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Original Article

Developing a Simple Conceptual Causal Model for Predicting Early Recurrence and Mortality after Curative Surgery for Colorectal Cancer Patients

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ABSTRACT

Introduction: Colorectal cancer (CRC) represents the second leading cause of cancer-related mortality. This study focused on the development of a robust conceptual causal model designed to predict early recurrence and mortality following curative surgery in colorectal cancer patients.

Methods: In this retrospective cohort study, we included 284 patients with colorectal cancer (CRC) who underwent surgery at the Imam Khomeini (RA) Clinic in Hamadan, Iran, between 2001 and 2017. Demographic characteristics, treatment modalities, and other relevant data were extracted from patient records. Predictors were analyzed using Generalized Structural Equation Modeling (GSEM) for survival analysis, employing an accelerated failure time (AFT) approach. Both unadjusted and adjusted time ratios (TRs) were calculated using STATA software.

Results: The results of our developed causal model indicated that receiving chemotherapy was significantly associated with a shorter survival time ratio (TR = 0.415, 95% CI: 0.290-0.593), and recurrence time (TR = 0.363, 95% CI: 0.190-0.696). Conversely, patients who underwent multiple chemotherapy sessions exhibited a longer survival time (TR = 2.130, 95% CI: 1.790-2.534) and recurrence time (TR = 2.206, 95% CI: 1.609-3.023). Age had a direct impact on the recurrence time (TR = 0.758, 95% CI: 0.602-0.955). Additionally, age had a significant direct effect on the receipt of chemotherapy, the cancer site, and the receipt of radiotherapy.

Conclusion: In summary, our study's causal model reveals that chemotherapy shortens survival time but multiple sessions can extend both survival and recurrence times. Age significantly affects recurrence time and chemotherapy receipt. These findings highlight the importance of personalized treatment strategies in colorectal cancer management.

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related death worldwide and the third most commonly diagnosed cancer.[1] Annually, 1-2 million people are diagnosed with CRC, with the highest rates in Western countries.[2] The prevalence of CRC is higher in men (10%) than women (9.2%).[3] In 2018, Asia has recorded the highest rates of both new colorectal cancer (CRC) cases (51.8%) and deaths (52.4%) per 100,000 population worldwide, encompassing all genders and age groups.[4] However, In countries with well-established screening programs for colonoscopy and faecal tests, such as Austria, the Czech Republic, and Germany, the incidence of colorectal cancer has significantly declined over time.[5]

A 2023 study on early recurrence causes is one of several recent studies on treatment strategies, death factors[6,7] and recurrence predictors that have been prompted by the growing public health concern that is CRC.[8] New gender-based strategies are being developed to improve colon cancer outcomes for women, taking into account the lower incidence of CRC in men.[9] In parallel, a cohort study comprising 9,134 patients has yielded important insights into a number of CRC-related topics, such as incidence, recurrence predictors, treatment approaches, and the relationship between targeted therapy and survival in metastatic CRC.[10] Depending on the patient's characteristics and the study conditions, different factors can affect recurrence and the interval between recurrence and death in CRC patients.[11,12] CRC risk factors include age, lifestyle, history of chronic illness, positive family history of the disease (especially in those diagnosed before age fifty), and diet.[2] Despite surgical resection being the primary treatment, 30%-50% of patients may die from recurrence,[13] with up to 80% of deaths occurring within two years post-resection.[7]

Previous studies on factors affecting CRC survival and recurrence have informed the current framework. It highlights that various factors, like gender-specific tumor locations, significantly impact CRC survival and recurrence.[14] also tumor location was associated with gender in both men and women.[15] Disease-free survival (DFS) in the chemotherapy group was significantly associated with stage disease.[16] A significant association between the likelihood of receiving chemotherapy was observed for Stages III and IV of the disease[17] and an additional association was identified between age and chemotherapy.[18] The patients in the chemoradiotherapy group were found to be significantly younger in the study of Kang.[16] A significant relationship was found between age and Cancer site[19] and also disease stage was associated with tumor location.[20]

Generalized structural equation modeling (GSEM) is a robust analytical method used to explore intricate relationships between variables, particularly in studies involving survival outcomes. This model offers a powerful framework for predicting patient outcomes, which can ultimately support the development of more effective treatment strategies and personalized care plans.[21] Recent studies have highlighted the importance of such models in improving prediction accuracy and tailoring interventions to individual patient profiles. Structural equation modeling (SEM) was employed in two studies to examine resilience models in colon cancer

patients, focusing on their flexibility indices.[22,23] Another study used it to compare the impact of post-surgical care programs on cancer patient survival.[24] Additionally, a study of 4,530 children in Uganda employed GSEM to examine the complex relationships between various risk factors affecting undernutrition.[21] GSEM efficiently evaluates survival outcomes in CRC patients by analyzing various predictors and complex variable connections. It's a promising method for aiding treatment decisions and improving patient outcomes by identifying factors linked to mortality and recurrence. This study aims to use GSEM to identify key predictors of survival and recurrence in CRC, considering various clinical, pathological, lifestyle, and treatment factors. The goal is to develop a comprehensive model for predicting CRC patient outcomes.

