

# Specific causes of recurrence after surgery and mortality in patients with colorectal cancer: A competing risks survival analysis

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**Background:** In situation where there are more than one cause of occurring the outcome such as recurrence after surgery and death, the assumption of classical survival analyses are not satisfied. To cover this issue, this study aimed at utilizing competing risks survival analysis to assess the specific risk factors of local-distance recurrence and mortality in patients with colorectal cancer (CRC) undergoing surgery. **Materials and Methods:** In this retrospective cohort study, 254 patients with CRC undergoing resection surgery were studied. Data of the outcome from the available documents in the hospital were gathered. Furthermore, based on pathological report, the diagnosis of CRC was considered. We model the risk factors on the hazard of recurrence and death using competing risk survival in R3.6.1 software. **Results:** A total of 114 patients had local or distant recurrence (21 local recurrences, 72 distant recurrences, and 21 local and distant recurrence). Pathological stage (adjusted hazard ratio [AHR] = 4.28 and 5.37 for stage 3 and 4, respectively), tumor site (AHR = 2.45), recurrence (AHR = 3.92) and age (AHR = 3.15 for age >70) was related to hazard of death. Also based on cause-specific hazard model, pathological stage (AHR = 7.62 for stage 4), age (AHR = 1.46 for age >70), T stage (AHR = 1.8 and 2.7 for T3 and T4, respectively), N stage (AHR = 2.59 for N2), and white blood cells (AHR = 1.95) increased the hazard of recurrence in patients with CRC. **Conclusion:** This study showed that older age, higher pathological, rectum tumor site and presence of recurrence were independent risk factors for mortality among CRC patients. Also age, higher T/N stage, higher pathological stage and higher values of WBC were significantly related to higher hazard of local/distance recurrence of patients with CRC.

**Key words:** Cause-specific hazard, colorectal neoplasms, competing risk, cumulative incidence, recurrence

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## INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy and the second leading cause of cancer death in the world. This cancer causes 9.2% of cancer-related deaths worldwide. The incidence of CRC has a constant or even decreasing trend in developed countries such as Western Europe, North America and the United States, but it is increasing in the Asian continent.<sup>[1]</sup> Therefore, more attention should be paid to our country in the prevention programs, as a vulnerable region.

Resection surgery in patients with CRC is the best treatment option, but the risk of mortality due to cancer increases because of local and distant recurrence of the tumor after resection.<sup>[2,3]</sup> About 60-80% of CRC recurrences occur 2 years after resection and 90% in the 1<sup>st</sup> 4 years. Furthermore, the survival of these patients is very poor in case of early recurrence.<sup>[4]</sup> Complete surgical resection is currently the mainstay of treatment for patients with locoregional CRC and improve survival if relapse and metastasis are detected early.<sup>[3]</sup> Moreover, the predicting recurrence and metastasis can help to

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select the appropriate treatment for patients with CRC after curative surgical resection.<sup>[5]</sup>

The survival in patients with CRC after the surgery is a main outcome. Early detection of recurrence following surgery is one of the major determinants of patients' survival. Recent decades, significant progression has been observed in the survival of patients undergoing lung or liver resection surgery for colorectal metastasis.<sup>[6]</sup> Five-year survival is raised about 35%–50% by effective chemotherapy progression, especially for patients with resectable liver disease compared to selective surgery, emergency surgery with adverse postoperative outcomes.<sup>[7]</sup> Therefore, finding determinant of survival for patients with CRC could be of great importance.

In survival studies, patients may experience multiple events that is called competing risk, such as local/distant recurrence and death due to different causes. In the presence of competing risks, classical methods of survival analysis such as log-rank test and Kaplan–Meier would lead to bias. Appropriate approaches that have been used are cumulative incidence function (CIF) to estimate of recurrence and death as well as cause-specific and subdistribution regression model (Fine-Gray model) to assess risk factors on hazard of events.<sup>[8]</sup>

Although many studies described incidence of the recurrence and the survival rates in patients with CRC in Iran,<sup>[9,10]</sup> according to the best of our knowledge there is no study (if any) that has simultaneously assessed the related specific risk factor of mortality and recurrence in these patients in Iran. Given that the subdistribution model focuses on estimating incidence or predicting prognosis and cause-specific model addresses etiologic questions in the presence of competing risks. Hence, this study aimed at assessing the risk factors on the recurrence and mortality of patients with CRC using cause-specific competing risk models.

