

RESEARCH ARTICLE

Survival Analysis and Prognostic Factors for Colorectal Cancer Patients in Malaysia

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Abstract

Background: Cancer survival analysis is an essential indicator for effective early detection and improvements in cancer treatment. This study was undertaken to document colorectal cancer survival and associated prognostic factors in Malaysians. **Materials and Methods:** All data were retrieved from the National Cancer Patient Registry-Colorectal Cancer. Only cases with confirmed diagnosis through histology between the year 2008 and 2009 were included. Retrieved data include socio-demographic information, pathological features and treatment received. Survival curves were plotted using the Kaplan-Meier method. Univariate analysis of all variables was then made using the Log-rank test. All significant factors that influenced survival of patients were further analysed in a multivariate analysis using Cox' regression. **Results:** Total of 1,214 patients were included in the study. The overall 3- and 5-year survival rates were 59.1% and 48.7%, respectively. Patients with localized tumours had better prognosis compared to those with advanced stage cancer. In univariate analysis, staging at diagnosis ($p<0.001$), primary tumour size ($p<0.001$), involvement of lymph nodes ($p<0.001$) and treatment modalities ($p=0.001$) were found to be predictors of survival. None of the socio-demographic characteristics were found to exert any influence. In Cox regression analysis, staging at diagnosis ($p<0.001$), primary tumour size ($p<0.001$), involvement of lymph nodes ($p<0.001$) and treatment modalities ($p<0.001$) were determined as independent prognostic factors of survival after adjusted for age, gender and ethnicity. **Conclusions:** The overall survival rate for colorectal cancer patients in Malaysia is similar to those in other Asian countries, with staging at diagnosis, primary tumor size, involvement of lymph node and treatment modalities having significant effects. More efforts are needed to improve national survival rates in future.

Keywords: Colorectal cancer - Malaysia - survival - prognosis - factors

Asian Pac J Cancer Prev, 17 (7), 3575-3581

Introduction

Colorectal cancer remains as significant cause of morbidity and mortality worldwide. It is the third most common cancer worldwide, behind lung and prostate cancers in men and only second to breast cancers in women. Colorectal cancer becomes fourth highest in cancer mortality when sexes are combined (Ferlay et al., 2015; American Cancer Society, 2015). Over the last few decades, many achievements were seen in managing colorectal cancer. These includes the availability of useful screening tool, progression in surgical technique, advancement in treatment modalities and many more (Xu et al., 2006; Huerta, 2008; Chokshi et al., 2010). As a result, patients can have a better prognosis and improved quality of life after diagnosed with colorectal cancer. Thus, the cancer survival analysis is an essential indicator for an effective early detection and improvements in cancer treatment.

Several local studies had analyzed data on colorectal

cancer survival, but the studied population was confined to single or two hospitals. For instance, Rashid et al. (2009) in their study of 107 colorectal cancer patients at University Kebangsaan Malaysia Medical Centre confirmed that the overall survival at five-year follow up was 40%. In another study by Kong et al. (2010) that involved a comparison of colorectal cancer survival rate between University Malaya Medical Center (UMMC) and Sarawak General Hospital (SGH), it was found that SGH has lower five-year survival rate compared with UMMC (45.7% vs. 60.5%). In the light to document the Malaysians survival rate and associated prognostic factor, the authors carry out analyses utilizing the data from the National Cancer Patient Registry-Colorectal Cancer.

Materials and Methods

This study was conducted using secondary data from the Malaysia National Cancer Patient Registry - Colorectal Cancer. This registry was established in October 2007

and registered with National Medical Research Registry (NMRR-07-49-242). The registry coordinating centre is based at Clinical Research Centre, Sultanah Bahiyah Hospital, Alor Setar, Kedah, Malaysia. The aim of the registry is to systematically collect data on all aspects of colorectal cancer relevant to its prevention and treatment. For the purpose of this study, only patients whose colorectal cancer diagnosis was confirmed by histology between the year 2008 and 2009 were included. Foreign nationals were excluded from the data analysis.

