Relationship of Preoperative Serum Uric Acid Level with Survival in Colorectal Cancer

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ABSTRACT

Objective: To investigate the prognostic significance of uric acid level in colorectal cancer in addition to conventional factors in terms of survival.

Study Design: Observational Study.

Place and Duration of Study: At the University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, between January 2012 and December 2019.

Methodology: A total of selected 332 patients, who underwent surgery for colorectal cancer between 2012 and 2019, were retrospectively reviewed. Patients with a history of neoadjuvant therapy due to rectal cancer, GUT disease, renal failure, stage 4 disease, emergency surgery and severe preoperative infection, were excluded from the study. Peripheral blood samples were collected about a week before the operation. Serum uric acid (SUA) values were measured and recorded.

Results: The patients comprised 198 males and 134 females with a mean age 62.2 ±11.7 years (14-91) years in total. Conventional surgery was performed in 228 patients, and laparoscopy in 104 patients. Uric acid level, number of pathological lymph nodes, number of pathological lymph nodes/total number of lymph nodes (LNO), perineural invasion, type of surgery and disease stage were found to be factors affecting the prognosis ($p < 0.05$). Uric acid cut off value of 5.3 or higher was found to be statistically significant in terms of survival.

Conclusion: Serum uric acid (SUA) value measured preoperatively was found to be a prognostic factor for colorectal cancer.

Key Words: *Serum uric acid (SUA), Colon cancer, Rectal cancer, Prognostic factor.*

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INTRODUCTION

According to the Globocan 2018 data of cancers worldwide, colorectal cancers (CRC) have the third highest incidence, and the second highest mortality rate. According to 2018 data, in colorectal cancer 1.8 million new cases were observed, resulting in 881,000 deaths.[1] Many studies have been conducted to predict the prognosis of colorectal cancer. The TNM classification is the most important prognostic factor acknowledged to date. T shows tumor penetration into the intestinal wall, N is the presence of nodal involvement, and M indicates distant metastasis.[2] However, the TNM classification includes only tumor-related factors and not host-related risk factors. Therefore, patients with the same TNM value may differ in respect of overall survival (OS).

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CEA, CA19-9, K-RAS, N-RAS, BRAF and microRNA have been found to be effective biomarkers.[3,4] Uric acid is a product of adenine and guanine-based purines of dietary metabolism. The level of uric acid in the blood increases in tumor lysis syndrome; and as a result of an increase in cellular turnover rate. It is excreted through the kidneys and intestine. It increases the incidence and mortality of cancer.[5,6] Therefore, the aim of this study was to investigate the effect of SUA level on colorectal cancer survival.

METHODOLOGY

A total of selected 332 patients, who underwent surgery for colorecal cancer at University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey, between 2012-2019, were retrospectively reviewed. Patients with a history of neoadjuvant therapy due to rectal cancer, gastrointestinal disease, renal failure, stage 4 disease, emergency surgery and severe preoperative infection were excluded from the study.

Peripheral blood samples were collected about one week before the operation, serum uric acid (SUA) values were measured and recorded. A record was made of patient age,

gender, type of surgery, total number of lymph nodes examined, number of pathological lymph nodes, perineural invasion, lymphovascular invasion, and the TNM stage (The 7th edition of the American Joint Committee on Cancer). Data were analysed using SPSS software. The overall survival (OS) time of the patients were calculated and the correlation between uric acid value and clinicopathological data of the tumor was evaluated.

Blood tests, PA chest radiography, abdominal tomography and colonoscopy were performed for all patients preoperatively. SUA levels and tumor markers were determined in routine blood samples taken one week prior to the operation. The patients with distant metastasis were assessed by a council including gastroenterology, medical oncology, radiation oncology, radiology and pathology physicians as to whether they were operable or not and then directed to medical oncology. Prophylactic antibiotherapy (1gr, cefazolin sodium, generic drug) was administered to all patients intraoperatively. Laparoscopic or conventional surgery was selected according to the localisation and the type of tumor. Loop ileostomy was performed in patients who underwent rectosigmoid resection and with suspicion of anastomotic safety. The patients were evaluated by medical oncology and radiotherapy physicians and received the necessary adjuvant treatments. At the end of the first year, follow-up colonoscopy was performed in all patients. Patients were then checked every three months for the first two years and every six months in the next three years. Complete blood count, biochemical tests and tumor markers (CEA, Ca 19-9) were examined at each follow-up visit in addition to history and physical examination.

