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FOBTs With Lower Detection Limits Increase the Colonoscopy Rates

Saptama Limitleri Daha Düşük Olan GGK Testleri Kolonoskopi Sayısını Artırır

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ABSTRACT

Aim: Colon cancer, accounting for almost 10% of all cancers in both genders worldwide, is the fourth most common cause of cancer-related deaths. Approximately 95% of cases are originated from adenomas. In recent years, early detection of colon-borne pathologies and precancerous changes have contributed to decreased mortality rates. Therefore, early diagnosis is necessary to prevent and treat colorectal cancer properly. We aimed to evaluate the correlation of fecal occult blood tests (FOBT) with different detection limits with colonoscopy results and the performance of the tests.

Material and Methods: The consistency of 3 different immunochemical FOBT (iFOBT) with cutoff values of 10, 30, and 50 ng/mL, which were used in a tertiary university hospital laboratory at different time periods, with colonoscopy results were analyzed retrospectively. The sensitivity, specificity, positive and negative predictive values of tests determined for adenoma-adenocarcinoma, advanced neoplasia, adenocarcinoma.

Results: We observed that as the cutoff values of FOBT increased, lesion detection rates decreased; 1/23, 5/22, 1/1 of the adenocarcinoma cases were not detected for the tests with detection limits of 10, 30, 50 ng/mL, respectively. The negative predictive values of the tests were above 97% for adenocarcinoma detection.

Conclusion: Changing the detection limit of the FOBT affects performance. Lowering the detection limit will facilitate the detection of adenocarcinoma patients and increase the number of colonoscopies performed due to false positive results.

Key Words: Adenocarcinoma, Adenoma, Colon Cancer, Fecal Occult Blood Test, FOBT

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ÖZET

Amaç: Dünya çapında her iki cinsiyette de tüm kanserlerin yaklaşık 10%'unu oluşturan kolon kanseri, kansere bağlı ölümlerin dördüncü en yaygın nedenidir. Vakaların yaklaşık 95%'i adenomlardan kaynaklanır. Son yıllarda, kolon kaynaklı patolojilerin ve kanser öncesi değişikliklerin erken tespiti, ölüm oranlarının düşmesine katkıda bulunmuştur. Bu nedenle, kolorektal kanseri önlemek ve uygun şekilde tedavi etmek için erken teşhis gereklidir. Farklı saptama limitleri olan gaitada gizli kan testlerinin (GGK) kolonoskopi sonuçları ile ilişkisini ve testlerin performanslarını değerlendirmeyi amaçladık

Materyal ve Metod: Üçüncü basamak bir üniversite hastanesi laboratuvarında farklı zaman dilimlerinde kullanılan 10, 30 ve 50 ng/mL cut-off değerlerine sahip 3 farklı immünokimyasal GGK testinin kolonoskopi sonuçları ile uyumu retrospektif olarak incelendi. Adenom ve adenokanser, ileri neoplazi, adenokarsinom için testlerin sensitivite, spesifite, pozitif ve negatif prediktif değerleri belirlendi.

Bulgular: GGK testinin cut-off değerleri arttıkça lezyon saptama oranlarının düştüğünü gözlemledik; Adenokarsinom vakalarının 1/23'ü, 5/22'si, 1/1'i tespit limitleri sırasıyla 10, 30, 50 ng/mL olan testlerde saptanmadı. Testlerin negatif prediktif değerleri adenokarsinom tespiti için 97%'nin üzerindeydi.

Sonuç: GGK testi tespit limitinin değiştirilmesi performansı etkiler. Tespit limitinin düşürülmesi adenokarsinom hastalarının tespit edilmesini kolaylaştıracak beraberinde yanlış pozitif sonuçlar nedeniyle uygulanan kolonoskopi sayısını artıracaktır.

Anahtar Kelimeler: Adenokarsinom, Adenom, Kolon Kanseri, Gaitada Gizli Kan Testi, GGK

INTRODUCTION

Colon cancer, which is the third most common worldwide, is the fourth most common cause of cancer-related deaths (1). In recent years, early detection of colon-borne pathologies and precancerous lesions and improvements in treatment protocols have contributed to decreased mortality rates (2). Rectal bleeding and changes in bowel habits are among the alarm symptoms of colorectal cancer (3).

