A New Risk-Scoring System for Colorectal Cancer and Polyp Screening by Turkish Colorectal Cancer and Polyp Study Group

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ABSTRACT

Background: *Colorectal cancer is one of the most commonly diagnosed types of cancer worldwide. An early diagnosis and detection of colon cancer and polyp can reduce mortality and morbidity from colorectal cancer. Even though there are a variety of options in screening tests, the question remains on which test is the most effective for the early detection of colorectal cancer. In this prospective study, we aimed to develop a simple, useful, effective, and reliable scoring system to detect colon polyp and colorectal cancer.*

Methods: *We enrolled 6508 subjects over the age of 18 from 16 centers, with colonoscopy screening. The age, smoking status, alcohol consumption, body mass index, polyp incidence, polyp size, number and localization, and pathologic findings were recorded.*

Results: *The age, male gender, obesity, smoking, and family history were found as independent risk factors for adenomatous polyp. We have developed a new scoring system which can be used for these factors. With a score of 4 or above, we found the following: sensitivity 81%, specificity 40%, positive predictive value 25.68%, and negative predictive value 89.84%, for adenomatous polyp detection; and sensitivity 96%, specificity 39%, positive predictive value 3.35%, negative predictive value 99.29%, for colorectal cancer detection.*

Conclusion: *Even though the first colorectal cancer screening worldwide is generally performed for individuals over 50 years of age, we recommend that screening for colorectal cancer might begin for those under 50 years of age as well. Individuals with a score ≥ 4 must be included in the screening tests for colorectal cancer.*

Keywords: *Colon cancer, polyp, screening method*

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INTRODUCTION

Colon cancer is one of the most frequently occurring cancers and the third leading cause of cancer deaths in the world.[1] It is an important health problem and a major cancer which is associated with morbidity and mortality. With the development of effective screening programs, colorectal cancer (CRC) incidence and mortality rates have been significantly reduced in people aged 50 and over. On the contrary, in adults under 50 years of age, the incidence and mortality rates of CRC have increased.[2]

Several studies have demonstrated an increase in CRC rates in individuals under the age of 40. Therefore, the issue has become one of crucial importance. Recently, Siegel et al[3] reported that CRC in patients under 45 years of age accounts for approximately 4% of all cases of CRC, and they also showed that CRC incidence rates increased by 22% from 2000 to 2013 among adults aged under 50 years. A different study proposed that CRC death rates also increased by 13% in those aged below 50 years. In addition, several studies about CRC projections for 2030-2035 have remarked that the rate of occurrence of CRC will almost double in young people from the age of 20.[4] According to the National Cancer Database, Dennis et al. showed that prognosis was worse in adolescent and young adult patients with stage IV colorectal cancer compared to adult patients. Early-onset CRCs are more likely to occur in the distal colon or rectum, which are poorly differentiated, have mucinous and signet ring features, and present at advanced stages.[5]

In light of these studies, CRC screening is important, particularly in young adults, since its efficiency in reducing CRC-related mortality has been proven. Even though there are a variety of options in screening tests, such as the fecal immunochemical test (FIT), the FIT-fecal DNA test, virtual colonoscopy, and colonoscopy,[6-9] the question remains in determining the most efficient screening test for early detection of CRC. Each screening method has both advantages and disadvantages. Patient education about screening tests, test characteristics (accuracy, degree of invasiveness, test preparation, required screening interval, and cost), and the clinician's recommendation may affect preferences. Patient preference is an important parameter, and although the choice of test must be predicated on high-quality screening test options that are accessible to the patient, there must be access to follow-up colonoscopy if it is needed. Therefore, we need a non-invasive and effective screening test.

Many studies have illustrated the increased occurrence of CRC in adults. To outline the extent of current understanding, explore potential risk factors such as obesity, alcohol, and sedentary lifestyles, and to identify the questions remaining, are the issues to be addressed.[10,11] Environmental factors and genetic factors can be remarkably significant in young adults with CRC.

