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Prognostic Factors for Survival in Patients with Colorectal Cancer in Iran between 2004-2015: Competing Risks Regression Analysis with Generalized Weibull Model

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ABSTRACT

Background: Colorectal cancer constitutes one of the most common causes of cancer mortality worldwide. The incidence of this malignancy has risen in Iran during the last years. This study aims to estimate the survival of colorectal cancer patients and its prognostic factors using parametric competing risks model.

Methods: In a retrospective study, we used data from 1060 patients with colorectal cancer in the cancer registry of the Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, from 2004 to 2015. Analysis was performed using parametric competing risks model with Weibull distribution. R software was used for all analyses with significance level set at 0.05.

Results: In total, 380 patients (35.8%) had died due to colorectal cancer, 49 patients (4.6%) had died for other causes, and 631 patients (59.5%) survived until the end of the study period. Mean survival for the 1060 patients was 59.96 ± 1.46 months with a median of 45.5 months. Multivariable analysis revealed factors such as age at diagnosis and body mass index (BMI) to significantly affect death by colorectal cancer ($p < 0.001$).

Conclusion: According to the findings of the generalized Weibull parametric competing risks model, only age at diagnosis and BMI were factors influencing the survival of colorectal cancer patients in this study.

Keywords: Survival Analysis, Competing Risks, Colorectal Cancer , Weibull Model

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INTRODUCTION:

Cancer is a major cause of mortality worldwide[1]. Colorectal cancer is characterized by abnormal growth and differentiation of cells in colon and rectum[2, 3]. It constitutes the third most common malignancy in the world and the second cause of cancer mortality. Annually, one million new cases and half a million deaths are reported for colorectal cancer. Its incidence is rising in Asian countries such as China, Japan, South Korea and Singapore[4, 5].

In Iran, colorectal cancer is the fourth most common malignancy in men and the second most common in women. The incidence of colorectal cancer is higher in Iran compared to other Asian countries[6]. In recent years, epidemiological studies have demonstrated the increasing rate of colorectal cancer in Iran[7]. Therefore, it warrants further investigation as a healthcare priority. Survival analysis is one type of investigation to determine the status of a disease and its associated factors. When studying cancer patients, it is possible that the recruited patients may expire for reasons other than the malignancy, giving rise to a situation known as competing risks. For instance, if a group of colorectal cancer patients die for reasons other than colorectal cancer, accurate evaluation of patient survival will be challenging[8]. Nevertheless, most studies addressing prognostic factors associated with survival of colorectal cancer patients use standard methods for survival analysis. In such studies, the researchers ignore the competing risks (considering them as censor), leading to bias in the findings[9].

For this reason, competing risks must be accounted for in analyses to yield a more accurate estimation of patient survival as well as the associated prognostic factors. In analyzing data of competing risks for each person, in addition to failure time, failure type (event type) is also considered. Parametric modeling is one of the methods used for analyzing competing risks data[10]. In this approach, survival time is assumed to follow a specific distribution, and analyses are based on this distribution. In parametric models, identifying the appropriate parametric distribution may be challenging, but when a flexible distribution is fitted on the data, it may be claimed as appropriate for these data[11, 12]. In 1993, Mudholkar introduced the generalized Weibull distribution which includes an additional shape parameter and is a generalization of the classical Weibull distribution. Thus, if a value of 1 is assigned to this parameter, it will transform into the classical Weibull distribution[13]. In this study, we used the generalized Weibull distribution for survival time as it is sufficiently flexible.

Considering the above and the increasing incidence of colorectal cancer over the last decades[14], the current study aims to investigate the prognostic factors associated with survival in colorectal cancer patients using a parametric competing risks model based on the generalized Weibull distribution.

METHODS:

In a retrospective study, we retrieved the data pertaining to 1462 patients referring to Taleghani Hospital, Tehran, who had their information registered at the Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, from 2004 to July 2015. Death was ascertained by calling the patients' next of kin. Causes of death were coded as death due to colorectal cancer or death due to other causes. For all patients, demographic characteristics (including age at diagnosis, sex, and family history of cancer) and clinical characteristics (including body mass index [BMI], tumor size, and tumor site) were recorded. Patients' survival was calculated in months by subtracting the date of diagnosis and the date of demise or censor. In this study, living individuals were considered as right censored. Some patients were excluded due to unknown survival status. For a number of patients, in addition to unknown data

of diagnosis, the last survival status remained unknown due to reasons such as unresponsiveness to telephone calls. In addition, incomplete information in clinical files of some patients resulted in missing data for important variables such as tumor stage or grade. Eventually, 402 patients were excluded for these reasons, and final analyses were performed based on 1060 colorectal cancer patients.