Although colonoscopy is accepted as the gold standard because it enables screening and treatment, it is not accepted first in the screening program due to its high cost, not being preferred by patients, and risk of complications (2, 4).

As a screening test, the fecal occult blood test (FOBT) is most frequently used because it is relatively inexpensive and non-invasive. Occult blood in feces can be mainly analyzed by two different measurement principles, guaiac-based (gFOBT) and immunochemical (iFOBT) methods. The gFOBT, which enables occult blood determination by determining the peroxidase activity of the heme molecule in stool, has disadvantages such as low sensitivity, requiring preliminary preparation because it is affected by dietary factors and subjective evaluation of the results (5-7). For these reasons, the World Endoscopy Organization recommended using iFOBT as a screening test in 2012 (1, 8). Although the evidence is limited, FOB tests can also be used for diagnostic purposes.

The difference in the antibodies used and the difference in their sensitivities can affect the diagnostic performance of the FOBTs. It is known that in screening tests false positivity rates increase as the detection limit decreases. In this context, we aimed to retrospectively investigate the consistency and correlation of 3 different iFOBT with cutoff values of 10, 30, and 50 ng/mL, used in our laboratory at different periods, with colonoscopy results and analyze the performance of the tests.

MATERIALS AND METHODS

This study was carried out in a tertiary university hospital retrospectively. In this context for FOBT, we have used Laboquick (Koroglu medical equipment, Izmir, Turkey) test kit with a sensitivity level of 30 ng/mL (in use 01.01.2018-31.03.2019), Acro Biotech (Acro Biotech Inc, CA, USA) with the

sensitivity level of 10 ng/mL (in use 01.05.2019-31.03.2020) test kit and Wondfo (Guangzhou Wondfo Biotech Co., China) test kit with the sensitivity level of 50 ng/mL (in use 01.11.2020-28.02.2021) in our hospital. Within the scope of the study, data on FOBT test results were obtained from the hospital database within the specified time intervals. The data of patients who underwent colonoscopy in the Gastroenterology clinic during the same periods were analyzed. Colonoscopy results and pathology reports were evaluated. Patients who underwent FOBT analysis within the specified periods and then underwent colonoscopy due to a positive FOBT result or due to symptom/screening indication despite a negative FOBT result were included in the study. 741 patients had FOB test and post-test colonoscopy reports and pathology reports of those with lesions. Of these patients, 92 were excluded from the study for various reasons. (Figure 1). A total of 649 patients were analyzed. (Laboquick-n: 327, Biotech-n: 260, Wondfo-n: 62). In all three tests, the analysis gives a qualitative result and is evaluated visually. The same laboratory personnel evaluated either test.

Those with known inflammatory bowel disease (n = 25), those who could not undergo colonoscopy due to insufficient bowel preparation (n = 13), those with visible bleeding (n = 3), patients whose FOBT result belongs to the post-colonoscopy period (n = 28), previously undergone colon surgery patients (n = 13), polyps whose subtype was not specified histologically (n = 3), uncompleted colonoscopies (n = 7) were excluded from the study (Figure 1.) In our hospital, a protocol has been determined in which patients who will undergo FOBT are told how to do it verbally and through visual tools. Patients in the menstrual period are avoided to collect a sample. The age, gender of the patients, and histopathological data regarding colonoscopy results were recorded. The study was designed in a double-blind way. The presence of hemorrhoids, anal fissure, diverticulum, angiodysplasia, and ectasia was accepted as "others" for this study.

