Head-to-head comparison of the test performance of self-administered qualitative *vs.* laboratory-based quantitative fecal immunochemical tests in detecting colorectal neoplasm

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Abstract

Background: Fecal immunochemical tests (FITs) are the most widely used non-invasive tests in colorectal cancer (CRC) screening. However, evidence about the direct comparison of the test performance of the self-administered qualitative a laboratory-based quantitative FITs in a CRC screening setting is sparse.

Methods: Based on a CRC screening trial (TARGET-C), we included 3144 pre-colonoscopy fecal samples, including 24 CRCs, 230 advanced adenomas, 622 non-advanced adenomas, and 2268 participants without significant findings at colonoscopy. Three self-administered qualitative FITs (Pupu tube) with positivity thresholds of 8.0, 14.4, or 20.8 µg hemoglobin (Hb)/g preset by the manufacturer and one laboratory-based quantitative FIT (OC-Sensor) with a positivity threshold of 20 µg Hb/g recommended by the manufacturer were tested by trained staff in the central laboratory. The diagnostic performance of the FITs for detecting colorectal neoplasms was compared in the different scenarios using the preset and adjusted thresholds (for the quantitative FIT).

Results: At the thresholds preset by the manufacturers, apart from the qualitative FIT-3, significantly higher sensitivities for detecting advanced adenoma were observed for the qualitative FIT-1 (33.9% [95% CI: 28.7–39.4%]) and qualitative FIT-2 (22.2% [95% CI: 17.7–27.2%]) compared to the quantitative FIT (11.7% [95% CI: 8.4–15.8%]), while at a cost of significantly lower specificities. However, such difference was not observed for detecting CRC. For scenarios of adjusting the positivity thresholds of the quantitative FIT to yield comparable specificity or comparable positivity rate to the three qualitative FITs accordingly, there were no significant differences in terms of sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios for detecting CRC or advanced adenoma between the two types of FITs, which was further evidenced in ROC analysis.

Conclusions: Although the self-administered qualitative and the laboratory-based quantitative FITs had varied test performance at the positivity thresholds preset by the manufacturer, such heterogeneity could be overcome by adjusting thresholds to yield comparable specificities or positivity rates. Future CRC screening programs should select appropriate types of FITs and define the thresholds based on the targeted specificities and manageable positivity rates.

Keywords: Fecal immunochemical test; Test performance; Colorectal neoplasm; Screening

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide.[1] It has been demonstrated that population-based screening via endoscopy and fecal occult blood tests (FOBTs) could be effective in reducing the mortality of CRC.[2-4] For the established screening modalities, FOBTs have been widely used due to their ease-of-use nature, low costs, and high compliance rates. As a newly developed method for the human hemoglobin (Hb) detection, fecal immunochemical test (FIT) has been widely used in population-based CRC screening programs in recent years, because of its superior diagnostic performance than traditional guaiac-based FOBTs.[5-7]

The results of FITs can be interpreted as dichotomous or continuous, referring to the qualitative or the quantitative FITs, respectively.[8,9] Generally, qualitative FITs determined the results as positive or negative based on the visual

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interpretation using the lateral flow immunochromatography method. As for quantitative FITs, the fecal Hb concentration was measured on automated devices using the immunoturbidimetric method, and the numeric results with test values above the pre-defined threshold were deemed as positive. Both types of tests have been widely implemented in the current CRC screening practice and appeared to be consistent in the test accuracy for detecting colorectal neoplasms.[10,11] However, given that the positivity thresholds of FITs varied across manufacturers, previous comparisons evaluating the two types of FITs at the positivity thresholds preset by the manufacturers were less sufficient to examine the exact differences in test performance.[12,13] Thus, a comprehensive assessment of test performance for different types of FITs is required to guide their application in the CRC screening.

In this article, we aimed to give a complete picture of the consistency or discrepancy of the diagnostic performance between the qualitative and the quantitative FITs. Using prospectively collected fecal samples from a large CRC screening trial in China, we conducted a head-to-head comparison of the performance of three self-administered qualitative FITs and one laboratory-based quantitative FIT in detecting colorectal neoplasm. Further exploration was conducted to investigate the associations between the sensitivities of FITs and sex, age, and other lifestyle factors. We anticipated that the findings would provide references for FIT-based CRC screening programs in the future.

Methods

Ethical approval

This trial was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College (No. 18-013/1615). All participants provided written informed consent.