Retrieved data include demographic information (e.g. age, gender, ethnicity, diabetes status, presence of family history of colorectal cancer and current status of the patient), pathological features and treatment received. The current status of registered patients (whether still alive or death) was ascertained by cross-checking the data with National Registration Department, Ministry of Home Affairs. Tumour was staged according to pathologic pTNM Staging system which is based on the size of the primary tumor (pT), the extent of spread to the nearby lymph nodes (pN), and the presence of metastasis (pM) (Greene et al., 2003).

The analyses were performed with IBM SPSS Statistics for Windows software version 20.0 (IBM Corp, Armonk, NY, USA). The frequencies of each demographic characteristic, the primary cancer site, type of treatment modalities, the surgical procedure performed, and cancer pathological features of all patients were obtained. No imputation was done on the missing data. To estimate survival rate, the survival analysis at three-year and five-year intervals were performed using the Kaplan-

Table 1. Demographic characteristics of colorectal cancer patients, 2008-2009

Demographic characteristics	n	(%)	Mean	(SD)
Age (years)			61.3	(12.49)
29 or less	15	(1.2)		
30-39	47	(3.9)		
40-49	162	(13.3)		
50-59	301	(24.8)		
60-69	365	(30.1)		
70 or more	319	(26.7)		
Gender				
Male	687	(56.6)		
Female	527	(43.4)		
Ethnicity				
Malay	481	(39.6)		
Chinese	519	(42.8)		
Indian	80	(6.6)		
Other	134	(11.0)		
Diabetes Mellitus *				
Yes	893	(78.5)		
No	245	(21.5)		
Family History of Colorectal Cancer **				
Yes	997	(92.3)		
No	83	(7.7)		
Current Status (Updated on June 2014)				
Death	599	(49.3)		
Alive	615	(50.7)		

*-missing data on diabetes status in 76 patients; **-missing data on family history of colorectal cancer in 134 patients

Meier method. The log-rank test was used to compare the survival rate for each variable. The multiple Cox proportional hazards regression analysis (using the 'enter' method) was carried out to explore the hazard ratio of associated factors on survival. Then the final model was adjusted for age, gender and ethnicity to reduce the bias. The probability value of less than 0.05 (p-value < 0.05) was considered as statistically significant.

Results

Patient characteristics

A total of 1214 patients diagnosed with colorectal cancer between January 2008 and December 2009 met the inclusion criteria for the study. Of this, 57.0% were male while 43.0% were female. The mean age of the patients was 61.3 years (standard deviation =12.49) with a majority of them were in the age group of 60-69 years (30.1%). Chinese was the most ethnic group diagnosed with colorectal cancer (42.8%), followed by Malay (39.6%), Indian (6.6%) and other ethnicity (11.0%). Other

Table 2. Site and Pathological Features of Colorectal Cancer Patients, 2008-2009

Characteristics	n	(%)
Primary Cancer Site (a)		
Caecum	60	(5.0)
Ascending colon	66	(5.5)
Hepatic flexure	46	(3.8)
Transverse colon	58	(4.8)
Splenic flexure	28	(2.3)
Descending colon	52	(4.3)
Sigmoid colon	256	(21.3)
Rectosigmoid	215	(17.9)
Rectum	380	(31.6)
Anorectal	20	(1.7)
Colon, unspecified	21	(1.7)
Staging at Diagnosis		
Stage I	139	(11.4)
Stage II	364	(30.0)
Stage III	416	(34.3)
Stage IV	295	(24.3)
Primary Tumour Size (b)		
pT1	34	(3.4)
pT2	138	(13.8)
pT3	649	(65.1)
pT4	177	(17.7)
Involvement of Lymph Node (c)		
pN0	501	(50.0)
pN1	291	(29.0)
pN2	210	(21.0)
Tumour Differentiation (d)		
Well	159	(15.7)
Moderate	810	(80.1)
Poor	43	(4.2)
Treatment Modalities		
Surgery + Chemotherapy + Radiotherapy	129	(10.6)
Surgery + Chemotherapy OR Surgery + Radiotherapy	372	(30.6)
Surgery only	655	(54.0)
Chemotherapy ± Radiotherapy	58	(4.8)

a-missing data on primary cancer site in 12 patients; b-missing data on primary tumour size in 216 patients; c-missing data on lymph nodes involvement in 212 patients; d-missing data on tumour differentiation in 202 patients