Statistical analysis of the data was made using IBM SPSS Statistics Version 24 package software. Qualitative data were shown with frequency and percentage, quantitative data as mean ± SD and median (25-75% quarter). Pearson Chi-Square, Fisher's Exact test and Chi-square trend analysis were used to compare categorical variables between groups, and the Mann-Whitney U-test was applied to compare continuous variables between groups. The cutoff value of the SUA results was calculated with ROC analysis. Cox Regression, Kaplan-Meier and Log Rank (Mantel-Cox) tests were used in survival analysis. A value of $p<0.05$ was considered statistically significant.

RESULTS

The patients comprised 198 (59.6%) men and 134 (40.4%) women, with a mean age of 62.9 ±12.1 years (14-85 years) for women, 61.8 ±11.4 years (31-91) for men, and 62.2 ±11.7 years (14-91) in total. Conventional surgery was performed on 228 (68.7%) patients, and laparoscopy on 104 (31.3%) patients. In 148 (44.6%) patients, tumors were observed to be localised in the rectosigmoid region, 56 (16.9%) patients in the sigmoid region, 44 (13.3%) patients in the ascending colon, 38 (11.4%) patients in the cecum, 16 (4.8%) patients in the splenic flexura, 14 (4.2%) patients in the hepatic flexura, 11 (3.3%) patients in the descending colon and 5 (1.5%) patients in the transverse colon.

Uric acid level, number of pathological lymph nodes, number of pathological lymph nodes/total number of lymph nodes (LNO), perineural invasion, type of surgery and disease stage, age, gender (males) were found to be factors affecting the survival ($p<0.05$, Table I).

Single Cox regression analysis for the effect of variables on survival revealed that uric acid, pathological lymph node number, LNO, N (N0-1 and N2-3), stage (stage 1-2 and stage 3), lymph node invasion and type of surgery had a statistically significant effect on survival ($p<0.05$). The cutoff value was determined as 5.3 mg/dl. ($p=0.044$, Figure 1). As the AUC value was calculated as 0.572 in the ROC analysis, higher values were studied as it was aimed to obtain AUC value >0.70. SUA values of ≥6 mg/dl were determined to have a greater effect on survival ($p= 0.038$, Table II). Cox regression analysis for the relationship of uric acid and survival according to cutoff values showed statistically significant effects of increased uric acid on survival at all cutoff values ($p<0.05$).

DISCUSSION

The results of this study showed that high values of SUA were an effective factor in terms of survival in colorectal cancers ($p=0.023$). The cutoff value was determined as 5.3 mg/dl. ($p=0.044$). However, since the AUC value was calculated as 0.572 in the ROC analysis, higher values were studied as it was aimed for the AUC value to be >0.70. SUA values of ≥6 mg/dl were determined to have a greater effect on survival ($p= 0.038$).

There are many factors affecting the prognosis of colorectal cancer, including human leukocyte antigen (HLA1), tumor depth, lymphovascular invasion, perineural invasion, histological type, and the number (<12) of lymph nodes removed in the operation.[7] In this study, uric acid level, number of pathological lymph nodes, number of pathological lymph nodes/total number of lymph nodes (LNO), perineural invasion, type of surgery, stage, age, and male gender were found to be factors significantly affecting survival ($p<0.05$).

The formation of uric acid occurs through the enzymatic reaction of xanthine oxidoreductase (XOR) with xanthine and hypoxanthine, which are produced by the digestion of foods and beverages containing purine nucleotides.[8] Uric acid increases as nucleic acid turnover product in pathological tissues with a high growth rate in cancer patients.[9]Therefore, it has been studied as a prognostic marker in several cancer types. As mentioned above, uric acid has always aroused interest in cancer research because of the complex physiology. However, it is a paradoxical issue. Uric acid is pro-oxidative in the intracellular environment but shows anti-oxidant effects in the extracellular environment.[10,11] As an anti-oxidant, it is a scavenger of oxygen radicals, thus reducing carcinogenic reactive oxygen species (ROS). ROS are potentially oncogenic as they increase cell mutation. As a pro-oxidant, uric acid initiates tumorgenesis in normal cells. It increases proliferation and migration in tumor cells by means of inflammatory stress and ROS.[12]

Table I: Mean distribution of age, uric acid level, lymph node number, LNO and survival time according to survival of cases.