In this prospective study, using a multi-center database, we aimed to develop a simple, useful, effective, and reliable scoring system to detect colon polyp and CRC. In addition, the objective of this research is to evaluate the capability and accuracy of our new simple scoring system for detecting CRC.

Main Points

- *According to our new scoring system, screening for colorectal cancer may start at age 45 in patients with a Turkish Colorectal Cancer and Polyp Study Group score (TCS) over 4.*
- *The national colorectal cancer screening program may be rearranged in the light of new multicenter community-based studies.*

MATERIALS AND METHODS

Study Participants

This prospective study was conducted from September 2016 to September 2017 at 20 different gastroenterology departments. The study was performed in accordance with the guidelines of the Declaration of Helsinki and written informed consent was obtained from all study participants before study enrolment. All analysis was evaluated from prospective files and colonoscopy and pathological examination results. Firstly, we sent the study forms to 20 different centers. However, 4 of the centers did not meet the requirements of the study's procedures, and therefore, their data were excluded from the study. Thus, the present study collected data from 8000 patients from 16 centers. Data from 1492 subjects were not included in this study owing to the lack of pathological examination and patients' information, and only the data collected from 6508 subjects were analyzed in this study. The participants completed the questionnaire regarding their age, sex, family history of CRC, alcohol and smoking status, and BMI. Pathological examinations were divided as hyperplastic polyp, adenomatous polyp, and serrated polyp. Colon cancer was defined by endoscopic and pathologic examination. Colonic neuroendocrine tumors were not included in this study. Smoking status was calculated

as pack years. Alcohol consumption was classified as no alcohol, mild alcohol (20 g/day), moderate alcohol consumption (20-50 g/day), and severe alcohol consumption (> 50 g/day). BMI index was calculated as a weight/height kg/m^2). Subjects were classified as being overweight if the BMI was 27 or above and of normal weight if BMI was 18 or above, but below 25. Colon polyp size, colon polyp region, and colon polyp number were recorded.

Inclusion Criteria

Subjects who visited the gastroenterology clinic were eligible for enrolment. The participation criteria included the following: males and females aged over 18 years, availability of informed consent forms, and asymptomatic status (subject showed no lower gastrointestinal symptoms, including of lower gastrointestinal tract bleeding, change in bowel habits, or unexplained anemia or weight loss). Moreover, we included individuals older than 50 years with familial history or non-specific abdominal symptoms such as bloating, abdominal pain not related to cancer, and patients with a positive fecal occult test.

Exclusion Criteria

A history of colonic diseases that might increase the risk for colorectal cancer (including colorectal neoplasm or inflammatory bowel disease), CRC screening test or examination of the colon (e.g., colonoscopy, barium enema, or computed tomography or magnetic resonance imaging of the colon, severe premorbid illnesses which may increase the risk of colonoscopy, for example, cardiopulmonary insufficiency, history of colorectal surgery, and any contraindication for colonoscopy). Each participant was informed that they would eventually undergo verification colonoscopy.

Colonoscopy and Colorectal Neoplasms

All the examining endoscopists were blinded to the detailed history of the patients. To ensure the quality of colonoscopy, we asked all the study sites to perform split-dose or same-day bowel preparation and spend more than 6 minutes during scope withdrawal. Colonoscopy findings, including neoplastic and non-neoplastic lesions, and the size and location of the detected lesions were recorded in a standard form.

Turkish Colorectal Cancer and Polyp Study Group Score (TCS)

Based on the TCS scoring system, the age, gender, family history of colon cancer, BMI, smoking status, and alcohol status were included in this analysis When we developed the simple scoring system to detect colorectal neoplasm and adenomatous polyp, different age groups were created: under 40, between 40 and 50, and above 50. After univariate analysis, we assigned some points to every age group. Male gender was set as 2 points, family history of CRC as 1 point, BMI above 30 as 2 points, and smoking status higher than 20 pack years was 2 points (Table 1). We made the calculation using the logistic regression analysis, and TCS scores were found to be 4 points and above.

