia National Cancer Registry Department but are available from the corresponding author on reasonable request.

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Conflict of interest

Authors declare there is no conflict of interest.

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