In this study, death due to colorectal cancer was considered as the outcome of interest, and death due to other causes was considered as competing risk. Thus, the type of event is considered in the analyses and the parametric competing risks model based on the generalized Weibull distribution is used for analyzing the data. The survival function of the generalized Weibull distribution is defined as:

$$S_j(t)=1-(1-e^{-\alpha j t^{\beta_j}})^{\gamma j} \quad J= 1,2$$

where j denotes the type of event. The Weibull model is a specific variant of the generalized Weibull model; when $\gamma = 1$, the generalized Weibull model is transformed into a Weibull distribution with two parameters (α, β)[15]. Therefore, to assess the goodness of fit of the generalized Weibull model, we used the likelihood-ratio test and the LR statistic. For this purpose, the hypothesis $H0: \gamma = 1$ is tested against $H1: \gamma \neq 1$; if rejected, the goodness of the generalized Weibull model for the current data is confirmed. R software was used for all analyses with significance level set at 0.05.

RESULTS:

Of 1060 colorectal cancer patients, 615 (58%) were men and 445 (42%) were women. Age at diagnosis ranged from 12 to 97 years, with mean ±

Table 1. Demographic and clinical characteristics of colorectal cancer patients by cause of death

Variable	Level	Number of Patients (%)	Death due to Colorectal Cancer	Death due to Other Causes	Mean Survival (SE)
Tumor Site	Colon	513 (48.4)	194 (51.1)	23 (46.9)	60.5 (2.8)
	Rectum	547 (51.6)	186 (48.9)	26 (53.1)	53.5 (1.84)
Sex	Female	445 (42)	144 (37.9)	18 (36.7)	58.8 (2.19)
	Male	615 (58)	236 (62.1)	31 (63.3)	55.6 (1.95)
Tumor Size	< 1 cm	182 (17.2)	64 (16.8)	2 (4.1)	69.19 (4.15)
	> 1 cm	878 (82.8)	316 (83.2)	47 (95.9)	54.4 (1.52)
Family History of Cancer	Positive	458 (43.2)	162 (42.6)	15 (30.6)	59.1 (2.31)
	Negative	602 (56.8)	218 (57.4)	34 (69.4)	55.3 (1.87)
Body Mass Index	< 24.9	590 (55.6)	245 (23.2)	283 (6.1)	115 (10.93)
	25 – 29.9	362 (34.2)	104 (9.8)	19 (1.8)	201.08 (10.49)
	> 30	108 (10.2)	31 (2.9)	1 (0.01)	240.36 (19.6)

standard deviation of 53.67 ± 0.46 years. The patients' survival from diagnosis to event (death due to colorectal cancer, or death due to other causes) or censor (end of study) was calculated in months. The competing risks included: myocardial infarction, gastric and renal cancer, and respiratory diseases. The mean survival of the 1060 patient was 56.96 ± 1.46 months with a median of 45.5 months. At the end of the study period, 380 patients (35.8%) had died due to colorectal cancer, 49 patients (4.6%) had died due to other causes, and 631 patients (59.5%) had survived. The median survival for patients expired due to colorectal cancer was 33 ± 1.83 months with 95% confidence interval (CI) of 29.5, 36.5. The mean BMI of patients was 24.5 ± 0.13 with 95%CI of 24.24, 24.75.

Other characteristics of categorical variables are presented in **Table 1**. According to this table, the hypothesis γ = 1 is rejected at the significance level of 0.05. Therefore, the generalized Weibull model is appropriate for colorectal cancer data in this study. Multivariable analysis demonstrated that factors such as age at diagnosis and BMI significantly affect death due to colorectal cancer ($p < 0.001$). Furthermore, the probability of survival diminishes with increasing age at diagnosis **(Table 2)**. Diagram 1 shows that according to the generalized Weibull competing risks model, survival was higher in patients diagnosed after 60 years of age compared to those diagnosed before 60 years of age.

Table 2. Results of fitting the generalized competing risks model to data of cancer patients

Variable	Level	Coefficient (SE)	95% Confidence Interval	Probability
Constant	-	-1.475 (0.024)	(-1.52, -1.48)	< 0.001*
Tumor Site	Colon	-0.057 (0.035)	(-0.124, 0.0011)	0.10
	Rectum	-	-	
Sex	Female	-0.026 (0.037)	(-0.098, -0.047)	0.5
	Male	-	-	
Tumor Size	< 1 cm	-0.020 (0.056)	(-0.129, 0.090)	0.072
	> 1 cm	-	-	
Family History of Cancer	Positive	-0.023 (0.036)	(-0.093, 0.046)	0.52
	Negative	-	-	
Body Mass Index	< 24.9	-	-	-
	25 – 29.9	-0.067 (0.037)	(-0.006, 0.14)	0.04
	> 30	-0.089 (0.066)	(-0.22, 0.042)	0.03
Age at Diagnosis	-	0.003 (0.000)	(0.003, 0.004)	< 0.001*
Shape Parameter (β)	-	0.0493 (0.006)	(0.48, 0.50)	< 0.001*
Shape Parameter (γ)	-	1. 73 (0.054)	(0.40, 0.52)	< 0.001*