	Survived	Ex	z	p
	Median (25-75)	Median (25-75)		
Age (years)	62 (54-68.25)	67.5 (57.75-74.25)	-3.327	0.001
Uric acid	5 (4-5.9)	5.35 (4.18-6.4)	-2.033	0.042
Total lymph node	13 (9-20)	14 (10-18)	-0.265	0.791
Pathological lymph node	0 (0-1)	1 (0-4)	-4.690	<0.001
LNO	0 (0-0.13)	0.11 (0-0.33)	-4.555	<0.001
Overall survıval	48 (33-61.5)	23 (10.75-34)	-9.881	<0.001

Mann-Whitney U-analysis.

Table II: Kaplan Meier survival analysis results with respect to cutoff values for uric acid.

	Median			X^2	p
	Estimate	Std. Error	95% Confidence Interval		
<6	40.000	2.333	35.426-44.574	4.540	0.033
X≥6	37.000	3.161	30.803-43.197		
<6.5	41.000	2.006	37.069-44.931	8.324	0.004
≥6.5	33.000	2.581	27.942-38.058		
<7.0	41.000	1.734	37.600-44.400	10.233	0.001
≥7.0	30.000	3.710	22.729-37.271		
<7.5	41.000	1.765	37.540-44.460	13.025	˂0.001
≥7.5	26.000	3.727	18.696-33.304		

Log Rank (Mantel-Cox)

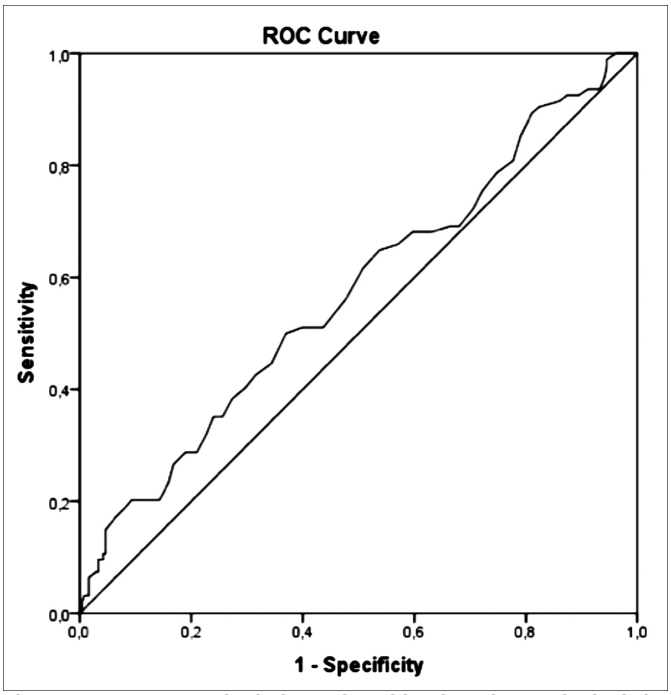

Figure 1: ROC curve depicting uric acid values in survival of the cases.

Ames *et al.* first asserted the probable protective effect of high levels of SUA on cancer in humans.[13] According to this hypothesis, xanthine oxidase, which plays an important role in the formation of SUA, also increases as SUA levels increase. Xanthine oxidase scavenges free oxygen radicals by inhibiting lipid peroxidase.[14] Especially in cardiovascular diseases, uric acid acts as an antioxidant in early stages of atherosclerosis while showing pro-inflammatory effects in later stages.[13-15] It can be considered that there is a likelihood that the same phenomenon that may also develop in cancer cells.

Whether low levels or high levels of SUA are effective in the cancer process is controversial in the literature. Kuo *et al*. considered low levels of SUA as a factor for an increase in cancer risk whereas Strasak *et al*. demonstrated that higher levels of SUA increased total cancer mortality.[16,17] In a meta-analysis, Yan *et al*. showed that high SUA levels increased total cancer incidence as well as mortality in digestive cancers. In particular, cancer incidence increased in men while cancer mortality increased in women.[6]

Cohort studies in the literature are also confusing. In a Taiwan study conducted with 354,110 participants, low SUA level was found to be compatible with high cancer incidence.[16] In contrast, in an Austrian study with 83,683 participants, high SUA level was found to be associated with increased mortality in all cancers.[17] A Chinese study with 8,274 participants reported that high levels of SUA increased the incidence of cancer only in diabetic female patients.[12,18]

Despite such confusion, high levels of SUA have been positively correlated with head and neck cancers, lymphoid

system cancers, hematological cancers, and digestive system and urinary system cancers in many studies. Chen *et al*. demonstrated that increased levels of SUA was an independent prognostic factor in esophageal cancer cases with RO resection.[19]

