

Factors Associated with Mortality among Patients with Colorectal Cancer at the Secondary Care Hospital in Southern Thailand: Hospital-Based Retrospective Cohort Study

Abstract

Background: Globally and in Thailand, the incidence of colorectal cancer (CRC) is third-ranked behind lung and breast cancer, respectively. This hospital-based retrospective cohort study aimed to determine factors associated with mortality among patients with CRC. **Methods:** This study was performed by using the secondary data of the cancer registry among patients with CRC registered in Phatthalung Hospital. Two hundred twenty-eight patients with CRC were diagnosed and followed up from January 2014 to December 2018. Multiple logistic regression analysis was used to analyze factors associated with mortality among subjects with CRC. **Results:** The results revealed that the proportion of mortality among subjects with CRC was 50.44% (115 cases) at six months of following up. Subjects who had an increasing age every ten years (adjusted odds ratio [OR_{adj}] = 1.40, 95 percent confidence interval [95% CI]: 1.09–1.80) were diagnosed with CRC at stage 3 (2.64, 1.19–5.84) and at stage 4 (11.63, 2.69–50.15) more likely to die. Also, subjects who received a combination of chemotherapy and radiotherapy treatment (3.44, 1.20–9.85), combination treatment of surgery, and postoperative care (2.46, 1.22–4.94) were more likely to die. Subjects who had not had surgery treatment were more likely to die (35.00, 7.44–168.27). **Conclusions:** In conclusion, factors such as the age of patients, stage of CRC, and treatment were associated with mortality among patients with CRC. Hence, medical and health professionals should consider these factors according to the treatment and optimization in patients with CRC.

Keywords: Colorectal cancer, death, mortality, staging of colorectal cancer, treatment

Introduction

Currently, cancer is the most significant medical and health problem worldwide. It is caused by changing chemicals to damage deoxyribonucleic acid (DNA) within the cells over time, leading to dysfunction and abnormal growth of cells. Colorectal cancer (CRC) is localized in the large intestine, which is the human body's last gastrointestinal and digestive system. CRC can be defined explicitly as colon cancer or rectal cancer, depending on its location.^[1] The onset develops in the inner lining of polyps, adenomatous, hyperplastic, and inflammatory polyps. Pathologically, 96% of CRC is adenocarcinoma.^[1]

Lifestyle is the leading cause of CRC. It is associated with food consumption such as: red meat, processed meat, high-fat food, and lack of physical activity.^[2] CRC is a preventable disease. It can be identified early by CRC screening using colonoscopy,

which is preferable to detect the abnormal cells growing up into polyps, pre-cancer, and later as cancer cells.^[2]

Globally, the International Agency for Research on Cancer reports that the burden of new cases and deaths from cancer was 18.1 million and 9.6 million in 2018. The incidence of CRC is the third-ranked behind lung and breast cancer, respectively.^[3] The highest incident rate of CRC is in Australia at 36.7 per 100,000 population, followed by Europe, East Asia, and North America at 30.32, 26.5, and 26.2 per 100,000 people, respectively. In Southeast Asia, the morbidity rate was 14.3, and the mortality rate was 7.9 per 100,000 people.^[4] In Thailand, CRC is the third most common cancer after lung and breast cancer, respectively. In 2018, the morbidity rate was 15.5, and the mortality rate was 8.4 per 100,000 people.^[5]

Phatthalung Province is situated in central southern Thailand. Geographically, it is the

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Access this article online

Website:
www.ijpvmjournal.net/www.ijpvm.ir

DOI:
10.4103/ijpvm.ijpvm_104_22

Quick Response Code:



How to cite this article: Maimard Y, Woradet S, Chaimay B. Factors associated with mortality among patients with colorectal cancer at the secondary care hospital in Southern Thailand: Hospital-based retrospective cohort study. *Int J Prev Med* 2023;14:13.

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hill and coastal plains of Songkhla Lake. The mid-year population is approximately 522,322.^[6] Two-thirds of the area in the province is used for agriculture and plantation (71.66%) of rubber, rice, and fruits.^[7] Totally, the ratio of physicians (127) and nurses (807) in Phatthalung Province is 2.48 and 15.72 per 10,000 people.^[8] Phatthalung Hospital is a standard secondary care facility with 450 beds and a referral hospital receiving patients from community hospitals within the province. From 2016 to 2019, the number of visitors in the outpatient departments was 4.11, 4.35, and 4.54 per patient. The number of day admission in in-patients departments was 4.80, 4.71, and 4.68 days per patient, respectively.^[9] Cancer is the first top-ranked cause of death among patients. The trend of cancer mortality fluctuated from 2016 to 2019 (101.80, 95.09, 101.93, 98.15 per 100,000 people, respectively). The mortality rate of all cancers increased from 2013 to 2018 (74.26, 40.6, 92.98, 97.56, 94.13, and 96.98 per 100,000 people, respectively). In addition, it was ranked as the fifth leading cause of mortality among hospitalized patients from 2017 to 2020.^[9] In particular, the incidence of CRC fluctuated from 2017 to 2019 (13.64, 11.73, and 18.89%).^[10]