## MATERIAL AND METHODS

### Study design and procedure

In this longitudinal study, we studied 254 Patients with CRC who had undergone curative resection at Imam Khomeini Clinic in Hamadan province, in the west of Iran, during 2004-2018.

The patients were diagnosed according to the pathology report. The time of resection was considered as the starting point for follow-up and time to event was taken into account from this point until the local/distance recurrence or death (as competing event) or end of follow-up, whichever came first. The last follow-up time was carried out by a telephone call.

### Main variables and measures

Demographic and clinical characteristics including sex (1: male; 2: female), age at diagnosis (years), body mass index (BMI: kg/m<sup>2</sup>), counts of platelets in the patient's blood (PLT) (A normal platelet count ranges from 150,000 to 450,000 platelets per microliter of blood), counts of white blood cell (WBC) (the normal number of WBCs in the blood is 4,500–11,000 WBCs per microliter (4.5–11.0 × 10<sup>9</sup>/L), hemoglobin (Hb: g/dl) (The normal range for hemoglobin is: For men, 13.5–17.5 g/dl. For women, 12.0–15.5 g/dl), tumor site (colon, rectum), tumor grade (good, moderate, and poor), tumor size (mm), pathological stage,<sup>[2-4]</sup> N stage (frequency of lymph node involvement: N0 = 0; N1 = 1–3; N2 = 3–9T stage (T2, T3 and T4), grade of tumor, having chemotherapy (1: Yes, 0: No) and having chemo-radiotherapy were collected based on hospital document. In this study, Multiple Imputation method was used to impute missing data in variables with <20% missing value. However, in variables where the amount of missing value was more than 20% an “unknown” category was added as a level of variable.

### Ethical considerations

The general (and not personal) information on the patients has been used in this study. The study protocol was approved by the institutional review board of Hamadan University of Medical Sciences (specific Ethics ID code: IR.UMSHA.REC.1397.835).

### Statistical modeling

Data were expressed as mean (standard deviation [SD]) and Median for numeric variables, and frequency (percent) for categorical variables. To model the hazard, we used competing risk model wherein the outcomes of interest were the incidence of local/distance recurrence and death before recurrence was considered as competing event. The CIF was estimated as the incidence of recurrence. Univariable and multivariable cause-specific hazard regression model was used to assess the relation between potential risk factors and the hazard of recurrence and mortality. In the multi-variable analyses, the relations were assessed simultaneously and the possible confounders' effect was adjusted. The hazard ratio (HR) was computed as the effect size of interest to measure the relationship between risk factors and time to recurrence and death. All statistical analyses were conducted using survival and cmprsk packages in R 3.6.1 (<https://cran.r-project.org/>) and the level of significance was set 0.05.

## RESULTS

### The profile of patients with colorectal cancer after resection surgery

Two-hundred and fifty-four patients with CRC underwent curative resection were included in the analysis, of them 108 patients died by the end of study. One hundred and

fourteen patients experienced recurrence over the study (21 local recurrences only with median time 14 months [ranged: 2–111], 72 distant metastasis only with median time 7 months [ranged: 1–77] and 21 with both local and distant recurrence with median time 15 months [ranged: 5–48]). The mean age of patients at diagnosis was 56.1 (SD 13.1) (ranged: 21–84) years. A number of 135 (53.1%) of them were male. The mean of BMI was 22.1 (SD 3.6) (ranged: 12.2–31.4). Table 1 present the other demographic and clinical characteristics of patients by two considered outcomes.