Methods

Study setting and design

In this retrospective cohort study, we included 284 patients with CRC who underwent surgery at the Imam Khomeini (RA) clinic in Hamadan, Iran between 2001 and 2017. Data on demographic and clinical characteristics were collected from patients' medical records. The primary aim of this study was to investigate the association between various risk factors and two outcomes - disease recurrence and mortality - in patients with CRC. Of the 284 patients included in the study, 131 experienced disease recurrence and 121 died during the follow-up period. The patients who died during the study were considered censored data.

Study measurements

Patient records were the source of all information for this study, including demographic variables such as gender (male or female), age at diagnosis (in years) and body mass index (BMI, in kg/m^2). Clinical variables related to surgery were also extracted, including radiotherapy(Received-CRT), cancer site, chemotherapy(Received-chemo) and morphology. all of which were divided into yes or no groups (no: 0; yes: 1) and analyzed. The number of chemotherapy sessions was divided into three groups: those who did not participate in chemotherapy sessions, those who participated in 1 to 6 sessions, and those who participated in more than 6 sessions. The grade (differentiation level) was categorized as good, moderate, or poor, while the disease stage was categorized as 1:B , 2:C , or 3:D . Tumor size was categorized into three groups: 1:<4, 2:>=4<7, and 3:>=7. PT-stage(1:T2; 2:T3; 3:T4; 4:Tx), and PN-stage(1:N2; 2:N3; 3:N4; 4:Nx)

The patients for this study were selected based on their medical records. The inclusion criteria were patients who had undergone surgery for CRC. Patients were excluded if they had other types of cancer or had not undergone surgery. The reason for this selection was to focus on the recurrence of CRC after surgery. To calculate the time to recurrence, the date of surgery was used as the starting point and the date of local or distant recurrence as the endpoint. The time was calculated in months. Patients who did not have a recurrence by the end of the study were considered censored for recurrence. Information on vital status and date of death was obtained from medical and administrative records. In this study, all deaths

were considered CRC deaths. In cases where patients died during the study period, they were considered censored observations, and their contact in.

Study size

Our study assessed sample size adequacy based on observed variables. With 13 risk factors and 284 patients, the sample size meets the general recommendation of at least 15 samples per variable.[25]

Statistical analysis

We used Generalized Structural Equation Modeling (GSEM) to model disease recurrence and survival, incorporating observed variables. We then created a conceptual causal model to illustrate the relationships between the variables. The model displayed the estimation of the time ratios of the definite effects of the paths between the observed variables and the outcomes (recurrence time and survival time). We also used the Accelerated Failure Time (AFT) model for unadjusted and adjusted time ratios to build a GSEM for survival analysis by multivariate modeling. Survival probabilities were compared between categories using Log-Rank tests. PT_Stage, PN_Stage, and disease stage served as mediators in these pathways. All statistical analyses were performed using Stata SE version 17 (StataCorp, College Station, Texas 77845, USA), and the statistical significance level was set at 0.05 for hypothesis testing.

Generalized Structural Equation Model

GSEM is a multivariate statistical model that integrates two generalized linear models (GLMs) and structural equations to facilitate the simultaneous modeling of complex regression equations. This approach can provide a powerful graphical representation that estimates measurement errors and interactions between variables.[26] GSEM can be seen as an extension of SEM that enhances its capabilities. GSEM allows the use of different types of variables and takes their distributions into account. It offers several advantages over alternative modeling methods, such as: 1) It allows the use of factor variable notation, especially in the context of Stata. 2) It allows the use of multilevel models. 3) It includes both generalized linear responses and linear responses.[27]

Results

Profile of the patients

In this study of 284 patients, 131 experienced disease recurrence and 121 died. Of all patients, 134 (47.2%) were women, while 56(42.7%) of the patients who relapsed were women and 71(58.7%) of those who died were men. Patients were divided into three groups based on their age at diagnosis: under 50 years, 51 to 70 years and over 70 years. The largest group was the second category, with 158(55.6%) patients, of whom 65(53.7%) died and 72(55.0%) had disease recurrence. The majority of patients (85.6%) underwent chemotherapy, of which 119(90.8%) relapsed and 109(90.1%) died. Those who did not undergo chemotherapy were 41(14.4%), of whom 12(9.2%) relapsed and 12(9.9%) died.
The number of chemotherapy sessions was divided into three categories: zero, less than 6

sessions and more than 6 sessions. 148(52.1%) people received more than six chemotherapy sessions, of whom 76 (58.0%) relapsed and 61(50.4%) died. Body mass index was also divided into three categories: normal, overweight and obese. 180 (63.4%) of patients were overweight, of whom 72(59.5%) died and 80 (61.1%) relapsed. For the categorical variables, disease stage variable was divided into three categories B, C and D, with most patients(133 ,46.8%) belonging to category B, of whom 23(19.0%) died and 28(21.4%) relapsed. Of the 284 patients, 173 did not relapse. Of these, 27(22.3%) died. On the other hand, 111 patients had a recurrence, of whom 110 (84.0%) had a recurrence and 94(77.7%) died. We calculated the median survival time of 61.0 months (95% CI: 42.2-79.8) and calculated the 1,3 and 5 years survival probabilities with their 95% CI, which were 86.9%, 62.1% and 50.4%(Table1).