Statistical Analysis

Numeric data are expressed as mean and SD, and categorical data are shown as number and proportion. The TCS scores of all study participants were calculated based on their age group, gender, family history of CRC in a first-degree relative, smoking history, and BMI. The 3 prevalent categories of colon polyps are adenoma, hyperplastic polyp, and serrated polyp. TCS points were calculated in association with the Asia-Pacific Colorectal Screening (APCS) score for risk groups and were compared among the groups. Numeric variables were compared with independent sample *t*-tests, and categorical variables were compared with χ^2 tests or Fisher's exact test. We developed the TCS system with univariate analysis, logistic regression analysis, and multiple modeling tests. The reported *P* values were for two-sided statistical tests and a *P* value < .5

Table 1. Turkish Colorectal Cancer and Polyp Study Group Score

Age (years)	
40-45	1
45-50	2
50 and over	4
Gender	
Female	0
Male	1
Smoking	
No smoking	0
20-30 pack years	1
30 pack years	2
BMI	
<30	0
>30	1
Family history	
No history	0
Positive	1

was statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 17.0 software (SPSS Inc.; Chicago, IL, USA).

RESULTS

Study Population

A total of 6508 subjects from 16 sites were included in this study. The mean age of the study subjects was 53.9 ± 13.4 years, and 47.4% patients were males (50.9%). When we evaluated the smoking status, we categorized them as 3 different types: 37% of the patients were occupational smokers, 23% of the patients were active smokers, and 14% of the patients had ceased smoking, in all study populations. The smoking-exposed patients, both those who were active and those who had quit smoking, were divided into 2 groups based on pack years. Of these, the smoking status of 53% of the patients in this group was 20 pack years. Alcohol consumption was 8.3% in all populations, of which 63% reported moderate and heavy alcohol consumption. Average BMI was 27.4 ± 4.8, and 26% of the patients had a BMI > 27 kg/m^2. Fourteen percent of the patients reported a family history. The demographic data (smoking consumption, alcohol intake, BMI, family history) of the study population are shown in Table 2.

Polyp and CRC Frequency

Polyp frequency was 30.9% (adenomatous and others) and CRC frequency was 2.3% in the study population. The frequency of adenomatous polyps among all poly types was 83.6%, 16.3% were hyperplastic polyps and 0.1% were neuroendocrine polyps. The regions of polyp detection were in the left colon (64%), the right colon (20%), and both left and right colon (16%). CRC was detected in the left colon (73%) and in the right colon (27%). With regard to gender, colon polyp frequency in male patients was found to be 37% and it was 27% in female patients ($P < .001$). CRC frequency was 3.8% in male patients and 1% in female patients. ($P < .001$). We also detected that adenomatous polyp occurred more frequently in the male patients compared to the female patients (86% in male, 80% in female, $P = .035$). CRC and colon adenomatous polyp frequency increased with increase in age (Figure 1).

Regression Analysis

Male gender, age group (40 years), BMI >30 kg/m^2, family history, alcohol consumption, and smoking (<20pack years) were included in the logistic regression analysis. Risk factors other than alcohol were considered independent risk factors in terms of adenomatous polyp.

Table 2. Demographic Findings

Variables	Results
Male/female (%)	47.4/52.6
Age (years)	53.9 ± 13.4
Smoking status (%)	
No smoking history	63
Smoking-exposed	37
Active smoking	23
Smoking cessation	14
Alcohol status (%)	
Absence of alcohol history	91.7
Presence of alcohol history	8.3
Mild alcohol consumption	3.2
Moderate-heavy alcohol consumption	5.1
BMI, (kg/m^2)	27.4 ± 4.8
Familial history (%)	14.5
CRC (%)	
Frequency	2.4
Localization	
Left colon	73
Right colon	27
Colon Polyp (%)	
Frequency	30.9
Adenomatous polyp	83
Hyperplastic polyp	16
Serrated polyp	1
Localization	
Left colon	64
Right colon	20
Both left and right colon	16

ROC Analysis for Age

When we assumed 50 years as a cut-off age, adenomatous polyp detection showed 73% sensitivity and 39% specificity. Furthermore, when we assumed age of 45 years as a cut-off age, we found 85% sensitivity and 41% specificity. However, we assumed that for the age of 40, specificity decreased significantly; sensitivity was 92% and specificity was 18%. Therefore, adenomatous polyp detection started at age 45. We detected similar results in CRC; for the age 50 it was 89% sensitive, with 36% specificity. If the stated age was 45 for colonoscopy screening detection for adenomatous polyp, specificity insignificantly changed to 35%, but sensitivity was significantly higher, at 94%.