The median follow-up time was 29.5 (percentile 25-percentile 75: 11.75–61) months. The median survival of all patients was 61 (percentile 25-percentile 75: 21–140) months. The 1-, 3-, 5-, and 10 years overall survival (OS) of patients was 0.88, 0.67, 0.51, and 0.42, respectively. Figure 1 shows the Kaplan–Meier survival curve for OS of patients according to tumor site.

### Results of uni- and multi-variable cause-specific hazard regression model

The results of uni- and multi-variable cause-specific hazard model to determine the association between the potential risk factors and the hazard of death was shown in Table 2.

Significant risk factor of the hazard of death in uni-variable cause-specific hazard model were age at diagnosis, pathological stage, tumor site, T stage, N stage, recurrence (All  $P < 0.05$ ). Furthermore, in the multi-variable model, the higher age at diagnosis (adjusted HR [AHR] = 3.15), higher pathological stage (AHR = 4.28 and 5.37 for stages 3 and 4, respectively), rectum tumor site (AHR = 2.45), and having recurrence (AHR = 5.11) were related to the higher hazard of death [Table 2].

### Results of cause-specific hazard of recurrence in the presence of competing risk

Table 3 presents the cumulative incidence of 1-, 2-, 3-, 4-, 5, and 10 years local/distance recurrence in CRC patients.

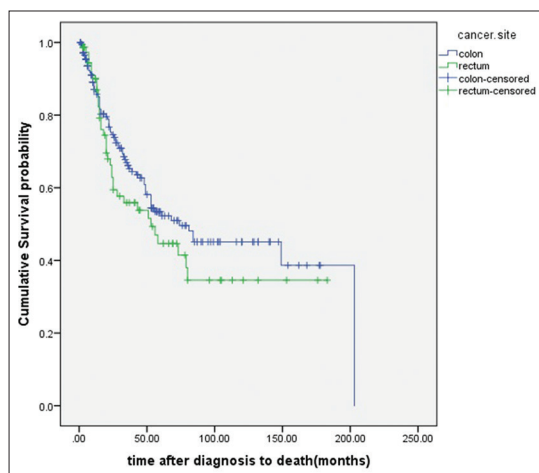


Figure 1: Kaplan–Meier estimates of overall survival according to tumor site

The 1 year cumulative incidence of distance recurrence was 25%, that is, 1 year after surgery about 25% of patients experienced distance recurrence. As shown in Table 3, 66% of patients within 10 years of follow-up, experienced local or distance recurrence. Also Table 3 shows that estimating 1-, 2-, 3-, 5-, and 10 years' cumulative incidence of local-distance recurrence by the category of variables using CIF. The results showed that the most recurrences occur in the 1<sup>st</sup> 3 years of follow-up after surgery for all variables. For example in male and female, 47% and 43% of recurrences occurred in the 1<sup>st</sup> 3 years respectively whereas from the third to the 5<sup>th</sup> year, only 7% recurrence observed in male and 4% in female [Table 3 CIF for category of gender].

The results of cause-specific regression models to test the potential risk factors of hazard for local/distance recurrence were shown in Table 4. According to the univariable model, six prognostic factor for the recurrence of CRC in the presence of death as a competing risk were age at diagnosis, T stage, pathological stage, N stage, HB, and WBC (All  $P < 0.05$ ). The results of multi-variable model showed that higher ages at diagnosis (AHR = 1.46), higher T stage (AHR = 1.8 and 2.7 for T3, T4, respectively), higher N stage (AHR = 2.59 for N2), higher pathological stage (AHR = 7.6 for stage 4) and higher values of WBC (AHR = 1.9) were significantly related to higher hazard of local/distance recurrence.

## DISCUSSION

This study was carried out to determine the cause-specific risk factors of hazard of death and local/distance recurrence in patients with CRC after resection surgery in the presence of competing risks. Using of competing risks models in this situation remove the bias than classical models.<sup>[11]</sup>

### Leading affected factor on hazard of death in patients with colorectal cancer

The survival probability in 1-, 3-, 5-, and 10 years were 88%, 67%, 51%, and 42%, respectively. The 5- and 10-year OS rates in the study by Sharkas *et al.* for CRC patients were 58.2% and 51.8%, respectively.<sup>[12]</sup> In the study conducted in four high-income countries, the 1-, 2-, 3-years OS were between 78%–88%, 70%–80% and 64%–75% respectively.<sup>[13]</sup> In the study by Lin *et al.* the 3-year OS was 68.7%.<sup>[14]</sup> Also another study in Iran, showed that 5 years OS was between 41% and 61%.<sup>[15]</sup> The results found in this study are in the line with the mentioned studies.

