Original Article

Epidemiology Section

Prognostic Factors on Survival of Rasoul-e-Akram Hospital Patients with Colorectal Cancer: A Survival Analysis

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ABSTRACT

Introduction: Colorectal Cancer (CRC) also called colon cancer or intestine cancer is characterised by cancerous growth of cells in the rectum, colon and appendix. CRC is the fourth most common form of cancer after skin, gastric, bladder and prostate cancers among Iranian population, since 6-8 people per 10,000 people suffer from this disease.

Aim: To evaluate the prognostic factors on survival of patients with CRC, in Rasool-e-Akram Hospital in Tehran, Iran.

Materials and Methods: The population under study included patients with CRC, admitted between 30 March 2010 to 29 March 2013, in Rasoul-e-Akram teaching hospital affiliated with Iran University of Medical Sciences, Tehran, Iran. The event was death from CRC and any other cause. Possible prognostic variables were selected from documents. A multivariate Cox regression model was performed to study the concurrent effect of parameters on survival after taking into account the parallel effect of residual factors.

Results: In this research 80 patients were studied. With respect to inclusion and exclusion criteria 68 patients were enrolled and data related to 68 patients were exposed to statistical analysis. Median and mean age of patients were equal to 55.5 and 55.0 years, respectively with standard deviation of 13.9 years. Only "Logarithm of White Blood Cell" showed a significant effect on survival of patients with CRC.

Conclusion: The results of our study showed the effect of WBC on survival of patients with CRC. Accordingly the increased one unit of log WBC increased the death hazard by 21.22 times in CRC patient.

INTRODUCTION

Colorectal Cancer (CRC) also called colon cancer or intestine cancer is characterised by cancerous growth of cells in the rectum, colon and appendix [1]. CRC is considered as the third most prevalent malignancy and the fourth leading cause of cancer-related mortality worldwide [2]. In 2018, the total of new patient cases with cancer (incidents) were reported to be 18,078,957 cases; approximately 10.2% of the people diagnosed with cancer, had CRC and about 9.2% of cancer deaths were related to CRC [3].

The incidence rate of CRC varies greatly worldwide [4]. In 2012, the highest incidence rate of CRC was found in the Republic of Korea (AGR=45) and the lowest incidence rate of CRC was found in Singapore (AGR=33.7 per 100,000) [5,6]. CRC incidence has been steadily increasing in developing countries [7]. The highest increase was recorded in Western Asia (including Israel and Kuwait) and in Eastern Europe (including Czech Republic, Slovakia and Slovenia) [2].

CRC is the fourth most common form of cancer after skin, gastric, bladder and prostate cancers among Iranian population, since 6-8 people per 10,000 people suffer from this disease. Also, it is considered as the fifth most common form of cancer among men and the third most common among women in Iran. Furthermore, about one fifth of cases of CRC in Iran occurs in people aged below 40 years old [8,9].

Several research have been done for cancer related financial hardship such as, lost time from work and lost productivity followed by travel costs and medical costs not covered by the government health insurance [10,11]. According to the most recent Canadian researches on the burden of disease, out of $16.1 billion (b) related to the medical costs of cancer, the direct) and indirect burden of cancer were reported as $4.2b and $11.9b, respectively [12].

Distant metastasis is the major cause of death in patients with CRC [13]. The development of overwhelming majority of CRC cases was found to be associated with environmental factors rather than heritable genetic mutations [12]. CRC has been known to have different biologic characteristics, treatment modalities, recurrence patterns and survival rates from those cancers occurring in the colon [14-18].

The survival in patients with CRC is an important point and, it is influenced by many factors such as: WBC (White Blood Cell), coffee consumption, use of antibiotics, sex, child-Pugh class, Carcino embryonic Antigen (CEA), KRAS gene status and red meat consumption [1,19-23]. Since separate analysis of CRC may provide more specific information on the prognosis, there is a need for further studies to find the prognostic factors and survival of patients with CRC. Therefore, the present research was aimed to determine the prognostic factors on survival of patients with CRC in Rasoul-e-Akram hospital in Tehran, Iran.