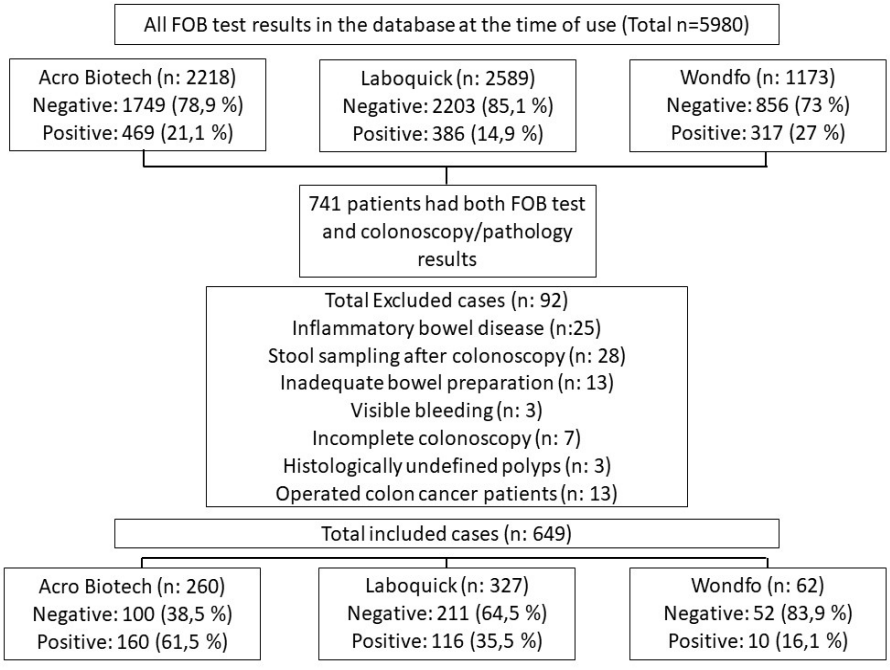

Figure 1. Summary of patients in the study. The distribution of FOBT results during the periods it was used in our laboratory is shown.

Fecal Occult Blood-iFOB / immunochromatography method

iFOBT kits are a rapid and lateral flow immunochromatographic test for the qualitative detection of occult blood in feces. Food restrictions are not required. The analytical sensitivity of the tests is 10, 30, and 50 ng/mL buffer for Acro Biotech, Laboquick, and Wondfo kits, respectively.

Colonoscopy

The reliability of colonoscopy results is related to the experience level of the practitioners. In our hospital, approximately 1500 colonoscopy procedures are performed annually by experienced gastroenterologists. In our gastroenterology clinic, colonoscopy is recommended for patients with at least one positive FOBT test.

All colonoscopies were performed with sedation and analgesia with propofol and fentanyl under the supervision of an anesthesiologist. Colonoscopy preparation is done with four liters of PEG (Polyethylene glycol) solutions applied before the procedure day. Pathologies suitable for resection are excised, a biopsy is performed for pathologies unsuitable for resection, and the sample is delivered to the pathology laboratory.

Pathological Examination

Experienced pathologists made all histological evaluations. Adenomas were categorized as <10 mm and >10 mm according to their size, as tubular, tubulovillous, and villous according to their histological features via pathological examination. The villous component was assessed as >20% villous by an experienced pathologist: in suspected cases, a second opinion from another experienced pathologist was requested until consensus was reached. Patients with dysplasia were categorized as low-grade and high-grade dysplasia. Adenomas larger than 10 mm adenomas with more than 20% villous components and those with high-grade dysplasia were accepted as the advanced adenoma group. The presence of advanced adenoma and invasive cancer was taken as the advanced colorectal neoplasia group.

Statistical Analysis

Statistical analysis was performed with IBM SPSS Statistics, Version 22.0 (SPSS Inc., Chicago, USA). Descriptive statistics of the groups were given as frequencies and percentages (n,%). Normality analysis of continuous numerical variables was performed with statistical tests (Kolmogorov-Smirnov and Shapiro-Wilk) and histogram graphics. Accordingly, normally distributed variables were reported as mean ± standard deviation, and variables that did not show normal distribution were notified as median (min-max). The performance of the tests was evaluated by calculating the sensitivity, specificity, positive predictive, and negative predictive values (NPV) in detecting adenoma-adenocarcinoma, advanced neoplasia, and adenocarcinoma based on colonoscopy and pathology results.

RESULTS

The mean±SD age of all patients is 56.34±16.7 years. 367 of the patients are male (56.5%). The pathologies detected are stated in Table 1. All of the cases of adenoma (n = 4), advanced adenoma (n = 1), and adenocancer (n = 1) had negative results with the Wondfo test kit. (Within the specified period, 5 of these six patients had one FOBT result, while 1 tubular adenoma patient had two negative results on the same test kit on different dates.)

Adenoma and adenocarcinoma detection rates were 40/260 (15.4%) for Biotech, 33/327 (10.1%) for Laboquick, and 0/62 (0%) for Wondfo tests. The rates of patients who underwent colonoscopy and were found to be normal despite positive test results were 42/260 (16.2%) for Biotech, 20/327 (6.12%) for Laboquick, 3/62 (4.8%) for Wondfo tests.