The factors associated with mortality among patients with CRC are little known in secondary care hospitals in southern Thailand. Previous studies have been conducted in university hospitals in Bangkok, Central Thailand,^[11] and tertiary care hospitals in Roi-Et, Northeastern Thailand,^[12,13] which have highly advanced medical care technology resulting in longer survival time among patients. Basically, the patients from community hospitals will be referred to receive a higher special treatment in secondary and tertiary care hospitals, respectively. Practically, secondary care hospitals play an important role in the hierarchy of the health referral system. However, secondary care hospitals may lack specialty, modern technology, and equipment in treatment. Therefore, the purpose of this study is aimed in determining the factors associated with mortality among patients with CRC. This study is the first study conducted in a secondary care hospital in southern Thailand to plan medical and nursing care among those with CRC.

Methods

Study design

This hospital-based retrospective cohort study was conducted between December 2019 and January 2020. We accessed the secondary data of the cancer registry among patients with CRC in Phatthalung Hospital, Phatthalung Province, Thailand. This study was approved by the Ethics Committee on Human Rights Related to Human Experimentation, Thaksin University, Thailand (COA. No. TSU 2019-041, REC No. 089 on 6 December 2019). The cancer registry database in the hospital was permitted to be used by the directors of Phatthalung Province.

Study participants

The study subjects were patients diagnosed with CRC (International Classification of Diseases and Related Health Problem 10th Revision; ICD-10: C18—Malignant neoplasm of the colon). We enrolled the subjects who registered into the cancer registry in Phatthalung Hospital from January 1, 2014 to December 31, 2018, and of these, 228 patients were diagnosed with CRC during the study period. The power of the study was performed using a continuity correction for a cohort study.^[14] We determined alpha (α) at 0.05, Z (0.975) at 1.959 and power (1- β) at 1.00. The proportion of deaths was 0.81 (98/121) among subjects at stages 1 and 2. The proportion of death was 0.30 (17/57) among subjects at stages 3, 4, and unknown. We yielded 100% of the power of the study.

Data collection

The data were retrospectively reviewed among subjects registered in the cancer registry between January 1, 2014 and December 31, 2018. The demographic characteristic factors were as the following: sex, age, marital status, race, religion, residential areas, and type of health insurance. The pathological and treatment factors were as follows: methods of diagnosis, tumor location, histological types, the grade of differentiation, stage of CRC, extension, metastasis, and treatment. The data were routinely recorded by professional nurses who were well trained in using the cancer registry program and cancer care. The demographic and pathological factors among subjects who were registered and physically examined at the first diagnosis with CRC were used to perform the analysis. In addition, the treatment factors derived from the post-diagnosis were used in this study.

The study subjects were followed up from the beginning diagnosis with CRC for six months. The data were derived and drawn from the cancer registry of Phatthalung Hospital to a datasheet which was ready to analyze in a statistical analysis program.

Data analysis

The demographic, pathological, and treatment factors were presented using descriptive statistics. Logistic regression analysis was used for bivariate and multivariate analysis to quantify the magnitude of the effect of factors on the subjects' mortality. The outcome of this study was mortality among subjects with CRC at six months from the beginning of diagnosis. It was a dichotomous outcome: alive and dead.

A multiple logistic regression analysis modeling method was used to evaluate potential factors on mortality. Initially, bivariate analysis of logistic regression was performed to account for possible demographic and clinical characteristics. A continuous variable, such as patient age, was categorized into groups. Factors with a *P* value

less than or equal to 0.25 on Wald's test during bivariate analysis were entered into the initial multivariate model. Using backward elimination, factors with a *P* value greater than 0.05 on Wald's test were eliminated. The *P* value of the partial likelihood ratio test was tested by model fitting. The final model included all possible factors. Results were presented as odds ratios (OR) with 95 percent confidence intervals (95% CI). No association was defined if OR = 1. A risk association was defined as OR was more significant than 1, and a positive association as OR was less than 1.