The log-rank test and the Kaplan-Meier curve analysis revealed a significant difference in the death and recurrence rates between the patient groups ($P < 0.001$). Patients who received less than six chemotherapy treatments had a higher incidence of events compared with those who did not receive chemotherapy, but the event rate decreased with more than six chemotherapy sessions ($P < 0.05$). The rate of non-terminal and terminal events increased significantly with an increase in disease stage and PT stage ($P < 0.001$), as shown in Figures 1-3. In the figures, the difference in survival is greater at some times than others and eventually approaches zero, especially for death after recurrence.

In the quest to find the optimal model, a variety

Table 1. Participants' profile

Characteristics	Frequency	Percentage	Characteristics	Frequency	Percentage
Age at Diagnosis (years)			Morphology (adeno)	281	98.9
50	91	32	Tumor size		
51-70	158	55.6	<4	72	25.4
70	35	12.3	4 < 7	160	56.3
Gender			7	52	18.3
Female	134	47.2	Disease stage		
Male	150	52.8	B	133	46.8
Grade (differentiation level)			C	84	29.6
Well-differentiated	117	41.2	D	67	23.6
Moderately differentiated	145	51.1	PT_Stage		
Poorly differentiated	22	7.7	T2	41	14.4
BMI			T3	202	71.1
Normal	46	16.2	T4	32	11.3
Overweight	180	63.4	TX	9	3.2
Obese	58	20.4	PN_Stage		
Cancer site			No	164	58.1
Colon	185	65.1	N1	83	29.2
Rectum	99	34.9	N0	25	8.8
Radiotherapy (yes)	89	31.3	NX	11	3.9
Chemotherapy (yes)	243	85.6			

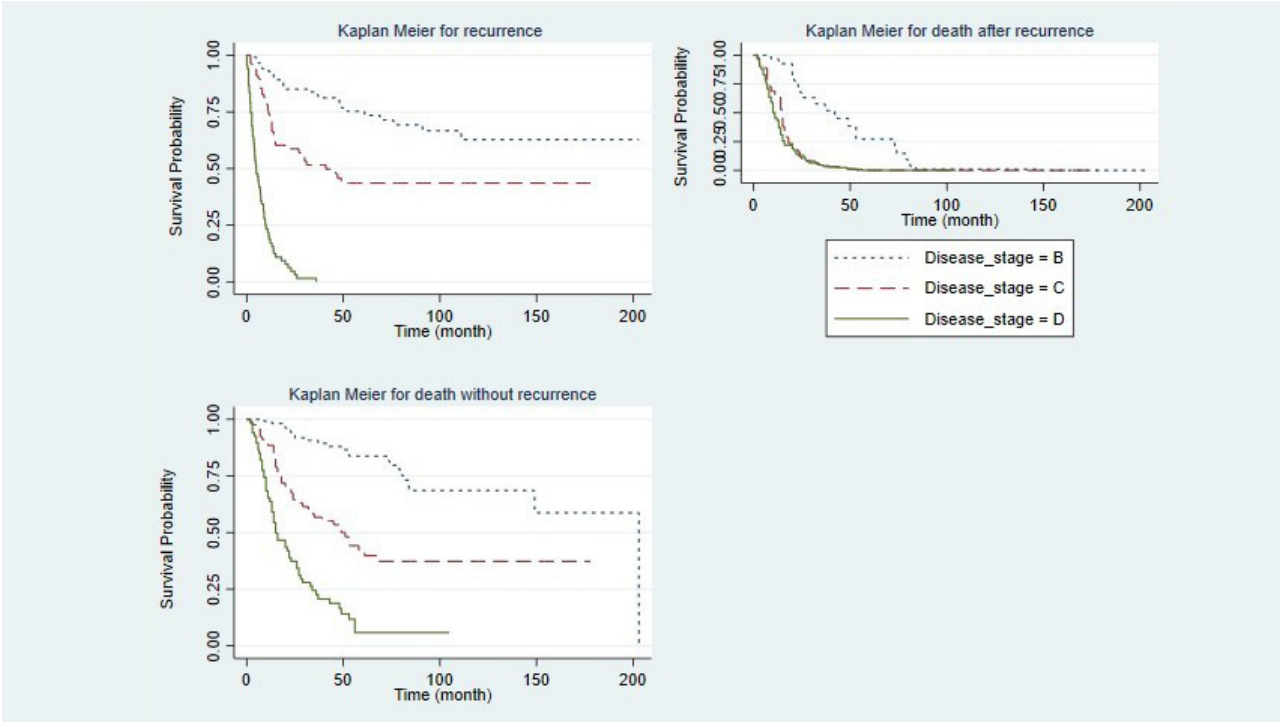

Figure 1. Adjusted survival probability for the events according to the Disease- stage