In a study assessing the relationship between stage 2-3 colorectal cancer and uric acid, Cetin *et al*. determined metastasis with uric acid levels >8.37 mg/dl, which acts first on the liver.[20] Sekcukbiricik *et al*. showed that the SUA level increased in metastatic colorectal cancer patients who responded to bevacizumab chemotherapy.[21] Linder *et al*. examined the relationship between colorectal cancer and uric acid and determined that the xanthine oxidase (XOR) level decreased in tumor cells compared to the normal level, and the XOR enzyme was correlated with cancer stage, progression and survival.[22] Hyperuricemia plays a key role in the development of gout disease, renal failure, hypertension, hyperlipidemia, diabetes and obesity.[23] In gout patients, the risk of oral cavity, pharynx, colon, liver, biliary tract, pancreas, lung, endometrium, kidney cancers and malignant melanoma was found to be increased, in a study of more than 16,000 out-of-control gout cases in Sweden (incidence ratio for all cancers was 1.25, 95% CI: 1.18-1.31).[24] The retrospective collection of data and assessment of single center results are the main limitations of this study.

CONCLUSION

SUA, which is a nucleic acid turnover product, can be considered to increase in the advancing stages of cancer; and high levels of SUA increase the mortality in colorectal cancers due to the progressive pro-oxidative effect. Therefore, close attention should be paid in the examination and treatment of colorectal cancer patients, particularly those with a SUA level of ≥5.3 mg/dl.

ETHICAL APPROVAL:
The study was approved by the local Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (AOH-13/4/2017-2017413).

PATIENTS' CONSENT:
The necessary consent forms were obtained from the patients for the study.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MAU: Data collection, drafting of manuscript and statistical analysis. The acquistion, analysis, or interpretation of data for the work, drafting the work or revising it critically for important intellectual content.
LD: Critical review of content and study planning.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68(6)**:394-424. doi: 10.3322/caac.21492.
2. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton HR, *et al*. Prognostic factors in colorectal cancer. college of American pathologists consensus statement 1999. *Arch Pathol Lab Med* 2000; **124(7)**, 979-94. doi: 10.1043/0003-9985(2000)124<0979:PFICC>2.0.CO;2.
3. Ciombor KK, Wu C, Goldberg RM. Recent therapeutic advances in the treatment of colorectal cancer. *Annual Reviews* 2015; **66**:83-95. doi: 10.1146/annurev-med-051513-102539.
4. Loupakis F, Yang D, Yau L, Fang S, Cremolini C, Whang W, *et al*. Primary tumor localisation as a prognostic factor in metastatic colorectal cancer. *JNCI J Natl Cancer Inst* 2015; **107(3)**:427. doi.org/10.1093/jnci/dju427.
5. Becker BF. Towards the physiological function of uric acid. Free radical biology & medicine. 1993; **14(6)**:615-31. doi: 10.1016/0891-5849(93)90143-i.
6. Yan S, Zhang P, Xu W, Liu Y, Wang B, Jiang T, *et al*. Serum uric acid ıncreases risk of cancer ıncidence and mortality: A systematic review and meta-analysis. *Mediators of inflamm* 2015; **2015**: 764250. doi: 10.1155/2015/764250.
7. Üstüner MA, İlhan E, Yeldan E, Argon A,Vardar E. Clinical and pathological factors affecting lymph node metastasis in patients operated on with the diagnosis of colorectal cancer. *J Tepecik Edu Res Hospital* 2016; **26(1)**:15-22.
8. Niskanen LK, Laaksonen DE, Nyyssönen K, Alfthan G, Lakka HM, Lakka TA, *et al*. Uric acid level as a risk factor for cardiovascular and all cause mortality in middle-aged men: A prospective cohort study. *Arch Intern Med* 2004; **164(14)**:1546-51. doi: 10.1001/archinte.164.14.1546.
9. Kolonel LN, Yoshizawa C, Nomura AMY, Stemmermann GN. Relationship of serum uric acid to cancer occurrence in a prospective male cohort. *Cancer Epidemiol Biomarkers Prev* 1994; **3(3)**:225-8.
10. Lanaspa MA, Sanchez-Lozada LG, Choi YJ, Cicerchi C, Kanbay M, Roncal-Jimenez CA, *et al*. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: Potential role in fructosedependent and -independent fatty liver. *J Biol Chem* 2012; **287(48)**: 40732-44. doi: 10.1074/jbc.M112. 399899.
11. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classic antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol* 2007; **293(2)**:C584-9. doi: 10.1152/ajpcell.00600.2006.
12. Yiu A, Hemelrijck MV, Garmo H, Holmberg L, Malmström H, Lambe M, *et al*. Circulating uric acid levels and subsequent development of cancer in 493,281 individuals: Findings from the AMORIS study. *Oncotarget* 2017; **8(26)**:42332-42. doi: 10.18632/oncotarget.16198.
13. Ames BN, Catheart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. *Proc*

