A Bayesian Approach to Model the Underlying Predictors of Early Recurrence and Postoperative Death in Patients with Colorectal Cancer

Leila Mahmoudi
Zanjan University of Medical Sciences
Ramezan Fallah
Zanjan University of Medical Sciences
Ghodratollah Roshanaei
Tabriz University of Medical Sciences
Mohammad AsghariJafarabadi (m.asghari862@gmail.com)
Zanjan University of Medical Sciences

Research Article

Keywords: Bayesian, semi-competing risks, death, early recurrence, colorectal cancer

Posted Date: July 6th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1757509/v1

Abstract

Objective: This study, aimed at using a Bayesian approach semi-competing risks technique to model the underlying predictors of early recurrence and postoperative death in patients with colorectal cancer (CRC).

Methods: This study was a retrospective cohort of 284 patients with colorectal cancer who underwent surgery referred to Imam Khomeini clinic in Hamadan from 2001 to 2017. The primary outcomes were the probability of recurrence, the probability of death without recurrence, and the probability of death after recurrence. The patients 'recurrence status was determined from patients' records. The Bayesian survival modeling was carried out by semi-competing risks illness-death models in R 4.1 software

Results: The results showed that gender(TR = 0.764 , 95% CI: 0.456 - 0.855), age at diagnosis (TR =0.764 , 95 % CI: 0.538 - 0.935), T_3 stage (TR = 0601 , 95 % CI : 0.530 - 0.713) , N_2 stage (TR = 0.714 , 95 % CI : 0.577 - 0.935) , tumor size (TR = 0.709 , 95 % CI : 0.610 - 0.929), Grade (differentiation level) (TR = 0.856 , 95 % CI: 0.733 - 0.988 for poor level , TR = 0.648 , 95 % CI : 0.503 - 0.955 for moderate level) and number of chemotherapy (TR =1.583 , 95 % CI: 1.367 - 1.863) was significantly related with recurrence . Also, age at diagnosis (TR= 0.396 , 95% CI : 0.313 - 0.532) , metastasis to other sites (TR = 0.566 , 95% CI : 0.490 - 0.835) , T_3 stage (TR = 0.363 , 95 % CI : 0.592 - 0.301), T_4 stage (TR = 0.434 , 95 % CI : 0.347 - 0.545) , Grade (differentiation level) at moderate level (TR = 0.527 , 0.95 %CI : 0.387 - 0.674), tumor size (TR = 0.595 95 % CI : 0.500 - 0.679) and number of chemotherapy (TR= 1.541 , 95% CI : 1.332 - 2.243) was the significantly predicted the death. Also, age at diagnosis (TR= 0.659, 95% CI: 0.559 - 0.803) and number of chemotherapy (TR= 2.029, 95% CI: 1.792 - 2.191) was significantly related to death after recurrence.

Conclusion: According to the specific results obtained for terminal and nonterminal events, appropriate screening strategies and the earlier detection of CRC leads to substantial improvements in the survival of patients.

Introduction

The third leading cause of cancer death is colorectal cancer and Dolly is high in colorectal cancer. The prevalence of colorectal cancer is higher in men than in women [1] Given that the burden of non-communicable diseases such as cancer is increasing, the goal is to reduce deaths from non-communicable diseases by 2030. The burden of colorectal cancer can be reduced by modifying factors such as diet, lifestyle, and early detection of polyps using screening [2]. Considering that surgery is the initial treatment, the recurrence rate in the first 5 years after surgery is 12.8% for local recurrence and 25.6% for distant metastasis [3] [4] in addition 60-80 % of recurrences of colorectal cancer appear in two years after surgery[5]. These patients have a low survival if early recurrence occurs [6]. If recurrence and metastasis of the disease are diagnosed early, it may be possible to improve survival with curative surgery [7] [8] and by predicting recurrence and metastasis, appropriate treatment of patients with colorectal cancer can be performed after surgery [9]. The main goal of follow-up programs after colorectal cancer treatment is to increase survival.

Several studies have been carried out to study the factors of efficacious recurrence and survival in patients with colorectal cancer. According to A. Inoue et al study, the 3 and 5-year survival rates in patients without recurrence were 88.4% and 87.6%, respectively. Also, multivariate analysis showed that only pT4 (HR: 4.06, 95%CI: 1.60-10.29, p=0.003) was a risk factor [5]. Another study was conducted to recognize factors affecting recurrence in patients with colorectal cancer at a regional Australian hospital [6]. The study by Heinemann and Karl aimed to provide a brief overview of clinics, diagnosis, and management of some of the best colorectal cancer predispositions [7] . as reported by Kim et al, The incidence of colorectal cancer was lower in men than in women, so they tried to improve the results of colorectal cancer in women by introducing new methods based on gender[8]. Zare-Bandamiri et al. (2017), in a 5-year cohort study, examined the effect of recurrence risk factors in patients with CRC after initial treatment. The impression of age, tumor location, lymphovascular invasion, and tumor stage on patient recurrence was significant [9]. Yamano et al. (2018) appraised the factors of efficacious recurrence and death in patients with colorectal cancer after curative surgery. Based on their findings, lymphovascular invasion and CEA[1] and prognostic factors including metastatic and venous invasion were identified as risk factors for recurrence in the colon and rectal cancer, respectively. [10].