Results

In the 228 subjects with CRC, the proportion of mortality among subjects was 50.44%. More than half of the subjects were males (55.26%), and nearly half were aged between 51 and 70 years (48.25%). The average (\pm SD) age among subjects was 64.82 (\pm 13.22) years. Most subjects were married, widowed, and divorced (95.17%). All subjects were Thai citizens (100%), and most subjects were Buddhist (96.49%). Two-thirds of subjects resided in rural areas (71.05%), and two-thirds had universal health insurance coverage (70.61%), as shown in Table 1.

The following is the pathological and treatment factors data among subjects with CRC, as shown in Table 2. Most subjects were diagnosed with histology (88.16%). One-third of the subjects had tumors located at the

rectum NOS (34.21%) and one-fifth had tumors at the sigmoid (22.37%). Most subjects had a histological type of adenocarcinoma (86.84%). Half of the subjects had

Table 2: Pathology and treatment among subjects with colorectal cancer (n=228)

Pathology and treatment factors	Number	Percent
Diagnosis		
Histology	201	88.16
Others (X-Ray, colonoscopy, ultrasound)	27	11.84
Tumor location		
Rectum NOS	78	34.21
Sigmoid	51	22.37
Colon NOS	42	18.42
Ascending to descending	25	10.96
Cecum	21	9.21
Recto sigmoid	11	4.82
Histological types		
Adenocarcinoma	198	86.84
Other carcinoma	30	13.16
Grade of differentiation		
Well	77	33.77
Moderate	114	50.00
Poor	7	3.07
Undifferentiated	20	8.77
Not Applicable	10	4.39
Staging		
I	3	1.20
II	54	23.68
III	71	31.14
IV	23	10.09
Unknown	77	33.77
Extent of colorectal cancer		
In situ	1	0.44
Localization	27	11.84
Direct extension	58	25.44
Regional lymph node	46	20.18
Distant metastasis	23	10.09
Not otherwise specified (NOS)	8	3.51
Unknown	65	28.51
Metastasis		
No	43	18.86
Yes	185	81.14
Unknown site of metastasis	121	53.07
Lymph node	39	5.70
Liver	13	10.96
Peritoneum	2	0.88
Other	2	0.88
More than one site	8	3.51
Treatments		
Surgery	77	33.77
Chemotherapy or Radiotherapy	23	10.09
Surgery and Chemotherapy/Radiotherapy/ Palliative/Supportive/Other	93	40.79
Not Surgery Treat by Chemotherapy and Radiotherapy or Supportive/Palliative/Other	35	15.35

Table 1: Demographic factors among subject with colorectal cancer (n=228)

Demographic factors	Number	Percent
Death		
Yes	115	50.44
No	113	49.56
Sex		
Male	126	55.26
Female	102	44.74
Age (Years)		
≤50	36	15.79
51-70	110	48.25
≥71	82	35.96
Mean±SD (Min: Max)	64.82±13.22 (28:90)	
Marital status		
Married/Widow/Divorced	217	95.17
Single	11	4.82
Religion		
Buddhism	220	96.49
Islam	7	3.07
Christianity	1	0.44
Resident areas		
Rural	162	71.05
Urban	66	28.95
Health insurance		
Universal coverage	161	70.61
Government and entrepreneur	63	27.63
Social security	4	1.75

moderate grades of differentiation (50.00%) and one-third had a well grade of differentiation (33.77%). One-third of the subjects were at stage 3 (31.14%) and an unknown stage (33.77%). One-fourth of the subjects had a direct extension of CRC (25.44%), and one-third of the subjects had an unknown extension of CRC (28.51%). Almost all subjects showed metastasis (81.14%), and one-third of subjects had surgical treatment (33.77%), with nearly half of subjects having a combination of surgery and/or chemotherapy, radiotherapy, palliative, and supportive care (40.79%).

Bivariate analysis using logistic regression analysis revealed that age, stage of CRC, and receiving treatment were significantly associated with mortality among subjects with CRC. Subjects who had an increasing age every ten years were 1.24 times more likely to die (OR = 1.24, 95% CI: 1.02–1.53). Subjects who were at CRC stage 3 were 2.56 times (OR = 2.56, 95% CI: 1.23–5.33), stage 4 were 15.69 times (OR = 15.69, 95% CI: 4.11–59.88) and unknown stage were 2.67 times (OR = 2.67, 95% CI: 1.30–5.52) more likely to die. Subjects who had chemotherapy/radiotherapy, surgery, and postoperative care and not surgery were 3.25, 2.55, and 41.25 times likely to die (OR = 3.25, 95% CI: 1.24–8.50; OR = 2.55, 95% CI: 1.35–4.84; OR = 41.25, 9.11–186.82). However, demographic factors (sex, marital status, religious, and residential areas) and pathological factors (tumor location, histological types, grade of differentiation, an extension of CRC, metastasis, and health insurance) were not associated with mortality among subjects, as shown in Table 3.