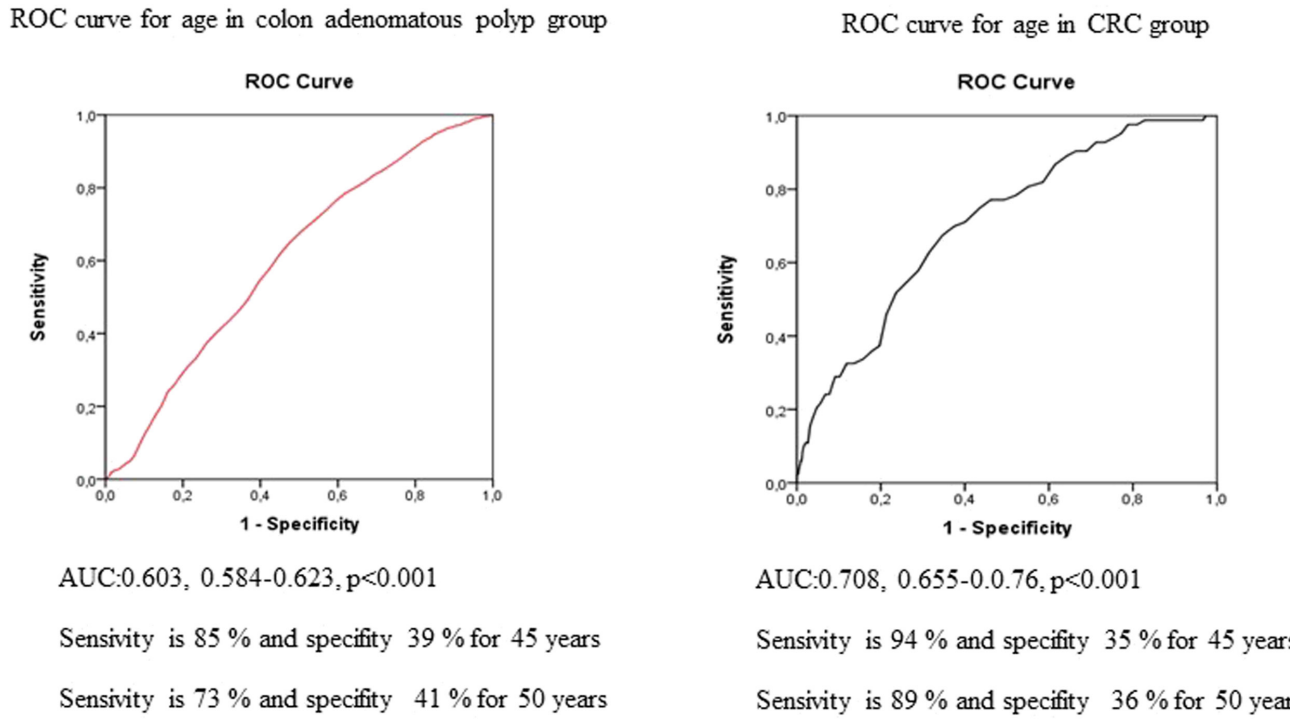

Figure 1. Receiver operating characteristic (ROC) curves for age in detecting colon adenomatous polyp and colorectal cancer.