Depending on the study conditions and the characteristics of patients, various factors may affect the recurrence and the interval between recurrence and death, and studies have shown that there is no appropriate agreement for its determinants [5] [6] [9]. On the other hand, Semi-competing risks refer to situations in which the main scientific interest in estimating and inferring concerning a non-terminal event (e.g., premature recurrence), the occurrence of which depends on a terminal event (e.g., death) [11]. Each of these must be properly considered so as not to cause bias in the results [12]. Few articles have considered them simultaneously, and most of them have been within the framework of the Cox model for the hazard function. Bayesian framework To analyze the AFT model for semi-competing risks data, which may include left-truncation and/or interval-censoring, are very robust. Therefore, this study aimed to identify the predictors of recurrence after curative surgery in patients with colorectal cancer and also to determine the factors affecting the duration of death after recurrence in these patients with a semi-competing risk approach under the illness-death model.

Methods

Study design and setting

This study is a retrospective cohort of 284 patients with CRC with resection referred to Imam Khomeini clinic in Hamadan from 2001 to 2017.

Predictors

All demographic and clinical/pathological information were extracted from patients' records, including demographic variables such as age at the time of diagnosis (years), gender (female:1; male:2), and Body Mass Index (BMI: kg/m^2), and clinical/pathological variables such as metastasis to other sites (no:0;

yes:1), cancer site (colon:1; rectum:2), surgery (no:0; yes:1), radiotherapy (no:0; yes:1), chemotherapy (no:0; yes:1), number of chemotherapy (0:no; 1:<6; 2:6+), morphology (0:no adeno; 1:adeno), grade (differentiation level) (1:well; 2:moderate; 3:poor), tumor size (1:<4; 2: >=4<7; 3:=>7), disease stage(1:B; 2:C;3:D), PT-stage(1:T2; 2:T3; 3:T4; 4:Tx), and PN-stage(1:N2; 2:N3; 3:N4; 4:Nx).

Main outcome variables

Patients' recurrence status was determined from patients' records. The time to recurrence of patients, the nonterminal event, was computed from the date of surgery to local or distant recurrence in months (totally considered to experience the nonterminal event), and individuals who did not have recurrence or death until the end of the study were considered as censors. The death of the patients, the terminal event, was computed from the date of surgery to their death according to the researchers' telephone follow-up.

Statistical analyses:

Data were explained as mean (SD), median (min-max) for the Numeric Normal and non-normal variables, respectively, and frequency (percent) for categorical variables. The occurrence rate of the nonterminal event (recurrence) and the terminal event (death) was computed per 1000 persons. Log-rank tests were carried out to compare the survival rates across age categories at the time of diagnosis, gender, BMI, metastasis to other sites, cancer site, surgery, radiotherapy, and chemotherapy, number of chemotherapy, morphology, grade, tumor size, disease stage, PT-stage, and PN-stage. Also, the adjusted survival curves were drawn for significant variables in the multivariable analysis. These parts of the analyses were conducted using Stata17 software (StataCorp, College Station, Texas USA). To assess the relationship of the variables mentioned above with the probability of the nonterminal event, the probability of the terminal event, and the conditional probability of the terminal event on the nonterminal event, semi-competing risks analysis was utilized under the illness-death model with AFT [1]assumptions specified by three hazard functions in the Bayesian illness-death models. In the Bayesian approach to estimation, a Gibbs random sampling algorithm was used to generate samples from the complete posterior distribution. Deviance information criterion (DIC) and Logarithm of the pseudo marginal likelihood (LPML) were considered to compare the model.

Accelerated failure time models for independent semi-competing risks data

The AFT assumption can be used to compare survival times. One of the AFT model assumptions is that the effect of covariates on survival time is multiplicative [13]. The following AFT model was considered for the data analysis

$$\begin{aligned}
\log(T_{i1}) &= \boldsymbol{x}_{i1}^{\top}\boldsymbol{\beta}_1 + \gamma_i + \epsilon_{i1}, \quad T_{i1} > 0, \\
\log(T_{i2}) &= \boldsymbol{x}_{i2}^{\top}\boldsymbol{\beta}_2 + \gamma_i + \epsilon_{i2}, \quad T_{i2} > 0, \\
\log(T_{i2} - T_{i1}) &= \boldsymbol{x}_{i3}^{\top}\boldsymbol{\beta}_3 + \gamma_i + \epsilon_{i3}, \quad T_{i2} > T_{i1},
\end{aligned}$$

Ti1 and Ti2 were considered as times to the non-terminal and terminal events, respectively. In each of the equations above, let xig be a vector of transition-specific covariates, let βg denote a vector of transition-specific regression parameters, and is assumed εig is a transition-specific random variable, g = 1, 2, 3. also, in each of expressions (1)−(3), γi is a study subject-specific frailty that instills positive dependence between the non-terminal and terminal events and It is assumed that γi is adopted from a normal distribution with zero mean and variance θ. In addition, it is assumed the variance component θ adopted a conjugated inverse gamma distribution, which is defined by IG (a (θ), b (θ)). For regression parameters βg is adopted non-informative flat prior on the real line parametric modeling was built on the log-Normal formulation and take the εig follows a Normal (μg, σ2g) distribution. for μ_g, was assumed Noninformative flat priors on the real line and for σ^2_g, independent inverse Gamma distributions, denoted IG ($a_g^{(\sigma)}$, $b_g^{(\sigma)}$).

To enrich the study also was used a semi-parametric framework. In many cases, due to the unrealistic features of some common models, including the thin tail of the normal distribution, compared to the distribution of the observed data, the results of parametric models are not satisfactory, therefore, semi-parametric models can enrich the study.

So for each ε_{ig} was adopted an independent non-parametric Dirichlet process mixtures (DPM) of Mg normal distributions with mean μ_{gr} and variance σ^2_{gr},$r\in\{1\ldots M_g\}$

Bayesian models were compared with two effective measures, DIC [1]and LPML[2] for recognizing the true model. The Smaller DIC values indicate that the model has a better fit for the data[14]. The Larger LPMl values also indicate that the model has a good fit for the data [15].