Based on multivariable analysis, we found that the hazard of death is to some potential risk factors. The hazard of death in higher ages (>70) was 3.15 (95% CI, 1.14, 6.49). Similarly, Aquina *et al.* demonstrated that the hazard of death in older age (>75) patients with colon cancer was 3.49 (95% confidence interval [CI], 3–4.06)<sup>[16]</sup> and the same results

**Table 1: Profile of patients with colorectal cancer after resection surgery by outcome**

Variable	Category	Death, n (%)		Recurrence, n (%)		Total, n (%)
		Yes	No	Yes	No	
Gender	Male	71 (52.6)	64 (47.4)	66 (48.9)	69 (51.1)	135 (53.1)
	Female	75 (63)	44 (37)	48 (40.3)	71 (59.7)	119 (46.9)
Age at diagnosis (years)	<50	48 (60.8)	31 (39.2)	34 (43)	45 (57)	79 (31.1)
	51–70	84 (59.2)	58 (40.8)	62 (43.7)	80 (56.3)	142 (55.9)
	>70	14 (42.4)	19 (57.6)	18 (54.5)	15 (45.5)	33 (13)
BMI (kg/m <sup>2</sup> )	<18.5	23 (52.3)	21 (47.7)	22 (50)	22 (50)	44 (17.3)
	18.5–25	96 (60.8)	62 (39.2)	67 (42.4)	91 (57.6)	158 (62.2)
	>25	27 (51.9)	25 (48.1)	25 (48.1)	27 (51.9)	52 (20.5)
Chemoradiotherapy	Yes	35 (51.5)	33 (48.5)	34 (50)	34 (50)	68 (26.8)
	No	111 (59.7)	75 (40.3)	80 (43)	106 (57)	186 (73.2)
Chemotherapy	Yes	118 (55.1)	96 (44.9)	102 (47.7)	112 (52.3)	214 (84.3)
	No	28 (70)	12 (30)	12 (30)	28 (70)	40 (15.7)
Pathological stage	2	104 (81.9)	23 (18.1)	28 (22)	99 (78)	127 (50)
	3	37 (48.1)	40 (51.9)	36 (46.8)	41 (53.2)	77 (30.3)
	4	5 (10)	45 (90)	50 (100)	0	50 (19.7)
Tumor site	Colon	107 (59.8)	72 (40.2)	81 (45.3)	98 (54.7)	179 (70.5)
	Rectum	39 (52)	36 (58)	33 (44)	42 (56)	75 (29.5)
Tumor grade	Well	68 (61.8)	42 (38.2)	42 (38.2)	68 (61.8)	110 (43.3)
	Moderate	70 (55.6)	56 (44.4)	63 (50)	63 (50)	126 (49.6)
	Poor	8 (44.4)	10 (55.6)	9 (50)	9 (50)	18 (7.1)
T stage	T2	30 (81.1)	7 (18.9)	7 (18.9)	30 (81.1)	37 (14.6)
	T3	109 (57.7)	80 (42.3)	85 (45)	104 (55)	189 (74.4)
	T4	7 (25)	21 (75)	22 (78.6)	6 (21.4)	28 (11)
N stage	N0	110 (71.9)	43 (28.1)	50 (32.7)	103 (67.3)	153 (60.2)
	N1	33 (44.6)	41 (55.4)	40 (54.1)	34 (45.9)	74 (29.1)
	N2	3 (11.1)	24 (88.9)	24 (88.9)	3 (11.1)	27 (10.6)
Tumor size (mm)	≤5	100 (57.5)	74 (42.5)	76 (43.7)	98 (56.3)	174 (68.5)
	>5	25 (58.1)	18 (41.9)	20 (46.5)	23 (53.5)	43 (16.9)
	Unknown	21 (56.8)	16 (43.2)	18 (48.6)	19 (51.4)	37 (14.6)
Recurrence	Yes	93 (81.6)	21 (18.4)	114 (100)	0	114 (44.9)
	No	15 (10.7)	125 (89.3)	0	140 (100)	140 (55.1)
Hb	Normal	24 (63.2)	14 (36.8)	15 (39.5)	23 (60.5)	38 (15)
	Abnormal	35 (55.6)	28 (44.4)	29 (46)	34 (54)	63 (24.8)
	Unknown	66 (43.1)	87 (56.9)	78 (51)	75 (49)	153 (60.2)
WBC	Normal	44 (56.4)	34 (43.6)	32 (41)	46 (59)	78 (30.7)
	Abnormal	12 (57.1)	9 (42.9)	13 (61.9)	8 (38.1)	21 (8.3)
	Unknown	65 (41.9)	90 (58.1)	77 (49.7)	78 (50.3)	155 (61)
PLT	Normal	38 (55.1)	31 (44.9)	30 (43.5)	39 (56.5)	69 (27.2)
	Abnormal	12 (63.2)	7 (36.9)	11 (57.9)	8 (42.1)	19 (7.5)
	Unknown	70 (42.2)	96 (57.8)	82 (49.4)	84 (50.6)	166 (65.3)