New Scoring System

Age is considered as an important factor in CRC and polyp screening, but age is not the only risk factor in polyp and CRC (ROC analysis shows Figure 1) Male gender, age (40 years), BMI (>30 kg/m^2, family history and smoking (<20 pack years) are also important factors in polyp and CRC occurrence. We devised a new scoring system for adenomatous polyp detection. These factor points are presented in Table 1. A score greater than 4 in adenomatous polyp detection indicated 81% sensitivity and 40% specificity. Odds Ratio: 2.3, 95% CI (2.3-3.6), $P < .001$. Positive predictive value: 25.68% (CI: 24.79-26.60). Negative Predictive Value: 89.84% (CI: 88.0-91.3). For CRC, the sensitivity was 96% and specificity 39%. Odds Ratio: 10.1, 95% CI (3.7-27.8), $P < .001$. Positive predictive value: 3.35% (CI: 3.11-3.59%). Negative predictive value: 99.29% (98.63-99.63%) (Figure 2).

We suggest that based on our scoring system, which is set as 4 points or above, physicians should screen carefully for colon polyp and colon cancer for every age group of patients if they have these conditions.

DISCUSSION

In this multi-center prospective study, we found that male gender, age, BMI, family history and smoking history, were independent risk factors for detecting colorectal neoplasia and polyp. Moreover, we also showed that a TCS score higher than 4 points is a reliable and successful indicator of CRC and colon polyp. The results of this study indicate that our scoring system is more useful and reliable for early colorectal polyp and cancer detection. Moreover, if subjects had more than 4 points according to our new scoring system, we strongly suggested that colonoscopy examination may be applied earlier than the age of 45. Other risk factors of smoking and BMI play an important role in colorectal cancer screening programs. Not all subjects have similar risk factors because each subject has individual risk factors as well. The exact age and family history are important, but they are not the only significant factors to initiate colon polyp and cancer screening.

Recent studies have shown that the age for colon polyp and cancer screening should be 45 years, due to the increasing rate of colorectal cancer. In a paper which was published in 2018 by the American Cancer Society (ACS), it was suggested that colorectal cancer screening would begin at the age of 50 for people who were in the average risk group.[12] After this report, ACS updated the recommendation by stating that adults aged 45 and older with an average risk of CRC should undergo regular screening. However, in 2017, the ASGE presented in