MATERIALS AND METHODS

Patients and Data Source

Rasoul-e-Akram hospital is a referral hospital located in the capital of Iran. The present study was a cross-sectional study which included patients with CRC admitted between 30 March 2010 to 29 March 2013 in Rasoul-e-Akram teaching hospital affiliated with Iran University of Medical Sciences, Tehran, Iran. Patients with rectum cancer were excluded from the study and only the patients with complete data were included in the study. The event was death from CRC and other causes were censored in the analysis. The survival time was calculated based on the sum of days starting from admission date until death from CRC or any other cause or end of the study (29 March 2013).

Sample Size

Considering the age as the principal variable and death rate of patients with CRC and also "coefficient of determination" or "R-squared

value" of age on other variables, 70 patients were estimated as the sample size by the PASS software. About 10% of attrition rate was assumed and then the final sample size increased to 80 patients. In our calculation type I error and power were reported by 5% and 80%, respectively.

Prognostic Variable

Possible prognostic variables were selected from patient's medical records including WBC (White Blood Cell), RBC (Red Blood Cell), Hb (Hemoglobin), BG (Blood Group), SC (Stage of Cancer), DM (Diabetes Mellitus), as well as age at first visit and gender.

STATISTICAL ANALYSIS

Descriptive statistics were done by measuring median, mean and standard deviation for quantitative variables and percentages/ counts for discrete parameters. Cox-model is frequently used in the case of studying the effect of variables on censored time-to-event outcome [24]. A multivariate Cox proportional hazards model was performed to study the concurrent effect of parameters on survival after taking into account the parallel effect of residual factors. Selection of best model was done based on manual and self-acted backward methods. Results of the analysis were shown in the form of regression estimates tables. Hazard ratios of outcomes under study were calculated for each parameter estimate as well as reporting the 95% of confidence intervals. Categorical covariates were compared with a pre-specified reference category. All analysis were made at a significance level of α=0.05 using SPSS software version 18.

RESULTS

In this study 80 patients were perused, off which 68 patients were enrolled with respect to inclusion and exclusion criteria and data related to 68 patients were used for statistical analysis.

Patients

Median and mean age of patients were 55.5 and 55.0 years, respectively with standard deviation of 13.9 years. The mean and standard deviation of WBC, RBC and Hb were equal to $7.9\pm3.2 10^9$/L, $4.0\pm0.5 10^{12}$/L and 11.1 ± 1.5 mmol/L, respectively. Males constituted 58.8% of the patients and 67.6% of them aged more than 50 years [Table/Fig-1]. More than half of the patients had at least stage III of CRC.

Factor	n	%
Gender		
Male	40	58.8
Female	28	41.2
Age		
<50 years	22	32.4
≥50	46	67.6
Cancer Stage		
0 and I	12	17.6
II	14	20.6
III	9	13.3
IV	33	48.5
Diabetes		
Yes	19	27.9
No	49	72.1
Death	14	20.6

[Table/Fig-1]: Demographic, clinical and laboratory variables in the study population (n=68).

In this study, other factors such as RBC, HB, diabetes, age, log WBC and stage were not different and there was no statistically significant difference between males and females (p-value >0.1), of the 68 study patients, death occurred in 14 (20.6%) patients by CRC (p-value=0.46).

[Table/Fig-2] shows the initial model for the evaluation of patients with CRC. In the backward method, all factors were included in the model and then only the significant variables remained. Log WBC was only found to have a significant effect on survival of patients with CRC. [Table/Fig-3] presents the results of backward selection. Hazard of death increased with the increase in log WBC, about 21 times for every unit. [Table/Fig-4] shows the cumulative survival of patients with CRC at mean of log WBC (1.98).

Variable	β	SE	Hazard ratio	p-value
Log WBC	5.95	2.27	383.47	0.009
RBC	-4.11	1.88	0.02	0.029
HG	1.33	0.64	3.77	0.037
Blood group (A)	0.91	1.26	2.47	0.472
Blood group (B)	-0.14	1.31	0.87	0.914
Blood group (AB)	-1.20	2.27	0.30	0.596
Blood group (O)	Reference			
Stage 1	2.74	2.07	15.54	0.185
Stage 2	-3.76	2.06	0.02	0.067
Stage 3	-0.04	1.12	0.96	0.971
Stage 4	Reference			
Diabetes	4.27	1.55	71.26	0.006
Sex	1.88	0.95	6.54	0.048

[Table/Fig-2]: Initial Cox proportional odds regression model for patients with CRC.