Study design and population

The analysis was conducted based on the strategies for colorectal cancer screening in China (TARGET-C) study which is a multicentered randomized controlled trial to compare the effectiveness of one-time colonoscopy, annual FIT, and annual risk-adapted screening strategy in CRC screening.[14,15] A total of 19,582 participants, aged 50 to 74 years from six centers in China, were enrolled in the TARGET-C trial at baseline from May 2018 to June 2019. Detailed inclusion and exclusion criteria have been described in our previous publication.[14] With signed informed consent, information including sociodemographic characteristics, history of bowel disease, clinical treatment, family history of cancer, disease history, and living habits was collected via a standardized epidemiological questionnaire. Colonoscopy appointments were scheduled for those who were assigned to the colonoscopy group, assessed at high-risk of CRC by the Asia-Pacific Colorectal Screening score, or had positive FIT results. Before the appointment, participants were requested to collect a stool sample per study protocol. There were overall 3825 participants undertaking colonoscopy in the

baseline screening phase per study protocol. For the present study, we included all the participants who underwent colonoscopy, had donated stool samples and valid test results for the three qualitative FITs and one quantitative FIT, leaving 3144 eligible participants for the final analysis.

Fecal sample collection

Participants eligible for undergoing colonoscopy received a study package that contained a sterile container (SARSTEDT, Nümbrecht, Germany), an ice bag, an insulated bag, a collection tissue, and a detailed instruction for stool collection. The participants were instructed to collect the fecal sample at home from a single bowel movement, with no specific diet or medicine restriction, and this procedure should be finished within 24 h before the colonoscopy appointment. After collection, the stool sample was required to be filled into the container, wrapped with an ice bag, and kept in a 4°C refrigerator at home. On the day of colonoscopy examination, the stool-filled container was handed over to hospital staff and was stored at −20°C temporarily within 1 month. Finally, the stool samples were delivered to the central biobank via cold chain logistics and were preserved at −80°C in the freezer for further analysis.

FIT

Before testing, the fecal samples were preprocessed following a standard operating procedure. Briefly, fecal samples were taken out by batch and thawed at ambient temperature (20–25°C) for 5 min. For each stool sample, one disposable, sterile knife was used to extract about 1 g stool from three different parts of the sample, which was subsequently transferred into a small, empty vial. The extracted stool was kept at ambient temperature until defrosted completely.

Three self-administered qualitative FITs (Pupu tube, New Horizon Health Technology, Hangzhou, China) and one laboratory-based quantitative FIT (OC-Sensor, Eiken Chemical, Tokyo, Japan) were used separately to test the preprocessed fecal samples according to their own manufacturers' instructions. The qualitative FITs were preset at three levels of positivity thresholds by the manufacturer in the present study. Specifically, the qualitative FIT with 8.0, 14.4, and 20.8 µg Hb/g threshold (equal to 100, 180, and 260 ng Hb/mL, respectively) was named as qualitative FIT-1, qualitative FIT-2, and qualitative FIT-3, respectively. The positivity threshold of quantitative FIT was recommended setting at 20.0 µg Hb/g (equal to 100 ng Hb/mL) by the manufacturer. Each fecal sampling device was a small tube containing a defined volume of buffer and was equipped with a lid to which a notched stick was attached. During collection, the stick was stabbed into different parts of the stool sample until the serrations on the stick were filled completely and then was inserted back into the tube.

The results of the self-administered qualitative FIT were visually interpreted as positive or negative by one single trained investigator according to the manufacturers'

manual within 10 min after collection. For the quantitative FIT, exact test results were outputted by the analyzer OC-Sensor io and values exceed the cutoff were deemed as positive. All laboratory staffs were blinded to the colonoscopy results.

Colonoscopy and pathology

Standardized forms recording the colonoscopy and/or pathology reports were collected, including information on the location, size, histology, and pathology of all lesions. For the present study, advanced adenoma was defined as adenomas ≥10 mm in size, with villous architecture, high-grade dysplasia, or intramucosal carcinoma. Advanced neoplasm included CRC and advanced adenoma. Regarding the location of the neoplasm, the proximal colon was defined as the splenic flexure and all segments proximal to it, and the distal colon/rectum included the descending colon, sigmoid colon, and rectum.