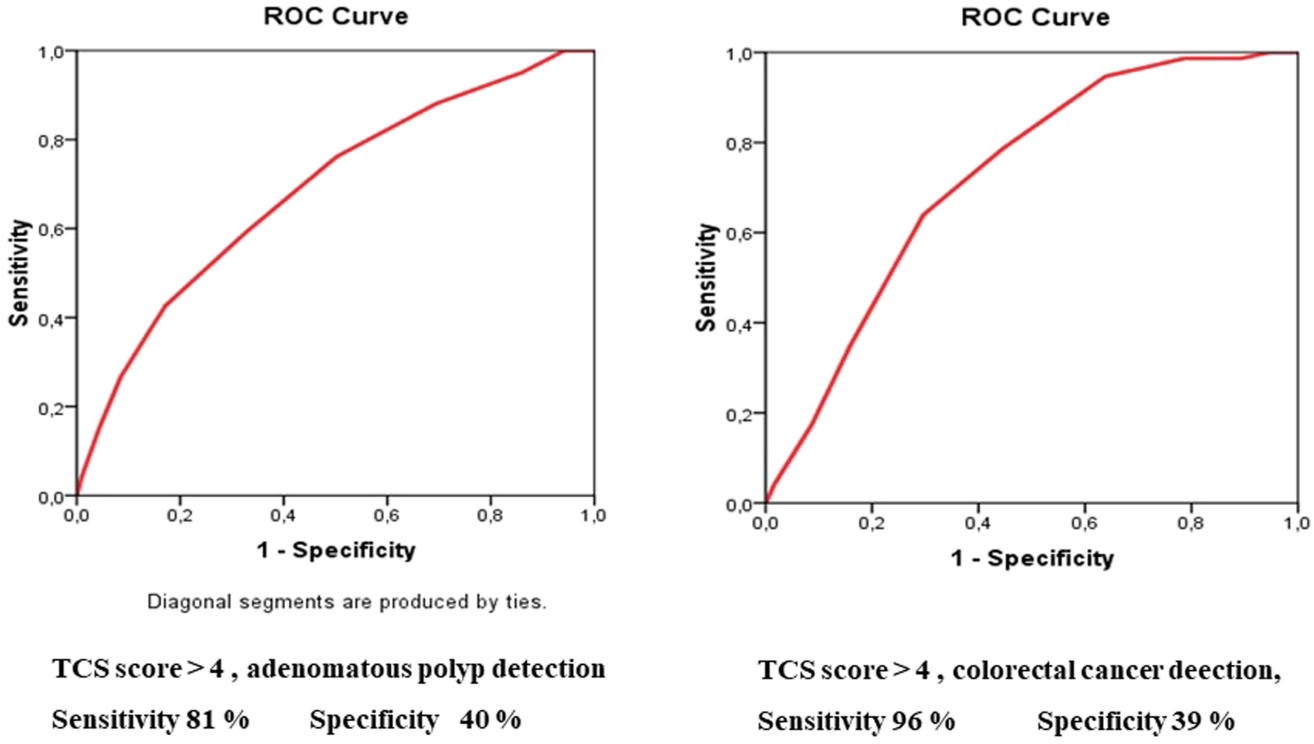

Figure 2. Receiver operating characteristic (ROC) curves for TCS score > 4 in detecting colon adenomatous polyp and colorectal cancer.

the guidelines that screening should begin at age 50 in average-risk persons, apart from African Americans from whom limited evidence supports screening at 45 years of age.[13] In addition, CRC incidence is rising in persons under 50 years of age, and thorough diagnostic evaluation of young persons with suspected colorectal bleeding is recommended. A considerable amount of literature has been published on early-onset CRC. The first serious discussions and analyses of CRC rates emerged in the 25th UEG Week Barcelona. Authors claimed that "The screening for colorectal cancer should begin at the age of 45." In the 2017 UEG congress, these authors suggested that colorectal screening should begin at the age of 45 years since they found colorectal cancer rate in individuals aged 40-45 years of age to be 8% higher compared to those 50-55 years of age. Our study concluded that colonoscopy examination for colon polyp and cancer detection should be initiated at least from 45 years of age. When age alone was taken into consideration as a risk factor for colon polyp and cancer, we showed that the ROC values for those who are 45 years old and 50 years old are similar. We demonstrated that sensitivity rate was better in people aged 45 compared to the ones aged 50. We also showed that the incidence rate of colon polyp and colon cancer would begin to increase at the age of 45.

The age may be the important indicator for starting to screen for CRC and polyp, but not the sole factor. A number of studies have shown that various factors including family history, obesity, smoking, and gender are also among the reasons causing colon polyp and cancer.[14-18] Obesity is a well-known major health problem worldwide. It is related to several types of cancer. In the literature, many authors have shown a positive association between obesity and colorectal cancer.[17,19,20] There are several responsible mechanisms that can help to explain the association between BMI and colorectal neoplasm. Obesity-related disorders including metabolic syndrome, insulin resistance, and high serum adipocytokine levels may play a role in the progression of CRC.[21,22] Indeed, BMI may be associated with early-onset colorectal neoplasm, Sanford et al[23] suggested that BMI is associated with younger age at diagnosis of colorectal cancer. In our study we showed that BMI is an important factor for colorectal neoplasia and adenomatous polyp. We also demonstrated that obesity rate in patients with CRC and colon polyp were higher than those patients without colon cancer or polyp. Furthermore, BMI >30 is independently associated with colon polyp and cancer. Reviewing the literature, some studies have reported a close relationship between smoking and moderate to high intake of alcohol.[23-27] In

this study, we showed a chart of smoking habits, especially heavy smoking status, to be a risk factor for CRC and polyp. However, we have found no significant correlation between alcohol consumption and adenomatous polyp and CRC. We used logistic regression analysis to assess the association between the risk factors and CRC. Obesity (BMI >30), smoking habits (>20 pack years), and male gender are independent risk factors for CRC and polyp.