Table 3. Univariate Survival Analysis on Socio-demographic Characteristics of Colorectal Cancer Patients, 2008 - 2009.

Variables	Number of Patients n	Number of Events n	Survival Rate, %				χ^2 (df)	p-value (d)
			3 years	(95% CI) ^c	5 years	(95% CI) ^c		
Overall	1214	615	59.1	(56.4,61.9)	48.7	(45.8,51.7)		
Age group (years)							9.86(5)	0.079
29 or less	15	6	73.3	(51.0,95.7)	66.7	(42.8,90.5)		
30-39	47	19	68.1	(54.8,81.4)	58.1	(43.5,72.7)		
40-49	162	72	63.6	(56.2,71.0)	54.2	(45.9,62.6)		
50-59	301	157	60.5	(54.9,66.0)	47.6	(41.9,53.4)		
60-69	365	202	54.0	(48.9,59.1)	44.1	(38.8,49.5)		
70 or more	324	159	58.9	(53.5,64.3)	49.0	(43.1,54.9)		
Gender							1.97(1)	0.161
Male	687	362	58.4	(54.7,62.1)	46.3	(42.4,50.3)		
Female	527	253	60.2	(56.0,64.3)	51.8	(47.4,56.2)		
Ethnicity							5.38(3)	0.146
Malay	481	256	54.9	(50.4,59.3)	46.4	(41.7,51.0)		
Chinese	519	257	60.5	(56.3,64.7)	49.6	(45.1,54.1)		
Indian	80	41	63.8	(53.2,74.3)	48.3	(37.3,59.4)		
Other	134	61	66.4	(58.4,74.4)	54.2	(45.3,63.1)		
Diabetes Mellitus							0.30(1)	0.586
Yes	245	119	60.8	(54.7,66.9)	51.1	(44.6,57.5)		
No	893	455	58.8	(55.6,62.0)	48.5	(45.0,51.9)		
Family History of Colorectal Cancer							0.30(1)	0.584
Yes	83	40	60.2	(49.7,70.8)	49.7	(38.4,61.1)		
No	997	507	59.2	(56.1,62.2)	48.6	(45.3,51.9)		

Note: ^c Survival analysis using the Kaplan-Meier method; ^d Log-rank test; 95% CI = 95% confidence interval

variables were described in Table 1.

Site and pathological features

The rectum was the primary cancer site involved in 380 patients (31.6%), while tumour was found at sigmoid colon in 256 patients (21.3%). Other anatomical sites involved were summarized in Table 2. More than one-third of the total patients (34.3%) were diagnosed with stage III at presentation. Only small proportion of patients (139, 11.4%) was presented earlier at stage I. According to the histology report, majority of the patients were detected with pT3 (65.1%), pN0 (50.0%) and moderately differentiated (80.1%).

Treatment modalities

One hundred twenty nine (10.6%) patients had received a combination of surgical resection, chemotherapy and radiotherapy while another 30.6% of patients had either surgery with chemotherapy or surgery with radiotherapy. More than half of the total studied patients (54.0%) only had surgical resection of the tumour as the cancer treatment. A small percentage of the patient did not have any surgical intervention. They received chemotherapy, radiotherapy or combination of both.