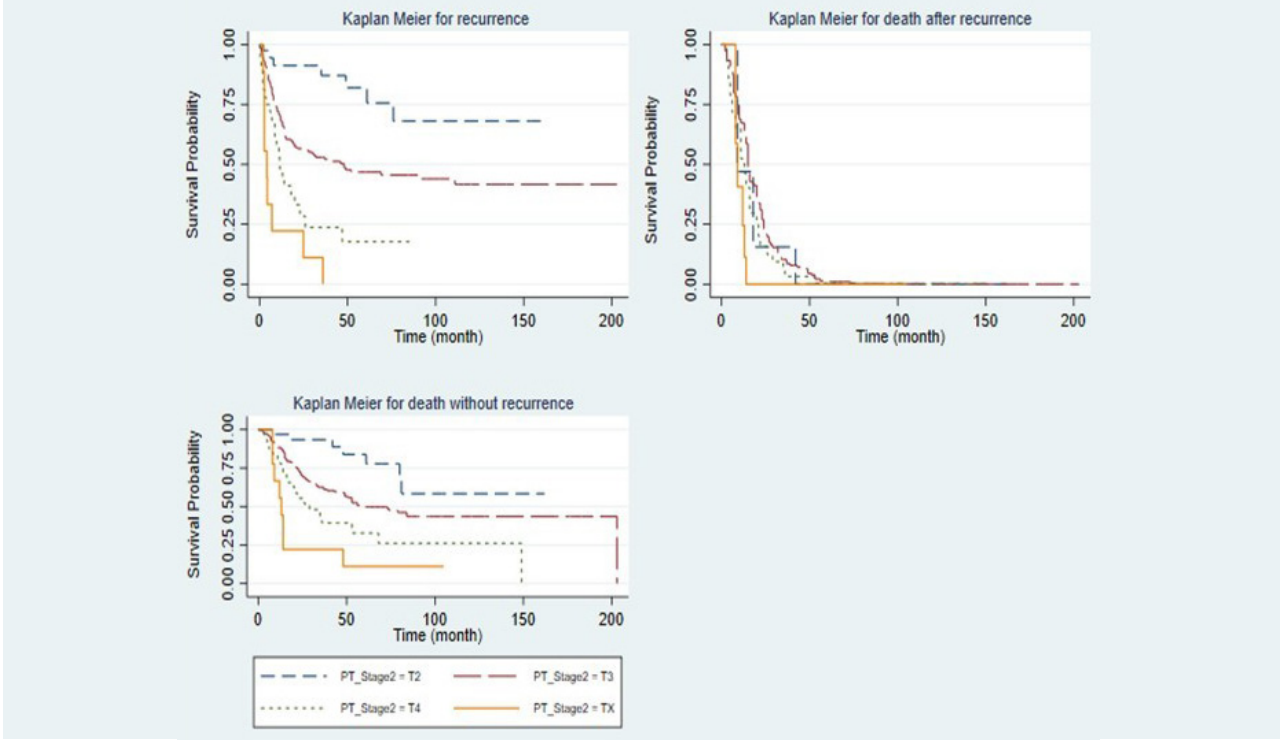

Figure 2. Adjusted survival probability for the events according to the PT- stage