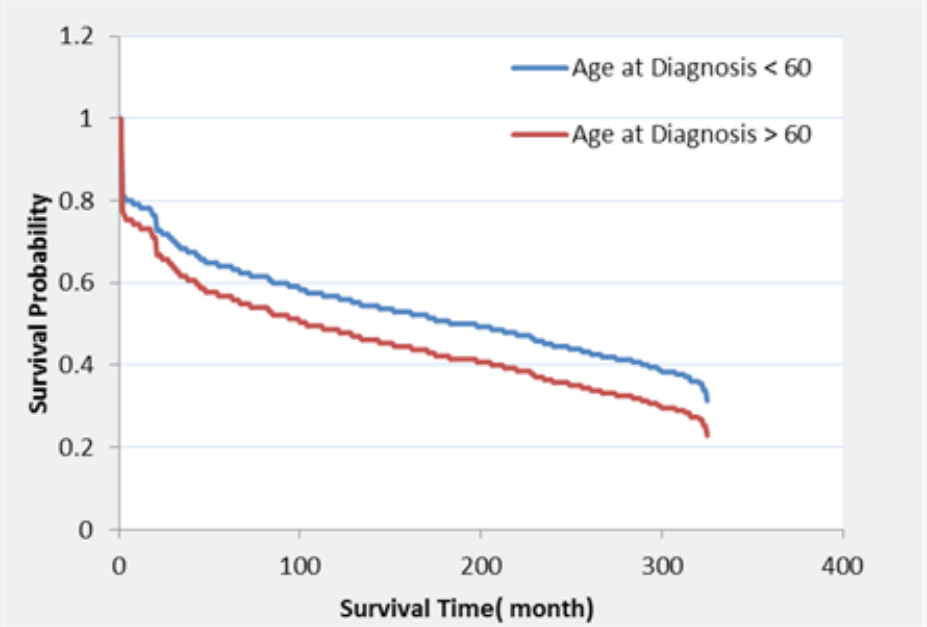

Figure 1. Survival curve by age at diagnosis according to the generalized Weibull model. Red line indicates patients diagnosed after 60 years of age.

According to the results of the generalized Weibull model, patients with BMI of 25 to 29.29, and those with BMI above 30 had higher survival and lower risk of death due to colorectal cancer compared to patients with BMI below 24.9. In general, patients with BMI above 30 had the lowest risk of death due to colorectal cancer. **Figure 2** depicts the survival of colorectal cancer patients by body mass index. Other variables, such as family history of cancer, tumor size, tumor site, and patient's sex were not found to be significant in multivariable analysis ($p > 0.05$).

DISCUSSION:

Considering the rising incidence of colorectal cancer over the last few decades in Iran, investigating the prognostic factors associated survival is crucial in these patients. In the current study, we evaluated the survival of patients with colorectal cancer as well as its associated factors using the generalized Weibull model with parametric competing risks analysis. According to the results, body mass index was identified as an independent variable associated with patients' survival, with increasing BMI values correlated with improved survival in patients with colorectal cancer. Previous studies on survival in colorectal cancer have yielded similar results[16]. A study by Hines et al. in 2009 reported that underweight was associated with higher mortality in colorectal cancer patients, while overweight and obesity reduced death[17].

Nevertheless, some studies have not found a significant relationship between body mass index and survival in colorectal cancer patients[3, 18]. In 2000, one study on men and women with colorectal cancer in the United States reported body mass index to influence both the incidence of colorectal cancer and survival of colorectal cancer patients[19]. Many studies have indicated that increased body mass