A multivariate analysis using a backward elimination method of logistic regression analysis revealed that age, stage of CRC, and treatment were significantly associated with mortality among subjects. Subjects who had an increasing age every ten years were 1.40 times more likely to die (OR_{adj} = 1.40, 95% CI: 1.09–1.80). Subjects who were at CRC stage 3 were 2.64 times (OR_{adj} = 2.64, 95% CI: 1.19–5.84) and stage 4 were 11.63 times (OR_{adj} = 11.63, 95% CI: 2.69–50.15) more likely to die. Subjects who had received chemotherapy and radiotherapy were 3.44 times (OR_{adj} = 3.44, 95% CI: 1.20–9.85), surgery and postoperative care were 2.46 times (OR_{adj} = 2.46, 95% CI: 1.22–4.94), and no surgery was 35.00 times (OR_{adj} = 35.00, 95% CI: 7.44–168.27) more likely to die, as shown in Table 4.

Discussion

In summary, an association between factors and mortality among subjects with CRC was found. Factors such as the age of patients, staging, and receiving treatment were more likely to increase the risk of mortality.

This present study is the first attempt to be conducted in a secondary care hospital in southern Thailand and shows the corresponding risk of patients' age on mortality. Increasing age every ten years was 1.40 times a risk of mortality

among subjects, as the human body degenerates with increasing age. The result of this present study is similar to the previous studies. Recent studies in the USA,^[15] Thailand,^[11] Jordan,^[16] and Taiwan^[17] showed that increasing age is the most significant risk of mortality among subjects with CRC. However, a study in Iran^[18] showed a minimal risk of age at diagnosis on mortality.

This present study showed that the staging of CRC is a risk of mortality among subjects with CRC. It is possible that the staging is a classification of the progression of the disease, i.e., the more stages of CRC, the more severity of the disease. This present study is relevant to previous studies conducted in the tertiary care hospitals in Central Thailand^[11] and Northeast Thailand,^[12,19] which showed that subjects who were at CRC stages 3 and 4 were at increased risk of mortality. In addition, the study^[20] in Malaysian tertiary hospitals found that subjects who were at stage 4 had a greater risk of mortality (HR = 4.61, 95% CI: 3.39–6.28). The study in Singapore^[21] retrospectively reviewed elderly subjects aged more than 70 years old who underwent surgery found that subjects who were at stages 3 and 4 were at a greater risk of mortality (HR = 6.18, 95% CI: 1.55–24.6; 17.9, 95% CI: 4.45–72.1).

In the Middle East, the three previous studies in Iran^[18,22,23] showed that subjects with CRC who were at stages 2, 3, and 4 were at increased mortality risk. In Europe and Australia, the study in France^[24] and Western Australia^[25] showed a similar risk of CRC staging on mortality. In addition, the study in Western Australia^[25] found that subjects who were at an unknown stage of CRC were three times more likely to die (HR = 2.97, 95% CI: 1.57–5.64). However, the study in Ghana^[26] showed that subjects who had an increasing stage of CRC had a greater risk of mortality, but not significant.

Regarding the correlation between age and stage, patients with advanced stages of the disease are generally treated by clinical practice guidelines and clinicians' decisions. In addition, we would like to confirm that this may have a little or not have a chance of correlation. In our study shows a non-linear and a fluctuated proportion, and a small sample size in each category of the variables of age and staging. Hence, it is possible that increasing age and a stage of disease may not be correlated. However, we considered that the variable of age was adjusted into the final model due to significant factors in literature reviews.

Regarding treatments such as chemotherapy and radiotherapy, surgery and postoperative care were associated with mortality among subjects. However, subjects who had no surgery were at a greater risk of mortality. These findings indicated that most subjects had advanced pathology that needed curative combination to extend their life longer. However, in the case of getting no surgery, it is possible that subjects were at the end stage of life, resulting in surgery being inappropriate.