Variable	β	SE	p-value	Hazard ratio	95% of CI for hazard ratio	
Log WBC	3.06	1.02	0.003	21.22	2.871	156.772

[Table/Fig-3]: Final Cox proportional odds regression model for patients with CRC.
Log: Logarithm; CI: Confidence interval
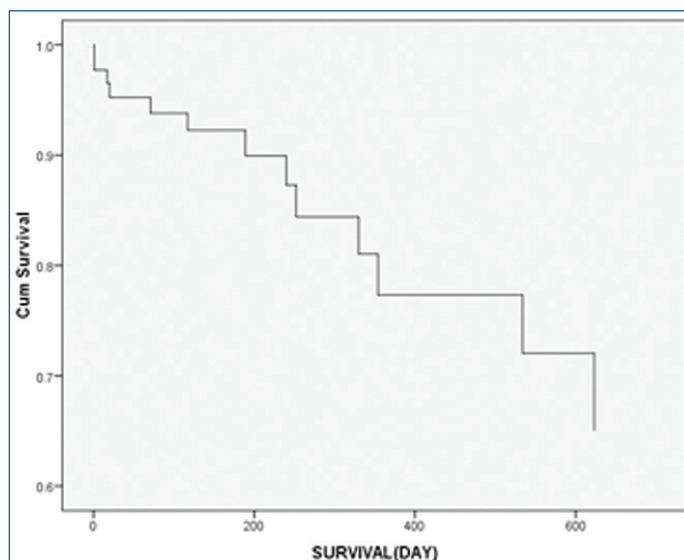
[Table/Fig-4]: Cumulative survival of patients with CRC at mean of LOG-WBC.

DISCUSSION

In this study, WBC, RBC, HG, BG, SC, DM, as well as age at first visit and gender were considered as prognostic factors on survival of patients with CRC. More than 50% of patients had at least stage III cancer, indicating the insouciance to refer the doctor.

For decades, the pivotal role of WBCs in wound healing and tissue repair has been recognised. Depending on the environment, WBC function is adaptive. For example, WBCs can be inflammatory, such that it hinders tissue repair under certain conditions such as active infection [25-27].

Lee YJ et al., at a cohort study conducted in Korea showed the association between WBC and the mortality risk of all cancers

but, they failed to show this association with the rough subgroup analyses of colon, prostate or breast cancers [18].

The results of the present study showed the significant effect of WBC on survival of patients with CRC. Accordingly, 1 unit increase in the log WBC caused 21.22 time increase in the death hazard in patients with CRC. The graph is also consistent with this result.

Alberts SR and Wagman LD ported the longer survival in patients with CRC who had liver metastasis when they used the new chemotherapy methods [13]. In 2014, a prospective cohort study was carried out to evaluate the effect of coffee consumption on CRC and the results showed the reduction of overall occurrence of colorectal tumors as a result of coffee consumption [1].

In a nested case-control study conducted Dik VK et al., showed the association between increasing use of antibiotics and increasing risk of CRC [22]. Previous studies showed that the global incidence of CRC is higher in men [8,23].

In a study conducted between 2007-2014, Lahti SJ et al., showed that child- Pugh class, CEA and KRAS gene status are the independent prognostic factors of overall survival in patients with unresectable CRC liver metastases [9].

LIMITATION

The missing information from patients such as CEA, or adjuvant chemotherapy was considered as a limitation of the present study, resulting in the lack of evaluation for other factors related to the survival of patients.

CONCLUSION

The results of the current study confirmed the effect of WBC on survival of patients with CRC. Accordingly, 1 unit increase in log of WBC caused the 21.22 time increase in death hazard in patients with CRC.

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REFERENCES

[1] Samanian S, Mahjoubi B, Mahjoubi F, Mirzaee R, Azizi R. Investigation of the genes MDR1/MRP1 and their relationship with clinical and para-clinical characteristics of colorectal cancer. Zahedan Journal of Research in Medical Sciences. 2013;15(7):31-34.