BMI=Body mass index; Hb=Hemoglobin; WBC=White blood cell; PLT=Platelets in the patient's blood

were found in other studies.<sup>[12,17-21]</sup> However, in the studies by Miyoshi *et al.*, Kaiser *et al.* and Newland, no significant results were found.<sup>[4,22,23]</sup> Therefore, earlier screening in younger adults in order to detect cases can decrease hazard of death in patients with CRC.

The hazard of death in rectum site of patients with CRC was 2.45 times more than that of colon site. Although some studies showed that the tumor site is related with hazard of death<sup>[21-23]</sup> but the finding Sharkas *et al.*<sup>[12]</sup> was not consistent with our results. We found that more advanced stage had an adverse relation with higher hazard of death (AHR higher

than 4 and 5 in stage 3 and 4, respectively). After resection for colon cancer in Storli *et al.*'s study, OS has adversely been affected by TNM stage.<sup>[18]</sup> Also in the studies by Aquina *et al.*, Jalaikhoo *et al.*, and Belot *et al.* in patients with colon cancer, higher stages were directly related to mortality.<sup>[4,16,17]</sup> Furthermore, in Sharkas *et al.*, Yu *et al.* (2019) and Storli *et al.* higher stages were directly related to death in patients with CRC.<sup>[12,18,21]</sup>

We estimated that 44.9% of patients experienced local/distant recurrence and 87.7% of the recurrences was diagnosed within the 1<sup>st</sup> 3 years after resection. In the

**Table 2: Results uni-and multivariable cause-specific hazard model for relation between potential risk factors and hazard of death in patients with colorectal cancer after surgery**