The sensitivity, specificity, and positive and negative predictive values of FOB tests for various pathologies based on colonoscopy

results and pathology reports are given in Table 2. As the detection limits of the tests increase, the sensitivity values decrease, and the specificity values increase. The negative predictive values of the tests were above 97% for adenocarcinoma.

Table 1. Demographic data of the groups and distribution of pathologies

	Biotech		**Laboquick**		**Wondfo**	
	Negative	**Positive**	**Negative**	**Positive**	**Negative**	**Positive**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age (years) (Median) (min - max)	56 (18 - 91)	60 (18 - 91)	57 (17 - 92)	58 (17 - 96)	58 (21 - 79)	50 (38 - 85)
Gender (F /M)	47 / 53	65 / 95	94 / 117	45 / 71	25 / 27	6 / 4
Others*	27 (27)	38 (23.8)	69 (32.7)	27 (23.3)	23 (44.2)	2 (20)
Normal morphology	46 (46)	42 (26.3)	93 (44.1)	20 (17.2)	16 (30.8)	3 (30)
Colitis, Ulseration	11 (11)	39 (24.4)	16 (7.6)	34 (29.3)	7 (13.5)	4 (40)
Hyperplastic polyp	0	1 (0.6)	1 (0.5)	2 (1.7)	0	1 (10)
Tubuler Adenom	11 (11)	10 (6.3)	19 (9)	12 (10.3)	4 (7.7)	0
Advanced Adenom	4 (4)	8 (5)	8 (3.8)	4 (3.4)	1 (1.9)	0
Adenocancer	1 (1)	22 (13.8)	5 (2.4)	17 (14.7)	1 (1.9)	0
Total	100	160	211	116	52	10

*Other pathologies include hemorrhoids, diverticula, anal fissure, angiodysplasia, ectasia

Table 2. Sensitivity, specificity, positive and negative predictive values of FOB tests for various lesions found in colonoscopy.

		Sensitivity	**Specifity**	**PPV**	**NPV**
		% (95% CI)	**% (95% CI)**	**% (95% CI)**	**% (95% CI)**
Adenom and Adeno-carcinoma	**Biotech**	71,43 (57,79-82,7)	41,18 (34,35-48,26)	25 (21,41-28,97)	84 (77,08-89,13)
	Laboquick	50,7 (38,07-63,4)	68,32 (62,31-73,91)	28,45 (22,78-34,88)	84,83 (81,17-87,89)
	Wondfo	0 (0-45,93)	82,14 (69,6-91,09)	0	88,46 (87,16-89,65)
Advanced Neoplasia	**Biotech**	85,71 (69,74-95,19)	42,22 (35,69-48,97)	18,75 (16,22-21,57)	95 (89,27-97,75)
	Laboquick	61,76 (43,56-77,83)	67,58 (61,89-72,9)	18,1 (13,93-23,19)	93,84 (90,79-95,92)
	Wondfo	0 (0-84,19)	83,33 (71,48-91,71)	0	96,15 (95,71-96,55)
Adeno-carcinoma	**Biotech**	95,65 (78,05-99,89)	41,77 (35,42-48,33)	13,75 (12,19-15,48)	99 (93,54-99,85)
	Laboquick	77,27 (54,63-92,18)	67,54 (61,97-72,77)	14,66 (11,5-18,49)	97,63 (95 - 98,89)
	Wondfo	0 (0-97,5)	83,61 (71,91-91,85)	0	98,08 (97,86-98,28)

PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval

DISCUSSION

Colorectal cancer is accounting for almost 10% of all cancers in both sexes. The incidence of increases at the age of 50 and over and approximately 95% of these are originated from adenomas. (9, 10). Considering that the transition from adenomatous polyps to adenocarcinoma takes an average of 10 years, screening tests to identify malignant polyps in the population are important in early diagnosis of colorectal cancer and reducing mortality and treatment costs (9-11).

Colonoscopy has been accepted as the gold standard method for detecting and screening colorectal pathologies (12). Although colonoscopy is accepted as a safe procedure, complications such as bleeding, bowel perforation, and cardiopulmonary damage can occur, and the morbidity of the patient under examination can increase (2, 10).