The Analyzes were carried out using R 4.1 software using the SemiCompRisks package [16]. The significance level was set at 0.05.

Results

Patients profile:

Out of 284 patients with resected CRC, 150 (52.8%) were male. A total of 121 (42.6%) patients died, and 131 (46.1%) patients had a recurrence, of which 105 (80.2%) patients died by the end of the study. In addition, there were 16 (10.5%) patients who experienced death without experiencing the recurrence. The recurrence rate was about 46% in the colon, and rectum cancer cities. The mean age at diagnosis of the patients was 55.6 (SD 13.1) years with an age range of 21–84 years. In addition, the mean age at diagnosis in patients with and without recurrence was 56.7 (SD 13.4) and 54.7 (SD 12.8) years, respectively. The median survival of patients was 61.0 (95% Confidence Interval (CI): 42.2–79.8) months. Besides, median survival was 47.0 (95% Confidence Interval (CI): 21.0–73.0) months for patients with

recurrence. The total percentage of recurrences by the end of the first, second, third, fourth, and fifth years were 64.1%, 82.4%, 89.3%, 93.9%, and 96.2%, respectively. Only 3.8% of recurrences occurred after five years and the median recurrence time in patients with and without recurrence was 7 and 46 months, respectively. Moreover, the 1-, 3-, 5- and 10-year survival probabilities were 86.9%, 62.1%, 50.4%, and 42.3%, respectively, for the terminal event of death, and the 1-, 3-, 5- and 10-year survival probabilities were 67.4%, 51.9%, 45.3%, and 40.3%, respectively for the nonterminal event of recurrence. The mean and median time distance between nonterminal and terminal events was 26.2 (95% CI: 19.1–33.2) and 10.0 (95% CI: 7.8–12.2) months, respectively. After disease recurrence, 1-, 3-, 5- and 10-year survival probabilities were 67.4%, 51.9%, 45.3%, and 40.3%, respectively.

Also, among patients who had a recurrence by the end of the study, 110 (84%) had metastases to other sites, 12 (9.2%) did not attend chemotherapy sessions, and 76 (58%) attended more than 6 sessions. 7 (5.3%) were in stage T2 and 92 (70.2%) were in stage T3, 11 (8.4%) were in stage Nx and 55 (42%) were in stage N0. Among patients who had died by the end of the study, 94 (77.7%) had metastases to other sites, 12 (9.9%) had not attended chemotherapy sessions, and 61 (50.4%) had attended more than 6 sessions, 7 (5.8%) were in stage T2 and 85 (70.3%) were in stage T3, 10 (8.3%) were in stage Nx and 45 (37.2%) were in stage N1.

Log-rank tests result

According to the results of log-rank tests the variables Age at Diagnosis (years)($p = 0.001$), Metastasis to other sites($p = < 0.001$), Number of chemotherapies ($p = 0.041$), Disease stage($p < 0.001$), PT -Stage ($p < 0.001$) and PN-Stage ($p < 0.001$) of the studied context became significant in both the nonterminal and terminal events. In recurrence and death outcomes, significantly higher outcome rates were observed among higher age categories, with substantially higher rates in age > 70 years. The rate of recurrences and death were 38.22, and 26.38 respectively. Also, those patients who had metastasis to other sites had much higher rates of both outcomes. The rate of recurrences and death were, 79.58, and 29.46 respectively. In addition, < 6 number of chemotherapies were associated with higher events than patients who had not had any chemotherapy. The rate of recurrences and death were, 17.40, and 16.38 respectively however, the rates decreased when coming into 6 + chemotherapies. Nonterminal and terminal event rates raised significantly as the disease stage, PT-stage, and PN-stage levels increased (All $P < 0.05$). Furthermore, comparing the occurrence rate in nonterminal and terminal events, it is evident that the occurrence rate is much higher in the recurrence than in the death outcome.

Model comparison

For Bayesian Independent AFT model with log-Normal baseline survival distribution DIC = 1633 and LPML = -811, for Bayesian Independent AFT model with DPM baseline survival distribution DIC = 1759 and LPML =-816. According to DIC and LPML, the Bayesian Independent AFT model with log-Normal baseline survival distribution was the best, hence the results of the optimal model were followed.

Result of Bayesian Independent Accelerated failure time models model with log-Normal based model

According to the results, the ratio of recurrence survival time was lower in men than women (TR = 0.764, 95% CI: 0.456–0.855). Age at diagnosis was associated with a decrease in the time ratio of all three outcomes (TR = 0.764, 95% CI: 0.538–0.935 for Recurrence, TR = 0.396, 95% CI: 0.313–0.532 for Death without recurrence, TR = 0.659, 95% CI: 0.559–0.803 for Death after recurrence). Metastasis to other sites was associated with a decrease in the time ratio of death without recurrence (TR = 0.566, 95% CI: 0.490–0.835). The number of chemotherapy sessions was associated with an increase in the proportion of time for all three outcomes (TR = 1.583, 95% CI: 1.367–1.863 for Recurrence, TR = 1.541, 95% CI : 1.332–2.243 for Death without recurrence, TR = 2.029, 95% CI : 1.792–2.191 for Death after recurrence) .Grade (differentiation level) at moderate level was associated with a decrease in the ratio of survival time of recurrence(TR = 0.648, 95% CI : 0.503–0.955) and death without recurrence (TR = 0.527, 0.95%CI : 0.387–0.674), but, at a weaker level it was associated only with a decrease in the time ratio of recurrence (TR = 0.856, 95% CI: 0.733–0.988). Tumor size decrease the time ratio of recurrence (TR = 0.709, 95% CI: 0.610–0.929) and death without recurrence (TR = 0.595 95% CI: 0.500–0.679). Disease stage (PT Stage) in T3 stage was associated with a decrease in time ratio of recurrence (TR = 0.601, 95% CI: 0.530–0.713) and death without recurrence (TR = 0.363, 95% CI: 0.592 – 0.301), in T4 stage, with a decrease in time ratio of death without recurrence (TR = 0.434, 95% CI: 0.347–0.545). Disease stage (PN Stage) at N1 level increased the time ratio of death without recurrence (TR = 1.974, 95% CI: 1.728–2.122) and N2 level also decreased the time ratio of recurrence (TR = 0.714, 95% CI: 0.577–0.935).