Variable	Category	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Gender	Male	1	-
	Female	0.66 (0.36–1.121)	-
Age at diagnosis (years)	<50	1	1
	51–70	1.11 (0.68–2.6)*	1.197 (0.59–2.37)
	>70	2.835 (1.15–7.5)*	3.15 (1.14–6.49)*
BMI (kg/m <sup>2</sup> )	<18.5	1	-
	18.5–25	0.75 (0.46–1.24)	-
	>25	0.82 (0.33–2.11)	-
Chemoradiotherapy	Yes	1	-
	No	2.28 (0.95–3.93)	-
Chemotherapy	Yes	1	-
	No	1.473 (0.58–3.73)	-
Pathological stage	2	1	1
	3	2.69 (1.36–5.36)*	4.28 (1.66–11.15)*
	4	7.45 (3.41–16.29)*	5.37 (1.75–17.46)*
Tumor site	Colon	1	1
	Rectum	2.17 (1.21–3.91)*	2.45 (1.32–4.41)*
Tumor grade	Well	1	-
	Moderate	1.22 (0.67–2.27)	-
	Poor	1.46 (0.49–4.4)	-
T stage	T2	1	1
	T3	1.23 (0.49–4.72)	1.07 (0.46–2.47)
	T4	1.93 (1.28–9.75)*	1.01 (0.39–2.64)
N stage	N0	1	1
	N1	1.65 (0.85–3.16)	0.92 (.48–1.79)
	N2	2.96 (1.12–7.83)*	1.81 (0.92–3.6)
Recurrence	No	1	1
	Yes	5.11 (2.67–9.69)*	3.92 (1.89–8.34)*
Tumor size (mm)	≤5	1	-
	<5	1.11 (0.56–1.57)	-
	Unknown	1.25 (0.57–1.98)	-
WBC	Normal	1	-
	Abnormal	0.96 (0.46–2.02)	-
Hb	Normal	1	-
	Abnormal	1.04 (0.89–1.53)	-
PLT	Normal	1	-
	Abnormal	1.02 (0.99–1.11)	-

\*P&lt;0.05. HR=Hazard ratio; BMI=Body mass index; Hb=Hemoglobin; WBC=White blood cell; PLT=Platelets in the patient's blood; CI=Confidence interval

line with our findings, the survival in patients with early recurrence decrease considerably so the significant impact of recurrence on hazard of death seems reasonable.<sup>[22]</sup> Hence, taking into account, the risk factors to improve the survival could be useful.

#### Leading affected factor on hazard of recurrence in patients with colorectal cancer

Although curative surgical resection is an effective treatment in patients with CRC, but the experience of recurrence after surgery are observed in some patients. In this regard we observed that, 87.7% of recurrence occurred within the 1<sup>st</sup> 3 years of follow-up (59.6% by the end of the 1<sup>st</sup> year, 80% by the end of the 2<sup>nd</sup> year and 87.7% by the end of the 3<sup>rd</sup> year). Furthermore, the results of CIF showed that the most

recurrence occurred within the 1<sup>st</sup> 3 years of follow-up across different category of risk factors [Table 3]. These results are supported by other studies showing that recurrence is most likely to occur within the 1<sup>st</sup> 2 years of an intended curative resection.<sup>[24,25]</sup> This emphasizes that the early years after resection should be considered with more attention.

The most common site of recurrence was the liver, lung and local with 41.7%, 15.8%, and 12% respectively. However, in Guyot *et al.* the most common site was the liver in the around 30% of cases.<sup>[5]</sup> Similar to our finding, some studies reported that the liver was the first most common and lung are the second sites of recurrence.<sup>[26]</sup> These findings showed that patients should be monitored carefully for liver and lung metastases during the period of postoperative surveillance.

**Table 3: Cumulative incidence of local/distance metastasis by potential risk factors for patients with colorectal cancer after resection surgery**