Studies have shown that sensitivity for iFOBT varies between 45-75%, specificity 35-94%, positive predictive values 10-60%, and negative predictive values between 97-99.5% (10, 13, 14). While the use of tests with low detection limits is expected to detect more colorectal cancer cases, in theory, it has been observed that this is not the practice case (5, 15). Even if the lower measurement limits are the same, the sensitivity and specificity of qualitative tests in detecting adenoma may be different (5). In addition, the location, size, and number of pathological tissues can be determinative of the diagnostic performance of tests (16, 17). Although the lower measurement limits are similar, it is stated that the variety of antibodies used in the tests may be one of the reasons for the performance difference of the tests (5).

Since pathological tissues may bleed intermittently, performing FOB tests repeatedly can increase the diagnostic performance of the tests. It has been shown that the rate of finding advanced neoplasia is higher if the FOB test is repeated twice (18).

Qualitative and quantitative results can be obtained with the iFOBT. Qualitative testing is more common in Turkey. Qualitative tests are insufficient to provide information about the colonic pathology's type, location, and size. It was stated that the concentration of hemoglobin in stool is less than the surface, so it should be reminded patients that they should take the sample from the surface (16, 19).

False-positive FOB results may increase colonoscopy rates and cause the patient's psychosocial adverse effects. In addition to the difference in antibodies used, the location and other factors that reduce sensitivity make it challenging to compare the tests with each other. Although we retrospectively compared the results of FOB applied to different patients, we obtained findings that support the literature. We found that the specificity and sensitivity of the FOB tests are consistent with the literature.

A screening method is needed for colorectal carcinoma screening. For most countries, an ideal strategy should be inexpensive, easily applicable, highly accurate, and accepted by individuals. When evaluating available resources, FOBT has become an attractive alternative. FOBT is a sensitive and specific screening method to predict the presence of polyps, neoplastic polyps in general, and primarily adenocarcinomas. FOBT has a high negative predictive value in detecting benign and malignant colorectal lesions.

When polyps are detected with colonoscopy, they should be examined histologically regardless of their size or morphology (20). Polypectomy reduces the incidence of colorectal cancer (9). A study reported that 40 of 310 patients who had at least one positive FOBT result had polyps and were resected. Most of the polyps were in the adenoma or advanced adenoma group and may progress to colorectal cancer (21). Precancerous lesions can progress to colorectal cancer within 10-15 years (22). Screening programs for the detection and removal of adenomas can increase the

survival rate by interrupting the progression of the adenoma to cancer and the development of neoplasia at an early stage (10). The positive results in our study for Biotech test 18/160; for Laboquick, 16/116 of them are in the tubular adenoma and advanced adenoma group. The detection of these pathologies is effective in changing the process of the disease. Therefore, algorithms including FOBT and colonoscopy can contribute to colorectal cancer detection and prevention.

Not all positive FOBT results can be evaluated colonoscopically. Although the number of FOBT-positive cases was in total high (n = 1172), our number of cases decreased relatively because each patient did not undergo colonoscopy in the relevant period. Although the Wondfo kit's cutoff value is higher, a higher rate of positivity (27%) may be because of symptomatic patient applications in the foreground due to pandemic conditions or due to the variety of hemoglobin antibodies used in the tests. However, since all of the cases of adenoma (n = 4), advanced adenoma (n = 1), and colon adenocancer (n = 1) patients had negative results, the first possibility is more substantial.

It is known that FOBT can result negatively in the presence of gastrointestinal pathologies. The amount of bleeding below the detection limit level, the tendency of pathologies to intermittent bleeding, right colon pathologies, and preanalytical factors of stool sampling may cause false-negative results (10). On the other hand, drugs such as alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids may give false-positive results due to GIS irritation (10).

It has been reported in the studies conducted with quantitative test kits, the decrease in the cutoff value from 100 ng/mL to 50 ng/mL increases the probability of finding advanced lesions in the colon from 2.4% to 3.1%, and the number of colonoscopies to be performed is from 4.5% to 7%. However, the number of colonoscopies resulting in normal morphology increased. Increasing the cutoff value from 100 ng/mL to 200 ng/mL decreased the rate of advanced adenoma detection from 2.4 to 1.8% without changing the rate of detecting colorectal cancer. The amount of colonoscopy performed with the guidance of the 200 ng/mL FOBT test decreased by 50% (3.2 to 7%) compared to the 50 ng/mL FOBT test, and the cancer miss rate increased by 14% (23).