Table 1
Predictors of nonterminal and terminal events utilizing Bayesian Independent AFT model with log-Normal baseline survival distribution

		Recurrence		Death without recurrence		Death after recurrence	
		TR	95% CI	TR	95% CI	TR	95% CI
Age at Diagnosis (years)	Trend effect	0.764	0.538–0.935*	0.396	0.313–0.532 *	0.659	0.559–0803 *
Gender	Male	0.596	0.456–0.855 *	0.666	0.363–1.074	0.951	0.697–1.203
Metastasis to other sites	Yes	0.735	0.589–1.022	0.566	0.490–0.835*	0.821	0.594–1.052
Number of chemotherapies	Trend effect	1.583	1.367–1.863 *	1.541	1.332–2.243 *	2.029	1.792–2.191 *
Grade	Well	Referent	—	—	—	—	—
(differentiation level)	Moderate	0.648	0.503–0.955 *	0.527	0.387–0.674 *	1.053	0.839–1.277
	Poor	0.856	0.733–0.988 *	0.558	0.380–1.030	1.310	0.875–1.174
Tumor size	Trend effect	0.709	0.610–0.929 *	0.595	0.500–0.679 *	0.893	0.781–1.010
PT-Stage	T2	Referent	—	—	—	—	—
	T3	0.601	0.530–0.713 *	0.363	0.592 – 0.301 *	0.983	0.746–1.414
	T4	0.962	0.872–1.319	0.434	0.347–0.545*	0.853	0.509–1.402
	TX	NC	NC	NC	NC	NC	NC
PN-Stage	N0	Referent	—	—	—	—	—

NC: not computable; CI: Credibility interval; TR: Time Ratio

Deviance information criterion (DIC = 1633), Logarithm of the pseudo marginal likelihood (LPML= -811)

The frailty component was significant in the multivariable model (Variance of frailties: 0.245, 95% CI (0.209–0.281)).

Trend effect: The model considered the trend effect for ordinal categorical variables. The variables BMI category, cancer site, surgery, radiotherapy, chemotherapy, morphology, disease stage could not be entered in the model in the multivariable model (All P > 0.05).

***: P < 0.05.**

		Recurrence		Death without recurrence		Death after recurrence	
		TR	95% CI	TR	95% CI	TR	95% CI
	N1	1.272	0.967–1.586	1.947	1.728–2.122	0.760	0.576–1.468
	N2	0.714	0.577–0.935 *	1.302	1.000–1.620	0.802	0.592–0.086
	NX	NC	NC	NC	NC	NC	NC
NC: not computable; CI: Credibility interval; TR: Time Ratio							
Deviance information criterion (DIC = 1633), Logarithm of the pseudo marginal likelihood (LPML= -811)							
The frailty component was significant in the multivariable model (Variance of frailties: 0.245, 95% CI (0.209–0.281)).							
Trend effect: The model considered the trend effect for ordinal categorical variables. The variables BMI category, cancer site, surgery, radiotherapy, chemotherapy, morphology, disease stage could not be entered in the model in the multivariable model (All P > 0.05).							
*: P < 0.05.							

Result of Bayesian Independent Accelerated failure time models model with DPM-based model

According to the analysis, the time ratio of recurrence (TR = 0.835) is lower in men than in women. Age at diagnosis was associated with a decrease in the time ratio of recurrence (TR = 0.956). Metastasis to other sites was associated with an increase in the time ratio of recurrence (TR = 1.063) and a decrease in the time ratio of recurrence after death experience (TR = 0.946). The number of chemotherapy sessions significantly increased the time ratio of death after recurrence (TR = 1.045).

Table 2

Predictors of nonterminal and terminal events utilizing Bayesian Independent AFT model with DPM baseline survival distribution

		Recurrence		Death without recurrence		Death after recurrence	
		TR	95% CI	TR	95% CI	TR	95% CI
Age at Diagnosis (years)	Trend effect	0.956	0.942 -0.970 *	0.996	0.906 - 1.135	0.999	0.961 - 1.037
Gender	Male	0.835	0.624 -0.972 *	1.006	0.945 - 1.177	0.977	0.977- 1.129
Metastasis to other sites	Yes	1.063	1.063 - 1.086 *	1.071	0.925 - 1.106	0.946	0.944 - 0.969*
Number of chemotherapies	Trend effect	1.069	0.989 - 1.069	1.019	0.909 - 1.147	1.045	1.045- 1.045
Grade	Well	Referent	—	—	—	—	—
(differentiation level)	Moderate	0.974	0.877 - 1.062	1.059	0.950 - 1.078	0.996	0.947 - 1.001
	Poor	0.944	0.721 - 0.961 *	1.067	0.852 - 1.225	0.966	0.834 - 0.975*
Tumor size	Trend effect	0.890	0.855 - 0.960 *	1.002	0.972 - 1.038	1.039	1.000- 1.206*
PT-Stage	T2	Referent	—	—	—	—	—
	T3	1.048	0.927 - 1.050	1.018	0.994 - 1.083	1.066	0.975 - 1.233
	T4	1.006	0.914 - 1.068	1.095	0.978 - 1.095	1.077	0.992 - 1.162
	TX	NC	NC	NC	NC	NC	NC
PN-Stage	N0	Referent	—	—	—	—	—
	N1	1.033	1.033- 1.077*	1.147	1.019 - 1.196 *	1.057	1.019 - 1.057
	N2	1.048	0.939 - 1.252	1.075	1.009- 1.251 *	0.874	0.835- 0.877
	NX	NC	NC	NC	NC	NC	NC