Variable	Category	Cumulative incidence (years)				
		1	2	3	5	10
Gender	Male	0.28	0.43	0.47	0.54	0.62
	Female	0.30	0.38	0.43	0.47	0.49
Age at diagnosis	<50	0.24	0.37	0.42	0.50	0.55
	51–70	0.26	0.37	0.42	0.48	0.55
	>70	0.54	0.68	0.68	0.69	0.71
BMI	<18.5	0.39	0.53	0.53	0.57	0.65
	18.5–25	0.24	0.34	0.41	0.48	0.55
	>25	0.35	0.48	0.51	0.55	0.55
Chemoradiotherapy	Yes	0.25	0.45	0.47	0.53	0.68
	No	0.31	0.38	0.44	0.50	0.52
Chemotherapy	Yes	0.22	0.26	0.29	0.34	0.39
	No	0.30	0.43	0.47	0.54	0.59
Pathological stage	2	0.08	0.15	0.18	0.25	0.37
	3	0.28	0.40	0.47	0.54	0.56
	4	0.78	0.96	1.00	1.00	1.00
Tumor site	Colon	0.31	0.41	0.47	0.54	0.55
	Rectum	0.24	0.40	0.40	0.44	0.61
Tumor grade	Well	0.26	0.34	0.39	0.46	0.48
	Moderate	0.31	0.45	0.49	0.54	0.64
	Poor	0.34	0.46	0.46	0.53	0.55
T stage	T2	0.10	0.10	0.14	0.19	0.33
	T3	0.29	0.41	0.45	0.51	0.56
	T4	0.50	0.71	0.76	0.83	0.91
N stage	N0	0.17	0.29	0.31	0.37	0.47
	N1	0.35	0.49	0.56	0.61	0.63
	N2	0.74	0.78	0.86	1.00	1.00
Tumor size	≤5	0.28	0.39	0.45	0.51	0.57
	>5	0.33	0.43	0.45	0.51	0.55
Hb	Normal	0.17	0.32	0.35	0.48	0.48
	Abnormal	0.24	0.39	0.47	0.52	0.56
WBC	Normal	0.17	0.33	0.40	0.48	0.51
	Abnormal	0.45	0.54	0.59	0.73	0.79
PLT	Normal	0.18	0.35	0.42	0.51	0.51
	Abnormal	0.44	0.51	0.59	0.69	0.79
Recurrence	Local	0.07	0.13	0.16	0.19	0.22
	Distance	0.25	0.34	0.38	0.42	0.44
	Local/ distance	0.32	0.47	0.54	0.61	0.66

BMI=Body mass index; Hb=Hemoglobin; WBC=White blood cell; PLT=Platelets in the patient's blood

We showed that age was other risk factor on hazard of recurrence. The mean (SD) age of all patients with local/distance recurrence was 57.2 (13.2) years, as well as the mean (SD) age of patients with early (<2 years) and late (>2) recurrence was 58 (13.4) and 54 (10.3) years, respectively. Also, higher ages based on uni- and multi-variable model was adverse factor of the hazard of recurrence. Similarly, Guyot *et al.*<sup>[5]</sup> Yu *et al.*<sup>[21]</sup> and Zare-Bandamiri *et al.*<sup>[25]</sup> showed that the higher ages has been significantly related to the recurrence of patients with CRC. In addition, in Belot *et al.*'s study, which assessed the factors influencing local and distant recurrence separately on patients with colon

cancer, age has been significantly related to local and distant recurrence.<sup>[17]</sup> Diagnosis in lower ages could have protective effect on the recurrence.

Adjuvant therapy such as chemotherapy and radiationtherapy, are often used before (neoadjuvant therapy) and after surgery to reduce the risk of recurrence.<sup>[27]</sup> Although in univariable analysis we found that the neoadjuvant therapy was significantly related to the recurrence, but after controlling the effect of other variables this association was not significant. Correspondingly, another study also showed that applying neither radiotherapy nor chemotherapy had significant effect on preventing recurrence.<sup>[28]</sup> By the way, surgery has been introduced as the main treatment strategy for CRC in early stage and the risk of cancer recurrence and mortality is significantly lower in patients who receive chemotherapy.

As a risk factor of recurrence, the stage of disease shows the amount of development of the disease and it has been defined one of the important factors in the choice of treatment and its success rate. We showed that higher tumor stage is directly associated with the more hazard of recurrence. As well, results of a study also suggested direct relationship of advanced stage with higher hazard of recurrence in patients with CRC.<sup>[29]</sup> In addition, Westberg *et al.* showed that early local recurrence in stage III primary tumor were more common compared with the late local recurrence.<sup>[20]</sup> Furthermore, the impact of pathological features including, T and N stage sharply increased the risk of recurrence after surgery in the present study. Trakarnsanga *et al.* showed that T stage is related to local recurrence and T and N stage are related to distance metastases.<sup>[30]</sup> Belot *et al.* showed that advanced stages increased the hazard of local recurrence and distance metastasis in colon cancer.<sup>[17]</sup> Miyoshi *et al.* demonstrated N stage had adverse effect on recurrence.<sup>[22]</sup> This demonstrates that patients with CRC should be screened and be found in early stages.