Survival analysis

The Kaplan-Meier estimates of the 3-year and 5-year survival rate after diagnosis (Table 3, Figure I) were 59.1% (95% CI = 56.4% to 61.9%) and 48.7% (95% CI = 45.8% to 51.7%), respectively. Younger age group patients had better survival compared to their older counterpart (more than 60 years old). Although Chinese patients had the most death events, but their five-year survival rate were slightly higher than Malay and Indian patient. The three and five-year survival rate based on staging was 77.0%

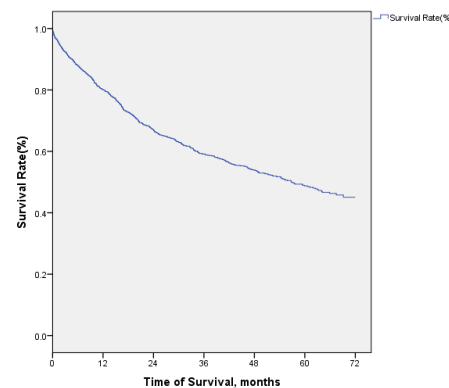


Figure 1. The Kaplan-Meier Curve of Overall Survival Rate for Colorectal Cancer Patients, 2008 - 2009

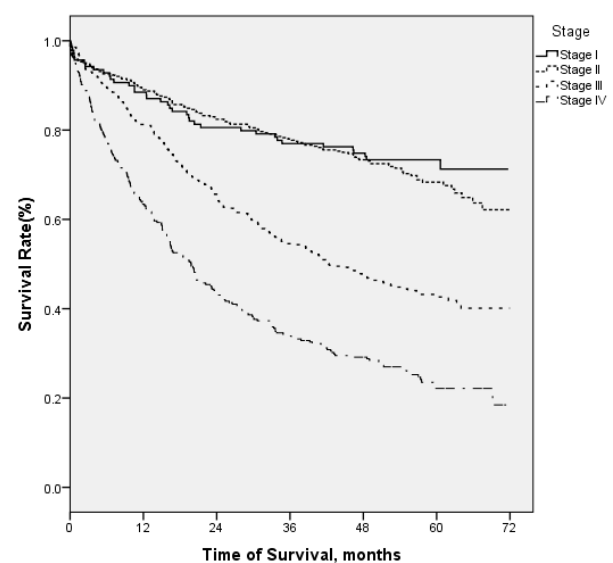


Figure 2. The Kaplan-Meier Curve of Survival Rate for Colorectal Cancer Patients by Staging, 2008 - 2009

Table 4. Univariate Survival Analysis on Primary Cancer Site and Pathological Features of Colorectal Cancer