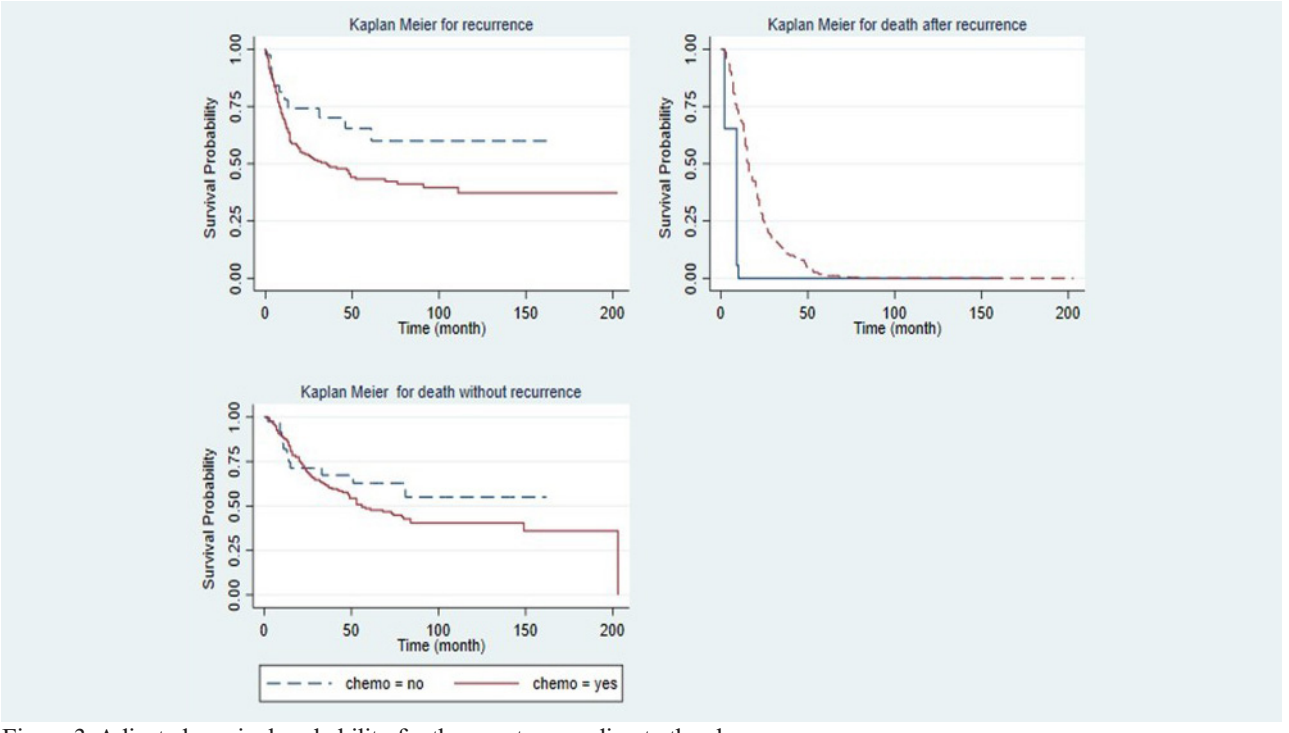

Figure 3. Adjusted survival probability for the events according to the chemo

of distributions were examined. The selection was based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), whereby a lower value of these criteria means a better model fit. After comparing the different models, there were no major differences between them, but the Log-normal model proved to be the most appropriate model due to the small values compared to the others (Table 2).

Table 2. Model Comparison Based on Akaike information and Bayesian information criteria in Survival Analysis

	AIC	BIC
Exponential	537.6461	621.5725
Weibull	532.5906	620.166
Log-normal	513.7307	601.306
Log-logistic	516.4131	603.9885

The optimal model is shown in bold.

Result of conceptual causal Log-normal model

Figure 4 illustrates the possible paths for the variables. The time ratio of recurrence time and survival time is determined based on each variable in each path in the causal diagram and the significance of the relationship is indicated with an asterisk. According to the results of the optimal model, an increase in recurrence time was associated with a corresponding increase in the survival time (TR=1.020, 95% confidence interval (CI): 1.018- 1.022). Receiving chemotherapy was significantly associated with a shorter survival time ratio (TR = 0.415, 95% CI: 0.290-0.593), and recurrence time (TR = 0.363, 95% CI: 0.190-0.696). Conversely, patients who underwent multiple chemotherapy sessions exhibited a longer survival time (TR = 2.130, 95% CI:

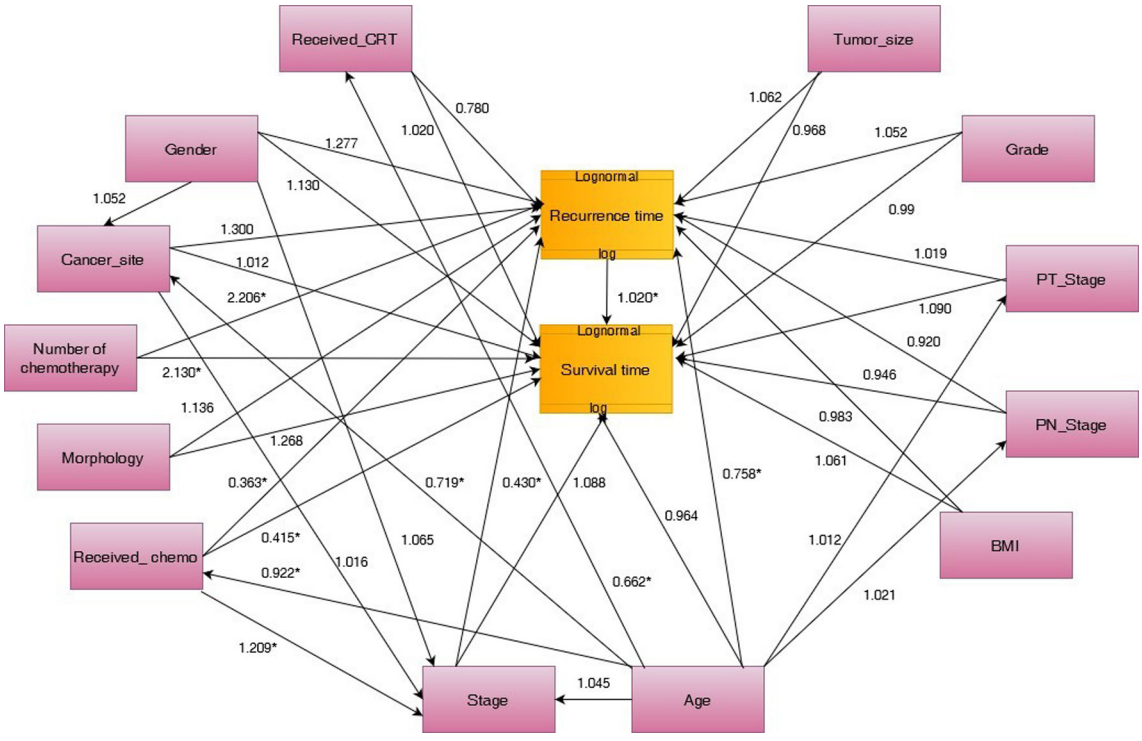

Figure 4. Causal model of the factors affecting recurrence time and survival time
Time Ratio is reported in the paths.
The model considered the trend effect for ordinal categorical variables: Age, BMI, number of chemotherapy, Grade, Tumor size, Stage, PT-Stage, PN-Stage
Gender =Male, Morphology= adeno, Cancer site= rectum, CRT= Yes, chemotherapy= Yes
Paths that were significant are indicated with an asterisk.
*: P <0.05

1.790-2.534) and recurrence time (TR = 2.206, 95% CI: 1.609-3.023) and as the number of chemotherapy sessions increased, survival time also increased. Age had a direct impact on the recurrence time (TR = 0.758, 95% CI: 0.602-0.955). In our study, we found that gender had no significant impact on either the recurrence time or the survival time. Disease stage was associated with a 57% reduction in recurrence time and was statistically significant (TR=0.430, 95% CI: 0.342- 0.540).