In addition, we found that the HB inversely and WBC directly were related to the hazard of recurrence in patients with CRC. Similarly, Stotz *et al.* showed that after surgical resection in patients with gastrointestinal stroma tumor, although the HB decreased and the WBC increased the hazard of recurrence but the relationships were not significant.<sup>[19]</sup>

### Strengths and limitations

This study utilized a statistical technique to estimate the hazard of death/recurrence excluding the bias that introduced by classical survival analyses such as ordinary cox regression. Interestingly, the results were found to be clinically supportable. Like other longitudinal studies, this study is prone to some limitations. First, the sample

**Table 4: Results of uni- and multi-variable cause-specific regression models for potential risk factors of hazard of local/distance metastasis for patients with colorectal cancer after resection surgery**

Variable	Category	Unadjusted HR (95%CI)	Adjusted HR (95%CI)
Gender	Male	1	-
	Female	0.83 (0.57-1.23)	-
Age at diagnosis (years)	<50	1	1
	51-70	1.23 (0.76-2.02)	1.02 (0.56-1.57)
	>70	2.01 (1.16-3.48)*	1.46 (1.1-1.85)*
BMI (kg/m <sup>2</sup> )	<18.5	1	-
	18.5-25	0.75 (0.46-1.22)	-
	>25	0.95 (0.53-1.68)	-
Chemoradiotherapy	Yes	1	-
	No	1.35 (0.9-2.02)	-
Chemotherapy	Yes	1	-
	No	1.67 (0.92-3.04)	-
Pathological stage	2	1	1
	3	4.32 (2.17-8.63)*	1.55 (0.64-3.19)
	4	11.37 (3.14-41.12)*	7.62 (3.46-16.92)*
Tumor site	Colon	1	-
	Rectum	1.35 (0.84-2.17)	-
Tumor grade	Well	1	-
	Moderate	1.27 (0.86-1.88)	-
	Poor	1.36 (0.66-2.8)	-
T stage	T2	1	1
	T3	2.71 (1.25-5.89)*	1.8 (1.1-4.7)*
	T4	6.48 (2.73-15.4)*	2.7 (1.5-8.4)*
N stage	N0	1	-
	N1	2.02 (1.33-3.1)*	1.12 (0.47-2.76)
	N2	5.41 (3.29-8.84)*	2.59 (1.13-6.1)*
Tumor size (mm)	≤5	1	-
	>5	1.05 (0.60-1.54)	-
HB	Normal	1	1
	Abnormal	0.51 (0.29-0.92)*	1.02 (0.66-1.58)
WBC	Normal	1	1
	Abnormal	2.34 (1.2-4.6)*	1.95 (1.11-3.26)*
PLT	Normal	1	-
	Abnormal	1.37 (0.69-2.79)	-

\*P&lt;0.05. HR=Hazard ratio; BMI=Body mass index; Hb=Hemoglobin; WBC=White blood cell; PLT=Platelets in the patient's blood; CI=Confidence interval

size of this study is relatively small with regard to utilizing the complex multi-variable models; however, the power in this study has not severely fallen. Studies with higher samples may lead to more accurate results. Second, the data used were collected from the Hamadan province which limit the generalizability of the results, more studies on other provinces could extend this generalizability. Third, due to the retrospective nature of this study, some information due to pathology report and history sheets in some patients' medical records may be imprecise. In addition, the data for some patients were missed due to lack of contact information or changing the phone number.

## CONCLUSION

Our study identified the independent potential predictive of demographic, histological and clinical features for recurrent

disease and death in patients with CRC undergoing resection surgery. There are numerous prognostic affecting on survival and recurrence in CRC. This study showed that older age, higher pathological, rectum tumor site and presence of recurrence were independent risk factors for mortality among CRC patients. Also age, higher T/N stage, higher pathological stage and higher values of WBC were significantly related to higher hazard of local/distance recurrence of patients with CRC. Therefore, the earlier detection of CRC leads to substantial improvements in survival and prevent the early recurrence.

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## Conflicts of interest

There are no conflicts of interest.

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