NC: not computable; CI: Credibility interval; TR: Time Ratio

Deviance information criterion (DIC = 1759), Logarithm of the pseudo marginal likelihood (LPML= -816)

The frailty component was significant in the multivariable model (Variance of frailties: 0.847, 95% CI (0.75-0.018)).

Trend effect: The model considered the trend effect for ordinal categorical variables. The variables BMI category, cancer site, surgery, radiotherapy, chemotherapy, morphology, disease stage could not be entered in the model in the multivariable model (All P>0.05).

*: P<0.05.

Discussion

This study aimed to utilize the Bayesian framework of semi-competing risks to model the effect of background and clinical characteristics on recurrence and postoperative death in patients with CRC. Therefore, the effect of these variables on the nonterminal event (recurrence), the probability of the terminal event (death), and the conditional probability of the terminal event on the nonterminal event. The illness-death model is utilized because of its association with common methods for survival analysis and also its software is available. Due to the nature of the studied data, there is a strong association between the terminal and non-terminal events. Therefore, the simple utilization of a univariate survival model for the non-terminal event, leads to an overestimation of the terminal event rates, because the analysis considers the terminal event as an independent censoring mechanism (Haneuse and Lee, 2016). Utilizing semi-competing risk analysis, the terminal event is considered a competing event, and the dependence between the two events is assumed to be part of the model specifications.

The Bayesian approach is a scientific and effective alternative to the frequent approaches. Bayesian design and analysis are possible due to computational advances and available software In considering the analysis of semi-competing risks data, the proposed Accelerated failure time illness-death model supply as a beneficial complement to the more traditional hazard-based approach of, say, Xu et al (2010) and Lee et al. (2015). We choose the best model using DIC and present the results of just the optimal model.

Wioletta Grzenda used a similar model to analyze the duration of her first job among young people. For this purpose, four Weibull, Gamma, Log-normal, and Log-Logistic models were proposed. Wioletta Grzenda used a similar model to analyze the duration of the first job among young people. For this purpose, four Weibull, Gamma, Log-normal, and Log-Logistic models with the Bayesian approach were proposed. Based on the comparison of the models using the DIC index, the gamma model was a good fit for the data [18] Kyu Ha Lee outlined a new Bayesian framework for an AFT illness-death model.DIC and LMPL indices were used to compare the models [19]. M. Ganjali conducted a study to evaluate the duration of unemployment in conditions where the pH was not assumed. For this purpose Bayesian log-logistic, log-normal, and Weibull AFT models were used [20]. Marcus Abiso Arango utilized three common

Bayesian joint models with AFT Weibull, log-normal, and log-logistics probability distributions. For comparison between models using DIC, AIC, and BIC indices, according to the results of analysis and comparisons, the common Bayesian logistics model was considered the final model.[21]

The results of the study in the AFT model with log-Normal based showed, that men compared with women and the Grade (differentiation level), PN Stage at N2 level, PT Stage in T_3 stage, and Tumor size were associated with a decrease in recurrence survival time. Also, older age was associated with decreased survival time in all three outcomes but more chemotherapy sessions were associated with increased survival time in all three outcomes. In addition, metastasis to other sites, Grade (differentiation level) at a Moderate level, Tumor size, and PT Stage in T_4 T_3 stage were associated with decreased time ratio of death without recurrence.

Recurrence affects survival and death in the first 5 years after recurrence in patients with curative resection, as reported in some studies [22][23][24]. In some studies, The 5-year cumulative recurrence rates were 4.9%, 11.0%, and 23.5% for stage I, stage II, and stage III tumors ($P < 0.001$), respectively. [4]. In patients with colon cancer, local recurrence was less than in patients with rectal cancer [25].

In this study, the postoperative survival rate was decreased in older ages, in the line of this study, Ahmad Reza Baghestani showed that age at diagnosis was significantly related to patients' survival time. [26], some studies reported similar results [27][28]. Also, in some studies, age was significantly associated with local recurrence and distance [29][30][31]. Also, according to the results of several studies, age is significantly associated with the survival of patients with colorectal cancer. In these studies, it has been reported that increasing the age of patients is associated with a decrease in patient survival. [32][33][34], But in some other studies, no significant association was reported [35][36][37][38]. In addition, several studies showed an effective and significant association between age and 5-year survival [39][31]. For that reason, early screening in adults to diagnose cases can increase the survival time ratio in patients with colorectal cancer. In line with the result, the ratio of recurrence survival time was lower in men than women. In some studies, sex was not significantly associated with survival time [40][27]. One possible explanation is due to socioeconomic factors. In the Artes and Müller study, men had lower survival than women [41]. in Heidarnia's study, 5-year survival in the second step was higher in women than men [31]. So appropriate screening strategies should be considered.

Metastasis to other sites was another factor that showed a significant association with nonterminal and terminal events. Other studies showed similar results [29][30]. According to Doğan Yazılıtaş studies, The rate of Grade I tumors was significantly upper in the group that had late metastasis (35.1% vs. 64.9%, $P = 0.001$)[42]. In this study metastasis to other sites was associated with decreased survival time of death without experiencing recurrence. Ryuk JP showed that the liver and lung were the first and second well-known sites of recurrence, respectively[25]. As a result, patients should be under intensive care in this regard.