Furthermore, receiving chemotherapy was significantly associated with the disease stage (TR=1.209, 95% CI: 1.087- 1.345). This indicated that the likelihood of receiving chemotherapy increases as the disease stage advances. Additionally, age had a significant direct effect on the receipt of chemotherapy, the cancer site, and the receipt of radiotherapy. The results, expressed as time ratios (TR) with their respective 95% confidence intervals (CI), were as follows: for chemotherapy, (TR= 0.922, 95% CI: 0.856- 0.994) for the cancer site, (TR= 0.719, 95% CI: 0.551- 0.937) and for radiotherapy, (TR= 0.662, 95% CI: 0.492- 0.889).

Discussion

The study aimed to uncover the relationships between the factors that influenced recurrence time and survival time in cancer patients. The

GSEM approach was used, which focused on the family and link function for the responses within the model. The study also aimed to determine the causal mechanism of the risk factors. The study examined the characteristics and outcomes of 284 cancer patients. The log-rank test and Kaplan-Meier curve analysis revealed a significant difference between the patient groups in terms of death and recurrence rates. Patients who had received less than six chemotherapy treatments had a higher event rate than patients who had not received chemotherapy. However, the event rate decreased with more than six chemotherapy sessions. The rate of non-terminal and terminal events increased significantly with an increasing disease stage and PT stage.

In the study, the predictors for time to recurrence were analyzed using the log-normal model. The study clearly showed that the risk factors that significantly influence both survival and time to recurrence are different. In this study, the variables number of chemotherapy sessions and receipt of chemotherapy had a direct impact on survival time and time to recurrence. Both age and stage had a direct and inverse effect on the time to recurrence of CRC. Receiving chemotherapy was associated with shorter survival and a shorter time to recurrence. However, a notable relationship was found between the increase in chemotherapy sessions and recurrence time and survival time. The ratio of recurrence time for the different age groups was less than one, suggesting that patients aged 51 to 70 years had a lower risk of recurrence than patients in other age groups.

All things considered, the study offered significant insights into the traits and results of cancer patients that may inform treatment choices and enhance patient outcomes. The results suggested that chemotherapy could have a significant impact on cancer patients' outcomes. Specifically, patients who had received fewer than six courses of chemotherapy were more likely to experience events such as death and disease recurrence compared to patients who had not received chemotherapy. However, the event rate decreased with more than six chemotherapy treatments. This result was consistent with other studies that had also investigated the relationship between chemotherapy and cancer outcomes.[28,29]

The study also found that disease stage was a significant predictor of recurrence time, which was also consistent with previous studies.[30,31] In addition, the study identified age as a predictor of recurrence time, with patients aged 51 to 70 years having a lower risk of recurrence than patients in other age groups. This finding was consistent with other studies that had found an association between age and cancer outcomes.[32,33] However, there were some differences between the results of this study and others. Some studies have reported that the use of chemotherapy for certain cancers might not have improved outcomes.[34,35] Other studies have identified various predictors of cancer progression, such as tumor size or molecular markers.[36–38]Overall, when comparing results with other studies, it is important to consider the specific context and characteristics of each study, as there may be differences in patient groups, treatment, protocols, and other factors that may influence results.

The research strengths and limitations

The study has several advantages and offers

insightful information on the survival rates of those with CRC. The main risk variables impacting survival and recurrence times were found in this study using the Generalized Structural Equation Modeling, along with the causal connections between these influencing risk factors. The GSEM model offers a versatile modeling technique that can handle complicated structures and is distinguished by the simultaneous examination of numerous variables. We were able to handle a combination of count, categorical and continuous variables with our model. It also made it easier to investigate causal relationships between variables. This study's validity is increased by the fact that its conclusions align with many of the key points in the present literature.

A number of limitations should be taken into account when interpreting the results of our investigation. Firstly, the results may not be as generalizable to wider groups due to the relatively small sample size of 284 individuals. To improve the generalizability of the findings, future studies should aim to include larger and more diverse patient populations. Second, because retrospective studies are prone to issues including missing data and insufficient medical records, the study's retrospective methodology raises questions regarding the validity of the data gathered. Additionally, prospective study designs could be employed to mitigate the challenges associated with retrospective data, such as missing information and incomplete medical records. Moreover, our study did not collect data on concomitant diseases, which may have complicated the association between the factors examined and the mortality or recurrence rate of the condition. Finally, the fact that this study was only carried out at one center may restrict the applicability of the findings to other organizations or centers To address the lack of data on concomitant diseases, future research should collect comprehensive information on patient comorbidities to better understand their influence on survival and recurrence rates. Additionally, the study lacked an external sample to validate the derived model, and the small sample size prevented data splitting for cross-validation. Future studies should consider this limitation and use larger or external datasets to validate and consolidate the conceptual model. Lastly, since this study was conducted at a single center, conducting multicenter studies would have helped ensure that the findings were more widely applicable across different institutions, enhancing the overall external validity of the study.