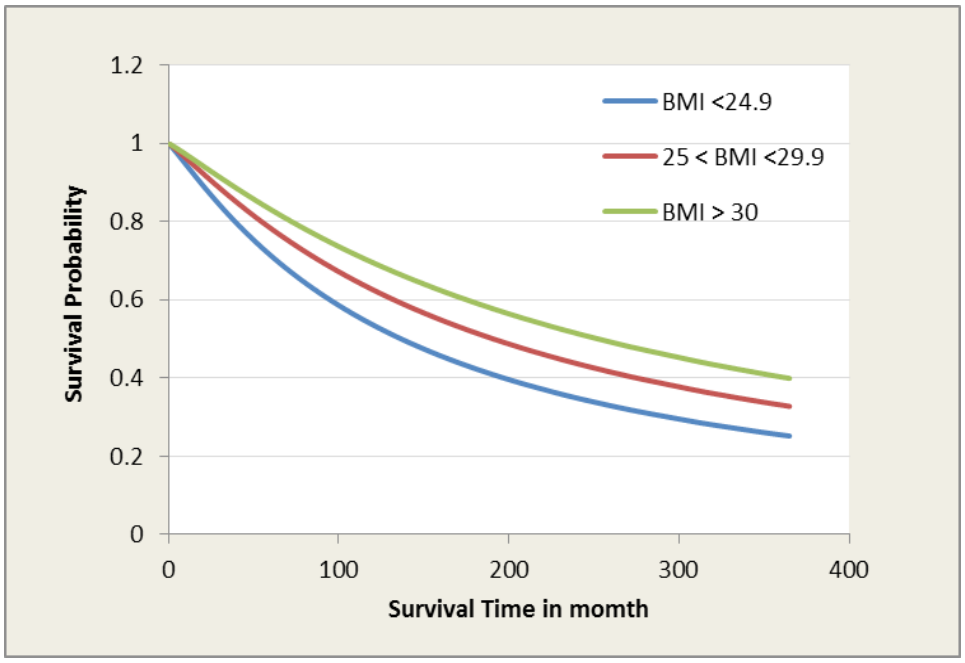

Figure 2. Survival curve by body mass index according to the generalized Weibull model

index increases the risk of colorectal cancer in men, but not women. In 2015, Maskarinec stated that body mass index does not significantly affect survival in colorectal cancer patients, but is an important risk factor for its incidence[20]. In 2016, Kocarnik demonstrated that the relationship between body mass index and survival of patients with colorectal cancer depends on the stage of the disease[21, 22]. The disparity in results may reflect the variations in the number of clinic-pathological factors considered in analysis as well as the type of population studied. Most studies on colorectal cancer have indicated age at diagnosis to affect patients' survival[23]. Similarly, out findings suggest that age at diagnosis has a significant impact on survival of patients with colorectal cancer, which is consistent with findings of Mehrkhani et al.[24]. Moreover, a study by Park et al. reported age at diagnosis as an influential factor for colorectal cancer[25]. In the present study, the mean age at diagnosis was lower than that reported by the American Association of Cancer in 2013[26]. In 2012, Pourhoseingholi et al. reported the mean age of colorectal cancer patients to be lower in Iran compared to Western countries[27, 28]. However, some studies, such as one by Roshanaei et al. have failed to indicate a significant difference[25].

In the current study, consistent with some previous studies[24], family history of cancer did not affect patients' survival. On the other hand, some studies have reported that colorectal cancer in a first-degree relative increases the risk of this malignancy by two to three-folds[30].

As mentioned before, in this study, we evaluated the survival of patients with colorectal cancer and its associated factors using the competing risks model based on generalized Weibull model. In the parametric approach, competing risks are not considered as censors, but the type of the event is fac-

tored in analyses. As noted by Huang & Chang[31] as well as Chin[32], considering the risks as censor may yield biased results. In addition, when the survival pattern follows a specific parametric model, the estimations made will be more accurate compared to the results of other methods, such as nonparametric approaches[33, 34]. In this study, a generalized Weibull distribution was considered for survival, and all analyses performed on this basis. The generalized Weibull distribution, with a third shape parameter, is sufficiently flexible and may cover different forms of the hazard function.

A limitation of this study was incompleteness of patient files, in terms of tumor stage and grade, which may substantially affect survival in patients with colorectal cancer. In 2009, Mehrkhani et al. (2009) and Baghestani et al. (2015) addressed the factors associated with survival in colorectal cancer patients. Their findings have revealed tumor stage and grade as two important and influential factors in survival of patients with colorectal cancer[16, 24].

The generalized Weibull distribution, with a third shape parameter, is sufficiently flexible and may cover different forms of the risk function. Based on this, we propose further analysis on on data of competing risks in colorectal cancer, using other parametric models such as the four-parameter lag logistic model which is more flexible compared to the generalized Weibull model.

CONCLUSION:

In this study, using the generalized Weibull model with competing risks, multivariable analysis revealed that factors such as age at diagnosis and body mass index significantly affect death due to colorectal cancer. Thus, with increasing BMI, the chance of survival increases and the risk of death due to colorectal cancer diminishes. Moreover, with increasing age at diagnosis, the change of survival is reduced.

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