Some authors needed to use simple screening tests to determine the relationship between environmental risk factors and colorectal cancer. The Asia-Pacific Colorectal Screening (APCS) score based on age, gender, family history, smoking, and BMI is a useful tool in stratifying asymptomatic Asian people.[28] Although the APCS scoring system is a non-invasive test, it has several limitations, the most significant being that the study included only patients older than 50 years. As it is known, the guidelines recommend screening for CRC for those older than 50 years. There is no information recommending how the screening is done in young adults below 50 years. Some guidelines recommend 45 years of age as sufficient to begin for screening. Overall, these studies highlight the need for screening methods for young adults. However, no previous study has investigated young adults. Colonoscopy is still the gold standard for diagnosing colorectal neoplasms and it also prevents CRC by removal of adenomas during the procedure. A recent study used modeling to estimate that 29 400 cases of CRC could be prevented during the next 5 years with screening at 45 years of age but stated that it would cost an incremental $10.4 billion, which is thought to be likely cost-effective.[29] Therefore, we need simple screening methods. Previous authors have developed scoring systems accounting for several risk factors.

Kaminski et al[30] developed a scoring system using some demographic features including age, sex, family history of CRC, smoking, and body mass index to estimate the likelihood of detecting advanced colorectal neoplasm. Their scoring system only requires simple demographic information, and includes individuals between 40 and 60 years old., which may be a limitation on its validity and applicability. Nonetheless, despite its good discrimination power, this scoring system divides people into 8 different categories which was more complicated. Moreover, its applicability has not been tested in the FIT-based screening scenario, which is the most popular in the Asia-Pacific region. Another scoring system was also developed by Tao et al[31] In their scoring system, 9 risk factors (sex, age, CRC family history, smoking, alcohol consumption, red meat consumption, nonsteroidal anti-inflammatory drug use, previous colonoscopy, and previous detection of polyps) are included in the scoring to identify people at risk for advanced colorectal neoplasms.[31] The strategy of triaging people to go for colonoscopy or none in these 2 studies is distinct from our current study incorporating FIT as a screening option. The necessity of collecting details on dietary habits or previous colonoscopy findings may also cause recall bias.

In this study, we developed a new scoring system for early detection of polyp and CRC. If the TCS score is 4 points or above, we showed that for CRC and polyp detection, sensitivity and specificity are higher than the age factor alone. For a score greater than 4 points, there is 81% sensitivity and 40% specificity for adenomatous polyp detection and 96% sensitivity and 39% specificity for CRC detection. According to our new scoring system, for patients over 50 years old, the sensitivity for CRC and polyp detection is remarkably high.

The most important limitation is that this study is a multicenter study which sometimes may lead to discrepancies in the colonoscopy findings between one center and another due to endoscopists' experience and the quality of colonoscopy devices.

In conclusion, we showed that our point system is quite simple and practicable compared to other scoring systems. We suggest that based on our scoring system, which is set as 4 points or above, physicians should screen carefully for colon polyp and colon cancer at every age group, for individuals who meet the conditions. In the future, large population-based studies are needed to evaluate the reliability and accuracy of our scoring system in early detection of CRC and polyp, especially in young patients.

Ethics Committee Approval: This study was approved by the Demiroğlu Bilim University Ethics Committee of Medical Research.

Informed Consent: N/A.

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REFERENCES

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gut. 2017;66(4):683-691. [CrossRef]

2. Loomans-Kropp HA, Umar A. Increasing incidence of colorectal cancer in young adults. J Cancer Epidemiol. 2019;2019:9841295. [CrossRef]

3. Siegel RL, Miller KD, Fedewa SA, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-193. [CrossRef]

4. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg. 2015;150(1):17-22. [CrossRef].