[2] Gandomani HS, Aghajani M, Mohammadian-Hafshejani A, Tarazoj AA, Pouyesh V, Salehiniya H. Colorectal cancer in the world: incidence, mortality and risk factors. Biomedical Research and Therapy. 2017;4(10):1656-75.

[3] Global Cancer Observatory. Colorectal cancer 2018. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf/. Accessed March 25, 2019.

[4] 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.

[5] Jung KW, Won YJ, Kong HJ, Oh CM, Cho H, Lee DH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer res treat. 2015;47(2):127.

[6] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

[7] Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev. 2010;19(8):1893-07.

[8] Höffken N, Leichsenring J, Reinacher-Schick A. Clinically relevant, gender-specific differences in colorectal carcinoma (CRC). Zeitschrift fur Gastroenterologie. 2015;53(8):782-88.

[9] Lahti SJ, Xing M, Kim HS. KRAS status as an independent prognostic factor of survival for unresectable colorectal cancer after Yttrium-90 radioembolization therapy. J Vas Interv Radiol. 2015;26(8):1102-11.

[10] Azzani M, Roslani AC, Su TT. The perceived cancer-related financial hardship among patients and their families: A systematic review. Supportive Care Cancer. 2015;23(3):889-98.

[11] Longo CJ, Fitch M, Grignon M, McAndrew A. Understanding the full breadth of cancer-related patient costs in Ontario: A qualitative exploration. Supportive Care Cancer. 2016;24(11):4541-48.

[12] Mirolla M. The cost of chronic disease in Canada. GPI Atlantic; 2004 Jan.; pp. 61:67. Available at: http://www.gpiatlantic.org/pdf/health/chroniccanada.pdf

[13] Alberts SR, Wagman LD. Chemotherapy for colorectal cancer liver metastases. Oncologist. 2008;13(10):1063-73.

[14] Park YJ, Park KJ, Park JG, Lee KU, Choe KJ, Kim JP. Prognostic factors in 2230 Korean colorectal cancer patients: Analysis of consecutively operated cases. World J Surg. 1999;23(7):721-26.

[15] Roncucci L, Fante R, Losi L, Di Gregorio C, Micheli A, Benatti P, et al. Survival for colon and rectal cancer in a population-based cancer registry. Eur J Cancer. 1996;32(2):295-302.

[16] Wolmark N, Wieand HS, Rockette HE, Fisher B, Glass A, Lawrence W, et al. The prognostic significance of tumor location and bowel obstruction in Dukes B and C colorectal cancer. Findings from the NSABP clinical trials. Ann Surg. 1983;198(6):743-52.

[17] Halvorsen TB, Seim E. Tumour site: A prognostic factor in colorectal cancer?: A multivariate analysis. Scandinavian Journal of Gastroenterology. 1987;22(1):124-28.

[18] Lee YJ, Lee HR, Nam CM, Hwang UK, Jee SH. White blood cell count and the risk of colon cancer. Yonsei Med J. 2006;47(5):646-56.

[19] Demeyer D, Mertens B, De Smet S, Ulens M. Mechanisms linking colorectal cancer to the consumption of (processed) red meat: a review. Crit Rev Food Sci Nutr. 2016;56(16):2747-66.

[20] Radmard AR. Five common cancers in Iran. Arch Iran Med. 2010;13(2):143-46.

[21] Nakamura T, Ishikawa H, Mutoh M, Wakabayashi K, Kawano A, Sakai T, et al. Coffee prevents proximal colorectal adenomas in Japanese men: a prospective cohort study. Eur J of Cancer Prev. 2016;25(5):388-94.

[22] Dik VK, van Oijen MG, Smeets HM, Siersema PD. Frequent use of antibiotics is associated with colorectal cancer risk: Results of a nested case-control study. Dig Dis Sci. 2016;61(1):255-64.

[23] McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr. 2018;37(4):1279-85.

[24] Cox DR. Regression models and life-tables. InBreakthroughs in statistics 1992 (pp. 527-541). Springer, New York, NY.

[25] Borysenko M., Beringer T. Functional Histology. Boston: Little Brown; 1984.

[26] Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. Nat Rev Rheumatol. 2012;8(3):133.

[27] King W, Toler K, Woodell-May J. Role of white blood cells in blood-and bone marrow-based autologous therapies. BioMed Research International. 2018;2018:6510842.

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