Variables	Number of	Number of	Survival Rate, %			χ^2 (df)	p-value ^d
	Patients	Events	3 years	(95% CI) ^c	5 years		
	n	n					
Primary Cancer Site						10.4(10)	0.403
Caecum	60	28	55.0	(42.4,67.6)	53.3	(40.7,66.0)	
Ascending colon	66	32	60.6	(48.8,72.4)	50.8	(38.5,63.0)	
Hepatic flexure	46	17	69.6	(56.3,82.9)	63.0	(49.1,77.0)	
Transverse colon	58	26	63.8	(51.4,76.2)	51.1	(36.6,65.6)	
Splenic flexure	28	13	60.7	(42.6,78.8)	60.7	(42.6,78.8)	
Descending colon	52	26	63.5	(50.4,76.5)	50.2	(36.0,64.4)	
Sigmoid colon	256	123	61.7	(55.8,67.7)	51.7	(45.4,58.0)	
Rectosigmoid	215	117	54.9	(48.2,61.5)	46.4	(39.6,53.2)	
Rectum	380	205	56.8	(51.9,61.8)	43.5	(37.9,49.0)	
Anorectal	20	14	60.0	(38.5,81.5)	32.0	(9.8,54.2)	
Colon, unspecified	21	9	76.2	(58.0,94.4)	53.3	(30.2,76.4)	
Staging at Diagnosis						193.9(3)	<0.001
Stage I	139	38	77.0	(70.0,84.0)	73.4	(66.0,80.7)	
Stage II	364	116	78.0	(73.8,82.3)	68.3	(63.3,73.4)	
Stage III	416	236	54.6	(49.8,59.4)	42.6	(37.7,47.6)	
Stage IV	295	225	33.9	(28.5,39.3)	22.1	(17.0,27.2)	
Primary Tumour Size						73.5(3)	<0.001
pT1	34	6	85.3	(73.4,97.2)	81.4	(67.8,95.0)	
pT2	138	44	79.7	(73.0,86.4)	66.9	(58.5,75.3)	
pT3	649	297	63.9	(60.3,67.6)	54.1	(50.1,58.1)	
pT4	177	125	43.5	(36.2,50.8)	26.5	(18.9,34.2)	
Involvement of Lymph Node						124.2(2)	<0.001
pN0	501	163	77.4	(73.8,81.1)	66.9	(62.5,71.3)	
pN1	291	156	58.4	(52.8,64.1)	44.9	(38.8,50.9)	
pN2	210	154	36.2	(29.7,42.7)	27.4	(21.2,33.6)	
Tumour Differentiation						3.96(2)	0.138
Well	159	76	62.3	(54.7,69.8)	51.7	(43.5,59.9)	
Moderate	810	391	61.5	(58.1,64.8)	51.2	(47.6,54.8)	
Poor	43	26	53.5	(38.6,68.4)	38.9	(24.1,53.7)	
Treatment Modalities						15.7(3)	0.001
Surgery + Chemotherapy + Radiotherapy	129	56	69	(61.0,77.0)	54.3	(44.5,64.0)	
Surgery + Chemotherapy or Surgery + Radiotherapy	372	177	63.4	(58.5,68.3)	53.2	(48.0,58.4)	
Surgery only	655	343	55.6	(51.8,59.4)	46.7	(42.7,50.7)	
Chemotherapy ± Radiotherapy	58	39	46.6	(33.7,59.4)	30.6	(17.9,43.3)	

^cSurvival analysis using the Kaplan-Meier method; ^dLog-rank test; 95% CI = 95% confidence interval

Table 5. Multivariate Analysis of Prognostic Factors Influencing Survival of Colorectal Cancer Patients

Variables	Adjusted HR	(95% CI)	p-value { ^c }
Staging at Diagnosis			<0.001
Stage I	1.00	(ref.)	
Stage II	0.88	(0.50,1.54)	
Stage III	1.50	(0.84,2.68)	
Stage IV	2.30	(1.29,4.09)	
Pathological Tumour Size			<0.001
pT1	1.00	(ref.)	
pT2	1.63	(0.69,3.89)	
pT3	2.38	(0.97,5.84)	
pT4	3.73	(1.50,9.27)	
Pathological Node Status			<0.001
pN0	1.00	(ref.)	
pN1	1.21	(0.89,1.64)	
pN2	1.90	(1.40,2.59)	
Treatment Modalities			<0.001
Surgery + Chemotherapy + Radiotherapy	1.00	(ref.)	
Surgery + Chemotherapy or Surgery + Radiotherapy	1.12	(0.79,1.57)	
Surgery only	1.71	(1.23,2.37)	
Chemotherapy ± Radiotherapy	1.17	(0.68,2.03)	

Note: ^c Multiple Cox proportional hazards regression analysis using the Enter method, adjusted by age, gender and ethnicity; HR = Hazard ratio; 95% CI = 95% confidence interval

and 73.4% for patients with stage I, 78.0% and 68.3% for those with stage II, 54.6% and 42.6% among patients with stage III, 33.9% and 22.1 % for patients with stage IV. These rates were presented in Table 4 and Figure II. In univariate analysis, staging at diagnosis, primary tumor size, involvement of lymph node, and treatment modalities were the significant factors ($p < 0.05$) on patient survival using Kaplan-Meier method.