According to This study Grade (differentiation level) and Tumor size were associated with a decrease in recurrence survival time. Grade (differentiation level) at a Moderate level, Tumor size was associated with decreased time ratio of death without recurrence. in some studies, patients with Stage III tumors had low recurrence rates [43][44].

As a complementary treatment after surgery, the number of chemotherapies was significantly related to greater survival of non-terminal and terminal events and non-terminal event condition of the terminal event. Several studies have reported that postoperative adjuvant therapy with fluorouracil and levamisole (as standard adjuvant chemotherapy) reduces mortality in patients with colorectal cancer.[45][46]. Additionally, in the study of Vassiliki L Tsikitis and Newland, chemotherapy effectively reduced the recurrence [47][48]. Therefore, chemotherapy can be suggested to decline the hazard of recurrence and death. In the present study, lower disease stages were generally connected with higher survival of recurrence, death without recurrence, and death after recurrence.

Depending on the stage of cancer, Cancer extent in the body is determined and appropriate treatment can be assigned according to the stage of cancer. In the present study, PT Stages in T_4, and T3 stages were associated with decreased time ratio of death without recurrence, and PN Stages at the N2 level, and PT Stages in the T_3 stage were associated with a decrease in recurrence survival time. Biyuan Wang reported that factors T3 to T4 were significantly and effectively associated with stage II CRC [49]. In Yuan-Tzu Lan's study, PT-stage(T4)and PN-stage(N2) were significantly related to early recurrence [50]. Also in the studies by Aquina et al., and Jalaeikhoo et al, the mortality rate was higher in patients with higher stages of colon cancer [51][52]. According to a study by A. Belot et al, In the higher stages of CRC, the rate of local recurrence and metastasis is higher [53]. Miyoshi et al discovered that the PN-Stage was effective on recurrence [54].

Limitation of the study:

The limitation was the difficulty in fitting Bayesian models, which was minimized by using appropriate approaches in modeling, selecting the appropriate initial values in the models, and selecting the appropriate amount of memory for the systems running the program. In particular, more cases are needed to achieve higher statistical power to find out significant differences that have been expressed as suggested or fundamental. Another limitation of the present study was its generalizability because the participants in this study were specific in terms of environmental, cultural, social, and geographical conditions, which should be generalized to other individuals and communities with caution. Data mining methods such as neural networks, classification algorithms, and regression trees automatically consider linear and nonlinear interaction relationships and possibly provide more accurate results. For our upcoming project, we intend to follow machine learning methods.

Conclusion

This study showed that gender, older age, higher pathological, higher T/N stage, and fewer chemotherapy sessions were significantly related to lower survival time ratio of patients with CRC. Therefore, the earlier detection of CRC and earlier screening leads to substantial improvements in the survival of patients.

Declarations

Ethics approval and consent to participate

The institutional review board of Zanjan university of medical sciences approved the protocol of the study (ethics code: A-11-1721-1). The participants' privacy was preserved. All participants filled and signed the informed consent and assent. Also, all methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

'Not applicable.'

Availability of data and materials

The data that support the findings of this study are available from MAJ, but restrictions are applied to the availability of these data, which were used under license for the current study, and are not publicly available.

Data are, however, available from the authors upon reasonable request by MAJ.

Competing interests

The authors declare that there is no conflict of interest.

Funding

This study was supported by a research deputy of Zanjan University of medical sciences.

Authors' contributions

All authors read and approved the final manuscript. LM and GR conceived the study and participated in the design and data collection. LM, GR, RF, and MAJ participated in the data analysis and manuscript preparation.

Acknowledgments

We would like to appreciate the collaboration of the department of biostatistics and epidemiology, the school of medicine, Zanjan University of medical sciences, for providing the environment for modeling data and manuscript writing.