Conclusion

In conclusion, our study highlights the complexity and variability of factors influencing early recurrence and mortality following curative surgery for colorectal cancer. By utilizing a log-normal model, we demonstrated that distinct risk factors govern survival and time to recurrence, with chemotherapy playing a critical role. While the receipt of chemotherapy was paradoxically associated with shorter survival and quicker recurrence, an increase in the number of chemotherapy sessions extended both survival and recurrence times. Furthermore, age and cancer stage emerged as significant determinants, with patients aged 51 to 70 years experiencing a lower recurrence risk compared to other age groups. These findings underscore the need for tailored post-surgical treatment strategies that consider both patient age and

chemotherapy intensity to optimize long-term outcomes in colorectal cancer 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: IR.ZUMS.REC.1400.419). The participants' privacy was preserved. All participants filled out and signed the informed consent and assent. Also, all methods were carried out according to relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are not publicly available. Data are, however, available from the authors upon reasonable request by LM.

Competing interests

The authors declare that there is no conflict of interest.

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Authors' contributions

S.A., Sh.A., Z.M., F.RSH., M.AJ., L.M. contributed to data analysis and manuscript preparation. Specifically, M.A.J. advised on the methodology and developed the theoretical framework. S.A designed the figure and revised the manuscript. Meanwhile, M.S. and G.R. conceived the study and participated in its design and data collection. All authors read and approved the final manuscript.

References

1. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019;16(12):713–32.

2. Mármol I, Sánchez-de-Diego C, Dieste AP, Cerrada E, Yoldi MJR. Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer. Int J Mol Sci 2017, Vol 18, Page 197 [Internet]. 2017 Jan 19 [cited 2023 May 17];18(1):197. Available from: https://www.mdpi.com/1422-0067/18/1/197/htm.

3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66(4):683–91.

4. Onyoh EF, Hsu WF, Chang LC, Lee YC, Wu MS, Chiu HM. The rise of colorectal cancer in Asia: epidemiology, screening, and management1. Onyoh EF, Hsu WF, Chang LC, Lee YC, Wu MS, Chiu HM. The rise of colorectal cancer in Asia: epidemiology, screening, and management. Curr Gastroenterol Rep. 2019;21:1–10. Curr Gastroenterol Rep. 2019;21:1–10.

5. Cardoso R, Guo F, Heisser T, Hackl M,

Ihle P, De Schutter H, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol. 2021;22(7):1002–13.

6. Alves CMM, Souza VGB, Bastos RR. Colorectal cancer mortality in mato grosso, brazil: Spatiotemporal trends. Geospat Health. 2020;15(1):123–30.

7. Ryuk JP, Choi GS, Park JS, Kim HJ, Park SY, Yoon GS, et al. Predictive factors and the prognosis of recurrence of colorectal cancer within 2 years after curative resection. Ann Surg Treat Res. 2014;86(3):143–51.

8. O'Reilly M, Linehan A, Krstic A, Kolch W, Sheahan K, Winter DC, et al. Oncotherapeutic Strategies in Early Onset Colorectal Cancer. Cancers (Basel). 2023;15(2).

9. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21(17):5167–75.

10. Koroukian SM, Booker BD, Vu L, Schumacher FR, Rose J, Cooper GS, et al. Receipt of Targeted Therapy and Survival Outcomes in Patients With Metastatic Colorectal Cancer. JAMA Netw Open. 2023;6(1):e2250030.

11. Mahmoudi L, Fallah R, Roshanaei G, Asghari-Jafarabadi M. A bayesian approach to model the underlying predictors of early recurrence and postoperative death in patients with colorectal Cancer. BMC Med Res Methodol. 2022;22(1).

12. Yagyu T, Yamamoto M, Tanio A, Hara K, Sugezawa K, Uejima C, et al. Risk factors for recurrence in elderly patients with stage II colorectal cancer: a multicenter retrospective study. BMC Cancer. 2022 Apr;22(1):390.

13. Tsikitis VL, Larson DW, Huebner M, Lohse CM, Thompson PA. Predictors of recurrence free survival for patients with stage II and III colon cancer. BMC Cancer. 2014;14(1):1–7.

14. Majek O, Gondos A, Jansen L, Emrich K, Holleczek B, Katalinic A, et al. Sex differences in colorectal cancer survival: population-based analysis of 164,996 colorectal cancer patients in Germany. PLoS One. 2013;8(7):e68077.

15. Chandio A, Chandio M, Shaikh Z, Khichi Z, Memon N, Brown MK. Does Gender Matter in Colorectal Cancer ? 2023;1–7.

16. Kang BM, Baek JH, Park SJ, Baek SK, Park KJ, Choi HJ, et al. Impact of Adjuvant Therapy Type on Survival in Stage II/III Rectal Cancer Without Preoperative Chemoradiation: A Korean Multicenter Retrospective Study. Ann Coloproctol. 2018 Jun;34(3):144–51.