On further analysis, Cox proportional hazards regression analysis was used to determine the hazard ratio of each variable on colorectal cancer patient's survival. All the predictor variables were included in the model and omitted one by one if the variable is highly not statistically significant to the outcome. The analysis revealed that staging at diagnosis (p -value < 0.001), primary tumor size (p -value < 0.001), involvement of lymph node (p -value < 0.001) and treatment modalities (p -value < 0.001) had a significant effect on patients' survival after adjusting the hazard ratio for age, gender and ethnicity (Table 5). For staging at diagnosis, the risk of colorectal cancer death was 2.30 times higher for those who were diagnosed with stage IV at presentation, compared to stage III (HR = 1.50), stage II (HR = 0.88) and stage I. For pathological tumor size and node status, pT4 and pN2 were 3.73 and 1.90 times as likely to die of colorectal cancer compared to others. For patient that only had surgical resection of the tumour as the cancer treatment, they were at the highest risk (1.71 times) to die from colorectal cancer compared to other modes of treatments.

Discussion

In Malaysia, the overall colorectal cancer survival rate at three years is 59.1% after diagnosis and decreased to 48.7% at five years. Improved survival at three and five-year can also be seen in patient with localized disease when compared to the patient with advanced stage cancer. However, there is a worrying situation when more than half of the studied population (58.6%) presented at the late stage (stage III and IV). The absolute reason for the delay in seeking treatment is unclear, but several studies suggested that inadequate knowledge of colorectal cancer and lack of awareness among the public could be the possible contributor to this problem (Harmy et al., 2011; Yusoff et al., 2012). More preventive services such as health education and control of cancer risk factors are needed to tackle this issue. Perhaps, the primary care doctors and family physician should be given a bigger role in educating the public. Not only involved in cancer-related promotional activities, but these frontline doctors can also help in identifying and recommending high-risk patients for early colorectal cancer screening and further expert management.

Overall 5-year survival for Malaysian patients diagnosed with colorectal cancer is lower than neighboring country, Singapore. Data from Singapore Cancer Registry shows that five-year survival rates were 57.0% and 58.9% in males and females in the periods of 2003 to 2007 (Teo and Soo 2013). On the contrary, Sudsawat et al. (2010) reported much lower survival of 287 patients diagnosed with colorectal cancer from the central region of Thailand.

They found that five-year survival rate was only at 38.6%, with colon cancer patients had longer median survival time than rectal cancer patients although the difference is not statistically significant. Our five-year survival rate was within the range of other Asian countries, which is between 29% and 69%. The highest survival rates of more than 65% have been reported in Israel and South Korea while India has the lowest prognosis (Allemani et al., 2015). Although more developed countries such as Australia, New Zealand, Canada, the United States and parts of Europe had the highest incidence rates of colorectal cancer, the patients there have a better survival rate (Globocan 2012). This distinct difference in survival rate with the developed regions reflect the effectiveness of the colorectal cancer screening programs implemented there which Malaysia do not have one at the moment. The effort to form national population-based screening program for colorectal cancer is already in the pipeline and the authors believed this screening program will increase early detection of cancer and improve the survival rate in near future.

Patient's survival is significantly influenced by several prognostic factors. Extensive studies had been conducted on the relationship between demographic characteristics, pathological findings and clinical factors on patient's survival after diagnosed with colorectal cancer. In line with other reports (Mehrkhani et al., 2009; Sudsawat et al., 2010; Akkoca et al., 2014), the analysis confirmed that pTNM staging at diagnosis is a strong revealed that affect patients' survival. In the present study, patients who were diagnosed with stage IV had the highest risk (hazard ratio of 2.30) of death among other colorectal cancer stages. This result was comparable with our neighboring countries performance. Thai patients with stage IV had much shorter survival duration (5-year survival rate of 0%) and a higher risk of death due to colorectal cancer (hazard ratio of 8.31) than stage I (Sudsawat et al., 2010). This could be due to a smaller number of the cohort used for survival analyzes.