References

1. C. P. Wild, B. W. Stewart, and C. Wild, *World cancer report 2014*. World Health Organization Geneva, Switzerland, 2014.
2. D. Alvares, S. Haneuse, C. Lee, and K. H. Lee, “SemiCompRisks: an R package for the analysis of independent and cluster-correlated semi-competing risks data,” *R J.*, vol. 11, no. 1, p. 376, 2019.
3. A. M. Abulafi and N. S. Williams, “Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy,” *J. Br. Surg.*, vol. 81, no. 1, pp. 7–19, 1994.
4. S. Manfredi, A. M. Bouvier, C. Lepage, C. Hatem, V. Dancourt, and J. Faivre, “Incidence and patterns of recurrence after resection for cure of colonic cancer in a well defined population,” *J. Br. Surg.*, vol. 93, no. 9, pp. 1115–1122, 2006.
5. A. Inoue *et al.*, “Risk Factors for Recurrence in Patients with Pathological Stage □ Colorectal Cancer,” *Gan To Kagaku Ryoho.*, vol. 48, no. 13, pp. 1938–1940, 2021.
6. J. Holt, H. Schwalb, H. Elbourne, L. Te Marvelde, and C. Reid, “Risk factors for recurrence in colorectal cancer: a retrospective analysis in a regional Australian hospital,” *ANZ J. Surg.*, vol. 91, no. 11, pp. 2482–2486, 2021.
7. K. Heinimann, “Hereditary Colorectal Cancer: Clinics, Diagnostics and Management,” *Ther. Umsch.*, vol. 75, no. 10, pp. 601–606, 2018.
8. Sung-Eun, H. Y. Paik, H. Yoon, J. E. Lee, N. Kim, and M.-K. Sung, “Sex-and gender-specific disparities in colorectal cancer risk,” *World J. Gastroenterol. WJG*, vol. 21, no. 17, p. 5167, 2015.
9. M. Zare-Bandamiri, M. Fararouei, S. Zohourinia, N. Daneshi, and M. Dianatinasab, “Risk factors predicting colorectal cancer recurrence following initial treatment: a 5-year cohort study,” *Asian Pacific J. cancer Prev. APJCP*, vol. 18, no. 9, p. 2465, 2017.
10. T. Yamano *et al.*, “Evaluation of appropriate follow-up after curative surgery for patients with colorectal cancer using time to recurrence and survival after recurrence: a retrospective multicenter study,” *Oncotarget*, vol. 9, no. 39, p. 25474, 2018.
11. J. P. Fine, H. Jiang, and R. Chappell, “On semi-competing risks data,” *Biometrika*, vol. 88, no. 4, pp. 907–919, 2001.
12. P. M. Odell, K. M. Anderson, and R. B. D’Agostino, “Maximum likelihood estimation for interval-censored data using a Weibull-based accelerated failure time model,” *Biometrics*, pp. 951–959, 1992.
13. M. Gail, K. Krickeberg, J. M. Samet, A. Tsiatis, and W. Wong, “Statistics for Biology and Health Series Editors.” Atlanta: Springer, 2012.
14. D. J. Spiegelhalter, N. G. Best, B. P. Carlin, and A. Van Der Linde, “Bayesian measures of model complexity and fit,” *J. R. Stat. Soc. Ser. b (statistical Methodol.*, vol. 64, no. 4, pp. 583–639, 2002.
15. J. S. Liu, “The collapsed Gibbs sampler in Bayesian computations with applications to a gene regulation problem,” *J. Am. Stat. Assoc.*, vol. 89, no. 427, pp. 958–966, 1994.
16. D. Alvares, S. Haneuse, C. Lee, and K. H. Lee, “SemiCompRisks: an R package for the analysis of independent and cluster-correlated semi-competing risks data,” *R J.*, vol. 11, no. 1, p. 376, 2019.

17. B. P. Carlin and T. A. Louis, *Bayesian methods for data analysis*. CRC Press, 2008.
18. W. Grzenda, “Modelling the duration of the first job using Bayesian accelerated failure time models,” *Acta Univ. Lodz. Folia Oeconomica*, vol. 4, no. 330, 2017.
19. K. H. Lee, V. Rondeau, and S. Haneuse, “Accelerated failure time models for semi-competing risks data in the presence of complex censoring,” *Biometrics*, vol. 73, no. 4, pp. 1401–1412, 2017.
20. M. Ganjali and T. Baghfalaki, “Bayesian analysis of unemployment duration data in the presence of right and interval censoring,” *J. Reliab. Stat. Stud.*, pp. 17–32, 2012.
21. M. A. Erango, A. T. Goshu, G. B. Buta, and A. H. Dessisoa, “Bayesian joint modelling of survival of HIV/AIDS patients using accelerated failure time data and longitudinal CD4 cell counts,” *Br J Med Med Res*, vol. 20, no. 6, pp. 1–12, 2017.
22. M. Kaibori *et al.*, “Predictors and outcome of early recurrence after resection of hepatic metastases from colorectal cancer,” *Langenbeck’s Arch. Surg.*, vol. 397, no. 3, pp. 373–381, 2012.
23. L. Viganò *et al.*, “Early recurrence after liver resection for colorectal metastases: risk factors, prognosis, and treatment. A LiverMetSurvey-based study of 6,025 patients,” *Ann. Surg. Oncol.*, vol. 21, no. 4, pp. 1276–1286, 2014.
24. Y. Yamashita *et al.*, “Risk factors for early recurrence after curative hepatectomy for colorectal liver metastases,” *Surg. Today*, vol. 41, no. 4, pp. 526–532, 2011.
25. J. P. Ryuk *et al.*, “Predictive factors and the prognosis of recurrence of colorectal cancer within 2 years after curative resection,” *Ann. Surg. Treat. Res.*, vol. 86, no. 3, pp. 143–151, 2014.
26. A. R. Baghestani, T. Daneshvar, M. A. Pourhoseingholi, and H. Asadzade, “Survival of colorectal cancer patients in the presence of competing-risk,” *Asian Pacific J. Cancer Prev.*, vol. 15, no. 15, pp. 6253–6255, 2014.
27. X.-P. Li *et al.*, “Colorectal cancer concealment predicts a poor survival: a retrospective study,” *Asian Pacific J. Cancer Prev.*, vol. 14, no. 7, pp. 4157–4160, 2013.
28. D. S. Morrison *et al.*, “Behavioural and metabolic risk factors for mortality from colon and rectum cancer: analysis of data from the Asia-Pacific Cohort Studies Collaboration,” 2013.
29. B. Alafchi, G. Roshanaei, L. Tapak, M. Abbasi, and H. Mahjub, “Joint modelling of colorectal cancer recurrence and death after resection using multi-state model with cured fraction,” *Sci. Rep.*, vol. 11, no. 1, pp. 1–10, 2021.
30. M. Safari, H. Mahjub, H. Esmaeili, M. Abbasi, and G. Roshanaei, “Specific causes of recurrence after surgery and mortality in patients with colorectal cancer: A competing risks survival analysis,” *J. Res. Med. Sci. Off. J. Isfahan Univ. Med. Sci.*, vol. 26, 2021.
31. M. A. Heidarnia, E. D. Monfared, M. E. Akbari, P. Yavari, F. Amanpour, and M. Mohseni, “Social determinants of health and 5-year survival of colorectal cancer,” *Asian Pacific J. Cancer Prev.*, vol. 14, no. 9, pp. 5111–5116, 2013.
32. V. Dancourt, C. Quantin, M. Abrahamowicz, C. Binquet, A. Alioum, and J. Faivre, “Modeling recurrence in colorectal cancer,” *J. Clin. Epidemiol.*, vol. 57, no. 3, pp. 243–251, 2004.