Natl Acad Sci USA 1981; **78(11):**6858-62. doi: 10.1073/pnas.78.11.6858.

14. Tanriverdi O, Cokmert S, Oktay E, Pilanci KN, Menekse S, Kocar M, *et al*. Prognostic significance of the baseline serum uric acid level in non-small cell lung cancer patients treated with first-line chemotherapy: A study of the Turkish descriptive oncological researches group. *Med Oncol* 2014; **31(10)**:217. doi: 10.1007/s12032-014-0217-z.
15. Rose DP, Hoffner SM, Baillargeon J. Adiposity, the meta-bolic syndrome, and breast cancer in African-American and white American women. *Endocr Rev* 2007; **28(7)**:763-7. doi: 10.1210/er.2006-0019.
16. Kuo CF, See LC, Yu KH, Chiou MJ, Luo SF. Significance of serum uric acid levels on the risk of allcause and cardiovascular mortality. *Rheumatology (Oxford)* 2013; **52(1)**: 127-134. doi: 10.1093/rheumatology/kes223.
17. Strasak AM, Rapp K, Hilbe W, Oberaigner W, Ruttmann E, Concin H, *et al.* Serum uric acid and risk of cancer mortality in a large prospective male cohort. *Cancer Causes Control* 2007; **18(9)**:1021-9. doi: 10.1007/ s10552-007-9043-3.
18. Deng Z, Gu Y, Hou X, Zhang L, Bao Y, Hu C, *et al*. Association between uric acid, cancer incidence and mortality in patients with type 2 diabetes: Shanghai diabetes registry study. *Diabetes Metab Res Rev* 2016; **32(3)**:325-32. doi: 10.1002/dmrr.2724.
19. Chena YF, Lia Q, Chena DT, Pana JH, Chena YH, Wenb ZS, *et al*. Prognostic value of pre-operative serum uric acid levels in esophageal squamous cell carcinoma patients who undergo R0 esophagectomy. *Cancer Biomark* 2016; **17(1)**:89-96. doi: 10.3233/CBM-160621.
20. Cetin A, Omar M , Calp S , Tunca H, Yimaz N, Ozseker B, *et al*. Hyperuricemia at the time of diagnosis is a factor for poor prognosis in patients with stage II and III colorectal cancer (uric acid and colorectal cancer). *Asian Pac J Cancer Prev* 2017; **18(2)**:485-90. doi: 10.22034/APJCP.2017.18.2.485.
21. Selcukbiricik F, Kanbay M, Solak Y, Bilici A, Kanıtez M, Balık E, *et al*. Serum uric acid as a surrogate marker of favorable response to bevacizumab treatment in patients with metastatic colon cancer. *Clin Transl Oncol* 2016; **18(11)**:1082-7. doi: 10.1007/s12094-016-1485-1.
22. Linder N, Martelin E, Lundin M, Louhimo J, Nordling S, Haglund C, *et al*. Xanthine oxidoreductase - clinical significance in colorectal cancer and in vitro expression of the protein in human colon cancer cells. *Eur J Cancer* 2009; **45(4)**:648-55. doi: 10.1016/j.ejca.2008.10.036.
23. Su J, Wei Y, Liu M, Liu T, Li J, Ji Y, *et al*. Anti-hyperuricemic and nephroprotective effects of Rhizoma dioscoreae septemlobae extracts and its main component dioscin via regulation of mOAT1, mURAT1 and mOCT2 in hypertensive mice. *Arch Pharm Res* 2014; **37(10)**:1336-44. doi: 10.1007/s12272-014-0413-6.
24. Boffetta P, Nordenvall C, Nyrén O, Ye W. A prospective study of gout and cancer. *Eur J Cancer Prev* 2009; **18(2)**: 127-132. doi: 10.1097/CEJ.0b013e328313631a