17. Du XL, Cai Y, Symanski E. Association between chemotherapy and cognitive impairments in a large cohort of patients with colorectal cancer. Int J Oncol. 2013;42(6):2123–33.

18. Lund CM, Vistisen KK, Dehlendorff

C, Rønholt F, Johansen JS, Nielsen DL. Age-dependent differences in first-line chemotherapy in patients with metastatic colorectal cancer: the DISCO study. Acta Oncol (Madr). 2018;57(11):1445–54.

19. Li P, Xiao Z, Braciak TA, Ou Q, Chen G, Oduncu FS. A relationship to survival is seen by combining the factors of mismatch repair status, tumor location and age of onset in colorectal cancer patients. PLoS One. 2017;12(3):e0172799.

20. Wang CB, Shahjehan F, Merchea A, Li Z, Bekaii-Saab TS, Grothey A, et al. Impact of tumor location and variables associated with overall survival in patients with colorectal cancer: A mayo clinic colon and rectal cancer registry study. Front Oncol. 2019 Feb 19;9(FEB):76.

21. Maniragaba VN, Atuhaire LK, Rutayisire PC. Modeling the Risk Factors of Undernutrition among Children below Five Years of Age in Uganda Using Generalized Structural Equation Models. Children. 2023;10(12):1926.

22. Chou YJ, Lin HY, Cooper BA, Lin BR, Jiang JK, Yang HY, et al. A resilience model for patients with colorectal cancer: A structural equation modeling analysis. Cancer Nurs. 2022;45(1):E83–90.

23. Cohen M, Baziliansky S, Beny A. The association of resilience and age in individuals with colorectal cancer: an exploratory cross-sectional study. J Geriatr Oncol. 2014;5(1):33–9.

24. Austin JD, Allicock M, Atem F, Lee SC, Fernandez ME, Balasubramanian BA. A structural equation modeling approach to understanding pathways linking survivorship care plans to survivor-level outcomes. J Cancer Surviv. 2020;14:834–46.

25. Siddiqui K. Heuristics for sample size determination in multivariate statistical techniques. World Appl Sci J. 2013;27(2):285–7.

26. Stata. STata Structural Equation Modeling Reference Manual. Release 17. 2015. 1-26 p.

27. Atuhaire L, Rutayisire PC. WHEN SEX MATTERS: A COMPARATIVE GENERALISED STRUCTURAL EQUATION MODEL (GSEM) FOR THE DETERMINANTS OF STUNTING AMONGST UNDER-FIVES IN UGANDA. 2022;

28. Chabner BA RT. Timeline: Chemotherapy and the war on cancer. Nat Rev Cancer. 2005;5(1):65–72.

29. Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, Manzione L, Illiano A, Barbera S, Robbiati SF, Frontini L, Piazza E, Ianniello GP, Veltri E, Castiglione F, Rosetti F, Gebbia V, Seymour L, Chiodini P PF. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. Lancet Oncol. 6(9):669–77.

30. Halabi M El, Horanieh R, Tamim H, Mukherji D, Jdiaa S, Temraz S, et al. The

impact of age on prognosis in patients with gastric cancer: experience in a tertiary care centre. J Gastrointest Oncol [Internet]. 2020 Dec 1 [cited 2023 Oct 6];11(6):1233. Available from: /pmc/articles/PMC7807276/.

31. Song YX, Gao P, Wang ZN, Tong LL, Xu YY, Sun Z, Xing CZ XH. Which is the most suitable classification for colorectal cancer, log odds, the number or the ratio of positive lymph nodes? PLoS One. 2011;6(12):e28937.

32. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association between epidural analgesia and cancer recurrence after colorectal cancer surgery. Anesthesiology. 2010;113(1):27–34.

33. Aryaie M, Roshandel G, Semnani S, Asadi-Lari M, Aarabi M, Vakili MA, et al. Predictors of Colorectal Cancer Survival in Golestan, Iran: A Population-based Study. Epidemiol Health. 2013;35:e2013004.

34. Group EBCTC. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.

35. Pacetti P, Paganini G, Orlandi M, Mambrini A, Pennucci MC, Del Freo A, et al. Chemotherapy in the last 30 days of life of advanced cancer patients. Support Care Cancer. 2015;23:3277–80.

36. Błogowski W, Bodnarczuk T, Starzyńska T. Concise Review: Pancreatic Cancer and Bone Marrow-Derived Stem Cells. Stem Cells Transl Med. 2016 Jul;5(7):938–45.

37. Chang GJ, Skibber JM, Feig BW, Rodriguez-Bigas M. Are we undertreating rectal cancer in the elderly? An epidemiologic study. Ann Surg. 2007 Aug;246(2):215–21.

38. Pesapane F, Rotili A, Botta F, Raimondi S, Bianchini L, Corso F, et al. Radiomics of MRI for the Prediction of the Pathological Response to Neoadjuvant Chemotherapy in Breast Cancer Patients: A Single Referral Centre Analysis. Cancers (Basel). 2021 Aug;13(17).