33. R. Ansari *et al.*, “Survival analysis of colorectal cancer in patients underwent surgical operation in Shariati and Mehr Hospital-Tehran, in a retrospective study,” *Govaresh*, vol. 12, no. 1, pp. 7–15, 2007.
34. M. Vakili, A. Aghakoochak, A. Pirdehghan, M. Shiryazdy, and A. Saffarmoghadam, “The survival rate of patients with colorectal cancer in Yazd during 2001-2011,” *SSU_Journals*, vol. 22, no. 3, pp. 1187–1195, 2014.
35. D. Q. Chong *et al.*, “Association of family history and survival in patients with colorectal cancer: a pooled analysis of eight epidemiologic studies,” *Cancer Med.*, vol. 7, no. 5, pp. 2192–2199, 2018.
36. H. Jayasekara *et al.*, “Associations of alcohol intake, smoking, physical activity and obesity with survival following colorectal cancer diagnosis by stage, anatomic site and tumor molecular subtype,” *Int. J. cancer*, vol. 142, no. 2, pp. 238–250, 2018.
37. J. A. Meyerhardt *et al.*, “Physical activity and survival after colorectal cancer diagnosis,” *J. Clin. Oncol.*, vol. 24, no. 22, pp. 3527–3534, 2006.
38. F. G. Fernandez, J. A. Drebin, D. C. Linehan, F. Dehdashti, B. A. Siegel, and S. M. Strasberg, “Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET),” *Ann. Surg.*, vol. 240, no. 3, p. 438, 2004.
39. H. Wrigley, P. Roderick, S. George, J. Smith, M. Mullee, and J. Goddard, “Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment, and host factors on observed and cause specific survival,” *J. Epidemiol. Community Heal.*, vol. 57, no. 4, pp. 301–309, 2003.
40. S. Azadeh, F. S. Reza, A. Sara, V. Mohsen, M.-D. Bijan, and Z. R. Zali, “Four years incidence rate of colorectal cancer in Iran: a survey of national cancer registry data-implications for screening,” *Asian Pacific J. Cancer Prev.*, vol. 13, no. 6, pp. 2695–2698, 2012.
41. M. J. Aarts, V. E. P. P. Lemmens, M. W. J. Louwman, A. E. Kunst, and J. W. W. Coebergh, “Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome,” *Eur. J. Cancer*, vol. 46, no. 15, pp. 2681–2695, 2010.
42. D. Yazilitas, N. Özdemir, C. Hocazade, N. S. Demirci, and N. Zengin, “The clinical and pathological features affecting the time of relapse in patients with early stage colorectal cancer,” *J. Cancer Res. Ther.*, vol. 12, no. 4, p. 1257, 2016.
43. T. André *et al.*, “Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial,” *J. Clin. Oncol.*, vol. 27, no. 19, pp. 3109–3116, 2009.
44. D. I. Obrand and P. H. Gordon, “Incidence and patterns of recurrence following curative resection for colorectal carcinoma,” *Dis. colon rectum*, vol. 40, no. 1, pp. 15–24, 1997.
45. N. Wolmark *et al.*, “The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03.,” *J. Clin. Oncol.*, vol. 11, no. 10, pp. 1879–1887, 1993.

46. A. Zaniboni, “Adjuvant chemotherapy in colorectal cancer with high-dose leucovorin and fluorouracil: impact on disease-free survival and overall survival.,” *J. Clin. Oncol.*, vol. 15, no. 6, pp. 2432–2441, 1997.
47. R. C. Newland *et al.*, “Competing risks analysis of the effect of local residual tumour on recurrence and cancer-specific death after resection of colorectal cancer: implications for staging,” *Pathology*, vol. 50, no. 6, pp. 600–606, 2018.
48. V. L. Tsikitis, D. W. Larson, M. Huebner, C. M. Lohse, and P. A. Thompson, “Predictors of recurrence free survival for patients with stage II and III colon cancer,” *BMC Cancer*, vol. 14, no. 1, pp. 1–7, 2014.
49. B. Wang *et al.*, “Tumor location as a novel high risk parameter for stage II colorectal cancers,” *PLoS One*, vol. 12, no. 6, p. e0179910, 2017.
50. Y.-T. Lan *et al.*, “Comparison of clinicopathological characteristics and prognosis between early and late recurrence after curative surgery for colorectal cancer,” *Am. J. Surg.*, vol. 207, no. 6, pp. 922–930, 2014.
51. A. M. Kaiser, J. Kang, L. S. Chan, and R. W. Beart, “The prognostic impact of the time interval to recurrence for the mortality in recurrent colorectal cancer,” *Color. Dis.*, vol. 8, no. 8, pp. 696–703, 2006.
52. C. T. Aquina *et al.*, “The impact of age on complications, survival, and cause of death following colon cancer surgery,” *Br. J. Cancer*, vol. 116, no. 3, pp. 389–397, 2017.
53. A. Belot, L. Remontet, G. Launoy, V. Jooste, and R. Giorgi, “Competing risk models to estimate the excess mortality and the first recurrent-event hazards,” *BMC Med. Res. Methodol.*, vol. 11, no. 1, pp. 1–9, 2011.
54. N. Miyoshi *et al.*, “Novel prognostic prediction models for patients with stage IV colorectal cancer after concurrent curative resection,” *ESMO open*, vol. 1, no. 3, p. e000052, 2016.