Among the pathological features, the size of the primary tumour and lymph nodes involvement were linked with survival outcome in univariate and multivariate analyses. Those with the tumour that has grown through the outer lining of the bowel wall (pT4) and presence of cancer cells in four or more nearby lymph nodes (pN2) significantly had poorer survival outcome. Tumour differentiation, however, was not associated with the patients' survival. These findings are in agreement with those from previous reports (Mehrkhani et al., 2009; Vaccaro et al., 2009; Kumar et al., 2015), highlighting the importance of pathological grading that have a significant impact on patient survival.

In term of treatment modalities received by the patient, those who had surgery only, had an adverse prognosis than patient with a combination of surgery, chemotherapy and radiotherapy. This group of patient carries 1.7-fold greater risk of dying from colorectal cancer than other modes of treatments. This finding denotes the importance of receiving other adjuvant therapy (chemotherapy or radiotherapy or both) to prolong the survival of colorectal cancer patient. Reasons for patient to defer from chemotherapy, radiotherapy or other treatment after surgery in the studied population is unknown and should

be the area for future research.

In the evaluation of socio-demographic factors (age group, gender, ethnicity, diabetes status, and family history of colorectal cancer), none of these were found to have a significant relationship in predicting the survival independently. This finding is conflicting with other recent studies, which report older age (Sudsawat et al., 2010; Patel et al., 2013; Lieu et al., 2014), male (Al-Ahwal et al., 2013; Oberoi et al., 2014), Chinese ethnicity (Du et al., 2002) and presence of diabetes (Siddiqui et al., 2008; Hong et al., 2014) as a prognostic factors for poorer survival rate. Locally, Kong et al. (2010) had also identified lower socioeconomic class as a strong predictor for late and more advanced stage at diagnosis, as well as poorer three and five-year survival rate for colorectal cancer. This situation could be due to limited access to specialized health care for early diagnosis and treatment services. In Malaysia setting, the tertiary hospitals, university hospitals and oncology centers are concentrated in an urban area. Due to geographical distance and transportation obstacles to the nearest health facilities faced by individual residing in certain remote area, there will be a delay in detecting colorectal cancer at early stage, hence delay in starting treatment and shorten their survival. Additionally, many of the health promotion campaigns were held in the main cities, hence contributed to a better awareness among the urban population. Therefore, it is important to reach out to the rural and low socioeconomic communities to improve colorectal cancer survival rates.

Certain limitation of this study should be noted. Firstly, the source of the data for this survival analysis was retrieved from the National Colorectal Cancer Registry, which consisted of 34 site data providers (SDPs). The majority were from government hospitals, with a small number from the university hospital and private centers. The authors do aware that many patients may seek cancer treatment from private centers, and this will undermine the current data analysis. Nevertheless, these results provided a glimpse into the present situation about survival rate of colorectal cancer patients in the country and served as a basis for future cancer education and screening activities. The effort is currently in progress to recruiting more private center as one of the SDP to strengthen the registry data collection. Secondly, the presence of missing data was one of the major problems faced during data collection and cleaning. To minimize this issue, the coordinating center for the registry provide continuous training on data collection and data entry for all SDPs.

In conclusion, the overall survival rate for colorectal cancer patients in Malaysia is generally within the range of other Asian countries. Early stage cancer had better survival than the advanced stage, but more than half of the population presented at stage III and IV. Further analysis revealed that staging at diagnosis, primary tumor size, involvement of lymph node and treatment modalities had a significant effect on colorectal cancer survival patients after adjusting the hazard ratio for age, gender and ethnicity. More preventive services, reaching out cancer-related promotional activities to rural and low socioeconomic communities, and formation of national population-based screening program are recommended

to improve national survival rate in future.

Acknowledgements

The authors gratefully acknowledge the assistance provided by all participating SDPs in providing vital data on colorectal cancer for this study analysis. The authors would specifically like to thank Director General of Health Malaysia for his permission to publish this article.

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