Table 3: Bivariate analysis of factors associated with mortality among subjects with colorectal cancer

Factors	% of Death	OR*	95% CI**	P
Sex				0.236
Female	58 (51.33)	1		
Male	68 (59.13)	1.37	0.81-2.32	
Age (years)				0.030
An increasing and every 10 years	NA***	1.24	1.02-1.53	
Marital status				0.336
Single	4 (36.36)	1		
Married/Widow/Divorced	111 (51.15)	1.83	0.52-6.44	
Religion				0.980
Buddhism	111 (50.45)	1		
Others (Islam and Christian)	4 (50.00)	0.98	0.55-2.09	
Residential area				0.428
Rural	79 (48.77)	1		
Urban	36 (54.55)	1.26	0.71-2.24	
Tumor location				0.116
Colon (Cecum to Descending, Colon NOS)	42 (47.73)	1		
Sigmoid	21 (41.18)	0.77	0.38-1.54	
Rectum (Recto sigmoid, Rectum: NOS)	52 (58.43)	1.54	0.85-2.79	
Histological type				0.959
Other carcinoma	15 (50.00)	1		
Adenocarcinoma	100 (50.51)	1.02	0.47-2.19	
Grade of differentiation				0.053
Low	91 (47.64)	1		
High	24 (64.86)	2.03	0.98-4.22	
Staging				<0.001
I and II	17 (29.82)	1		
III	37 (52.11)	2.56	1.23-5.33	
IV	20 (86.96)	15.69	4.11-59.88	
Unknown	41 (53.25)	2.67	1.30-5.52	
Extension of colorectal cancer				0.141
In situ/Localization/Direct Extension	38 (44.19)	1		
Regional Lymph Node/Distant Metastasis/Not Otherwise Specified (NOS)	77 (54.23)	1.49	0.87-2.56	
Metastasis				0.567
No	20 (46.51)	1		
Yes	95 (51.35)	1.21	0.62-2.36	
Treatment				<0.001
Surgery	22 (28.57)	1		
Chemotherapy/radiotherapy	13 (56.52)	3.25	1.24-8.50	
Surgery and postoperative care	47 (50.54)	2.55	1.35-4.84	
Not surgery	33 (94.29)	41.25	9.11-186.82	
Health insurance				0.952
Government/Enterprise/Social security	34 (50.75)	1		
Universal coverage	81 (50.31)	0.98	0.56-1.74	

*OR=Odds ratios, **95% CI=95 percent confidence interval, ***NA=Not available

Our study showed that one-third of subjects were at stages 3 and 4 (41.23%), and most subjects showed metastasis (81.14%). This present study is similar to previous studies. The two studies in Thailand^[12,13] found that subjects who had received chemotherapy after surgery had their risk of mortality more than halved (55% and 57%, respectively). In addition, the study in Japan^[27] showed that CRC subjects over 80 years who had received chemotherapy after surgery had a 15% reduction in the

risk of mortality. However, the study in France,^[24] USA,^[15] and Thailand^[19] indicated that subjects with CRC had a greater risk of having no surgery.

Limitations

Limitations of this study were found. The potential factors were unaccounted for in this study, including: underlying diseases, carcinoembryonic antigen, smoking, alcohol drinking, body mass index, etc., which led to

Table 4: Multivariate analysis of factors associated with mortality among subjects with colorectal cancer

Factors	Crude OR* (95% CI**)	Adjusted OR* (95% CI**)	P
Age (An increasing every 10 years)	1.24 (1.02-1.53)	1.40 (1.09-1.80)	0.007
Stage			0.001
1 and 2	1	1	
3	2.56 (1.23-5.33)	2.64 (1.19-5.84)	
4	15.69 (4.11-59.88)	11.63 (2.69-50.15)	
Unknown stage	2.67 (1.30-5.52)	1.63 (0.71-3.74)	
Treatment			<0.001
Surgery	1	1	
Chemotherapy/Radio therapy	3.25 (1.24-8.50)	3.44 (1.20-9.85)	
Surgery and postoperative care	2.55 (1.35-4.84)	2.46 (1.22-4.94)	
Not Surgery	41.25 (9.11-186.82)	35.00 (7.44-168.27)	

*OR=Odds ratios, **95% CI=95 percent confidence interval

confounding factors. During 2014–2016, many suspected cases that had signs and symptoms relevant to CRC were not pathologically confirmed due to a lack of pathological oncology physicians. They were referred to visit tertiary care hospitals; these may have more minor cases with CRC than actual in this study.

Conclusions

Factors such as the age of patients, staging, and receiving treatment were associated with mortality among patients with CRC. Results suggested that medical and health professionals consider these factors regarding the therapy to optimize the care among patients with CRC.

Ethics approval and consent to participate

This study was approved by the Ethics Committee on Human Rights Related to Human Experimentation, Thaksin University, Thailand (COA. No. TSU 2019-041, REC No. 089 on 6 December 2019).

Availability of data and materials

The cancer registry database in the hospital was permitted to be used by the directors of Phatthalung Hospital.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 02 Apr 22 Accepted: 04 Jul 22

Published: 18 Feb 23

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