The fact that the qualitative FOBT is manufactured at different threshold values allows for selecting a test kit with the appropriate detection limit for the screening program. Which cutoff value to choose may vary depending on the intended pathology detection rate, population-related factors (prevalence of CRC, the participation rate in screening programs, etc.), and colonoscopy capacity, labor competence. The optimum cutoff of immunochemical FOBT may differ in various populations considering such variables. It may change over time because performance is dependent on the prevalence of colorectal cancers and advanced adenomas. Choosing the appropriate cutoff value should be determined by clinician-laboratory communication, taking into account the mentioned parameters. Our experiences suggest that clinicians are unaware that tests with different cutoff levels are used in the laboratory. They gave feedback on the high rate of false-positive results in specific periods. Therefore, considering the performance of the tests and our colonoscopy capacity, a cutoff value of 30 ng/mL has been determined as ideal for our hospital.

As can be seen, the decrease in the cutoff values will increase the probability of finding advanced lesions as well as the number of colonoscopies required. Although it is desirable to keep the cutoff values low and thus detect the majority of advanced adenoma and colon cancer cases, an increase in the rate of false positivity may cause many colonoscopies. Studies have reported that 40-50% of colonoscopies

performed due to positive FOBT results result in normal morphology (21). Despite the disadvantages such as high cost, the uncomfortable procedure for patients, the presence of risks that cannot be neglected, and unnecessary use of labor, it is necessary to make the right choice between the advantage of detecting as many precancerous or cancerous lesions as possible (23, 24). It is essential to determine the appropriate cutoff values to use the country's resources logically.

Studies conducted with quantitative tests suggested that a threshold value below 100 ng/mL would be feasible and acceptable in screening programs in countries with sufficient resources and colonoscopy capacity. However, when resources and colonoscopy capacity are not enough, cutoff values above 100 ng/ml (up to 200 ng ml) decrease the need for colonoscopy, will result in a relatively limited missing rate for colorectal cancer, a lower but still relatively high detection rate of advanced adenoma (23).

Limitations of the Study

Most of our patients have a single FOBT result for the specified kits. It should be kept in mind that test performances may change by increasing the number of tests applied, and pathology detection rates may increase with the number of FOBTs for each patient. Since our study is based on retrospectives, the history of drugs that may predispose to bleeding, such as nonsteroidal anti-inflammatory drugs or anticoagulant therapy, is unknown. Since we are a tertiary hospital, the FOB test is applied for screening purposes or to aid in the diagnosis of patients with symptoms. The lack of symptom information of our patients can be considered as another limitation.

Since our study is retrospective, FOBT results belong to different patients, and the performances of the kits in the same samples have not been evaluated. However, the number of patients is sufficient for Biotech and Laboquick tests, but the Wondfo kit was used under pandemic conditions. The delay of elective colonoscopy procedures in hospitals to reduce the risk of COVID-19 transmission and its use for a relatively shorter period may evaluate this test less than ideal.

One of the advantages of our study is that clinicians did not know which brand test was used in which period and what the detection limit was. Prospectively designing large-scale studies on the same patient samples may be necessary for more reliable results.

CONCLUSIONS

Changing the cutoff value of FOB tests affects the performance of the test. Generally, decreasing the cutoff value will increase sensitivity but decrease specificity and vice versa. An increase in sensitivity will improve the detection of patients with colorectal cancer or advanced adenoma. In contrast, the resulting decrease in specificity will increase the number of colonoscopies due to false-positive results, resulting in loss of labor and unnecessary use of resources. It would be appropriate to select the cutoff value that will meet the intended performance characteristics, considering variables such as the prevalence of CRC, colonoscopy capacity, and professional clinician competence.

DECLARATIONS

Ethics Approval

The study was conducted in compliance with the Helsinki Declaration, and ethical approval was taken from the ethics committee of Recep Tayyip Erdogan University before the study (Date:29.06.2021, Decision number: 2021/120).

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Conflict of interest

None

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