5. Ahnen DJ, Wade SW, Jones WF, et al. The increasing incidence of young-onset colorectal cancer: a call to action. Mayo Clin Proc. 2014;89(2):216-224. [CrossRef]

6. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996;348(9040):1472-1477. [CrossRef]

7. Allison JE, Fraser CG, Halloran SP, Young GP. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver. 2014;8(2):117-130. [CrossRef]

8.Kim DH, Pickhardt PJ, Taylor AJ, et al. CT colonography versus colonoscopy for the detection of advanced neoplasia. N Engl J Med. 2007;357(14):1403-1412. [CrossRef]

9. Ahlquist DA. Multi-target stool DNA test: a new high bar for non-invasive screening. Dig Dis Sci. 2015;60(3):623-633. [CrossRef]

10. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjønneland A. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. BMJ. 2010;341:c5504. [CrossRef]

11. Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. Am J Epidemiol. 2009;170(7):863-872. [CrossRef]

12. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-281. [CrossRef]

13. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: Recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2017;86(1):18-33. [CrossRef]

14. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah population database. J Natl Cancer Inst. 1994;86(21):1618-1626. [CrossRef]

15. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001;96(10):2992-3003. [CrossRef]

16. Phipps AI, Baron J, Newcomb PA. Prediagnostic smoking history, alcohol consumption, and colorectal cancer survival: the Seattle colon cancer family registry. Cancer. 2011;117(21):4948-4957. [CrossRef]

17. Alsheridah N, Akhtar S. Diet, obesity and colorectal carcinoma risk: results from a national cancer registry-based middle-eastern study. BMC Cancer. 2018;18(1):1227. [CrossRef]

18. Zhou H, Shen Z, Zhao J, Zhou Z, Xu Y. Distribution characteristics and risk factors of colorectal adenomas. Zhonghua Wei Chang Wai Ke Za Zhi. 2018;21(6):678-684.

19. Yang Z, Wei X, Pan Y, Min Z, Xu J, Yu B. Colon cancer combined with obesity indicates improved survival-research on relevant mechanism. Aging. 2020;12(23):23778-23794. [CrossRef]

20. Nam GE, Baek SJ, Choi HB, et al. Association between abdominal obesity and incident colorectal cancer: a nationwide cohort study in Korea. Cancers. 2020;12(6):1368. [CrossRef]

21. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013;62(6):933-947. [CrossRef]

22. Sălăgeanu A, Tucureanu C, Lerescu L, et al. Serum levels of adipokines resistin and leptin in patients with colon cancer. J Med Life. 2010;3(4):416-420.

23. Sanford NN, Giovannucci EL, Ahn C, Dee EC, Mahal BA. Obesity and younger versus older onset colorectal cancer in the United States, 1998-2017. J Gastrointest Oncol. 2020;11(1):121-126. [CrossRef]

24.Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J Natl Cancer Inst. 2000;92(22):1831-1836. [CrossRef]

25. Chia VM, Newcomb PA, Bigler J, Morimoto LM, Thibodeau SN, Potter JD. Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and nonsteroidal anti-inflammatory drug use. Cancer Res. 2006;66(13):6877-6883. [CrossRef]

26. Eaton AM, Sandler R, Carethers JM, Millikan RC, Galanko J, Keku TO. 5,10-Methylenetetrahydrofolate reductase 677 and 1298 polymorphisms, folate intake, and microsatellite instability in colon cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(8):2023-2029. [CrossRef]

27. Slattery ML, Anderson K, Curtin K, Ma KN, Schaffer D, Samowitz W. Dietary intake and microsatellite instability in colon tumors. Int J Cancer. 2001;93(4):601-607. [CrossRef]

28. Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. Gut. 2011;60(9):1236-1241. [CrossRef]

29. Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-effectiveness and national effects of initiating colorectal cancer screening for average-risk persons at age 45 years instead of 50 years. Gastroenterology. 2019;157(1):137-148. [CrossRef]

30. Kaminski MF, Polkowski M, Kraszewska E, Rupinski M, Butruk E, Regula J. A score to estimate the likelihood of detecting advanced colorectal neoplasia at colonoscopy. Gut. 2014; 63(7):1112-1119. [CrossRef]

31. Tao S, Hoffmeister M, Brenner H. Development and validation of a scoring system to identify individuals at high risk for advanced colorectal neoplasms who should undergo colonoscopy screening. Clin Gastroenterol Hepatol. 2014;12(3):478-485. [CrossRef]