Statistical analysis

Comparison of the test performance was conducted for the detection of CRC, advanced adenoma, advanced neoplasm, and any neoplasm among the three qualitative FITs (8.0, 14.4, and 20.8 μg Hb/g) and one quantitative FIT (20 μg Hb/g) at preset manufacturers' positivity thresholds, respectively. Furthermore, given that qualitative FIT had a fixed threshold, the thresholds of the quantitative FIT were adjusted to yield similar specificity, positivity rate, or the same Hb concentration as the qualitative FIT. Several indicators and their 95% confidence intervals (CIs) were calculated to evaluate test performance, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). 95% CIs were calculated using the Clopper-Pearson method. Specificity and NPV were calculated based on participants' absence of advanced neoplasm. Youden index was calculated for the test accuracy of detecting advanced neoplasm. In addition, positive likelihood ratio (LR+) and negative likelihood ratio (LR−) were also determined with their 95% CIs.[16] Receiver operating characteristic (ROC) analysis was conducted, and the areas under the curves (AUCs) were determined for the quantitative FIT. Based on the sensitivities of FIT for colorectal neoplasms reported by previous studies,[11,17,18] the sample size used in the current study had 80% to 90% power in detecting CRC with the targeted sensitivity of 53% to 93%, had 94% to 96% power in detecting advanced adenoma with targeted sensitivity of 10% to 36%, and had 96% to 99% power in discriminating other colorectal neoplasms with targeted specificity of 90% to 97%.

Subgroup analyses were performed by sex (male and female) and age (50–59 and 60–74 years), respectively. Subgroup analyses were also conducted among the average-risk population ($n = 1356$) who were randomized into the colonoscopy group in the first phase screening of the TARGET-C study. Comparison of sensitivities was calculated between the qualitative and the quantitative FITs for detecting site-specific CRC and advanced adenoma (proximal vs. distal), and size-specific advanced adenoma (<10, 10 to <15, 15 to <20, and ≥20 mm) at

thresholds adjusted to comparable specificity and at preset manufacturers' thresholds, respectively. The multivariate logistic regression model was used to assess the association of sensitivity for advanced neoplasm and relevant risk factors including age, sex, body mass index (BMI), smoking status, alcohol drinking, medical history of non-steroidal anti-inflammatory drugs (NSAIDs) or anti-coagulant drugs, family history of CRC among first-degree relatives. Statistical differences of each diagnostic accuracy index were compared between the two types of FIT with the Chi-square test. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing: Vienna, Austria).[19] P values < 0.05 were considered statistically significant.

Results

Sample characteristics

Overall, 3825 participants underwent colonoscopy in the baseline screening phase of the TARGET-C trial. After excluding participants without fecal samples or having inadequate samples, we finally included 3144 samples in the analysis, which had available test results for the three qualitative FITs and one quantitative FIT. The included samples were comprised of 24 (0.8%) CRCs, 230 (7.3%) advanced adenomas, 622 (19.8%) non-advanced adenomas, and 2268 (72.1%) participants without significant findings at colonoscopy. A majority of CRC was located at the distal site (17/24, 70.8%), while most advanced adenomas was located at the distal site (129/230, 56.1%). Only 6.5% of advanced adenoma had <10 mm in diameter. The mean age (standard deviation) of included samples was 60.4 ± 6.3 years, and 51.5% (1619/3144) were male. Detailed basic characteristics of included participants are shown in Table 1.

Test characteristics of the FITs at the recommended cut-offs

Table 2 shows overall diagnostic accuracy for various findings at the preset manufacturer thresholds. The positivity rates decreased from 12.1% for the qualitative FIT-1 to 4.5% for the qualitative FIT-3 as the positivity threshold increased, and all of them are significantly higher than the quantitative FIT (2.8%). Except for no difference in CRC detection, the qualitative FIT-1 and the qualitative FIT-2 had increased sensitivities but decreased specificities for other types of colorectal neoplasms when compared with the quantitative FIT. The sensitivities of advanced adenomas were 33.9% (95% CI: 28.7%–39.4%; $P < 0.001$) for the qualitative FIT-1 and 22.2% (95% CI: 17.7%–27.2%; $P = 0.004$) for the qualitative FIT-2, both of which were higher than for the quantitative FIT (11.7%, 95% CI: 8.4%–15.8%). However, the heterogeneity in sensitivity disappeared for various colorectal neoplasms between the qualitative FIT-3 and the quantitative FIT. For example, similar sensitivities of advanced adenomas were observed between the qualitative FIT-3 and the quantitative FIT (17.0% [95% CI: 13.0%–21.6%] vs. 11.7% [95% CI: 8.4%–15.8%]; $P = 0.143$). Significant higher Youden index for detecting advanced neoplasm was observed only for the comparison of qualitative FIT-1 vs. quantitative FIT (qualitative vs. quantitative: 28.8% vs.

Table 1: Characteristics of 3144 participants and their advanced findings at colonoscopy.

Items	N (%)
Age, years	
50–59	1381 (43.9)
60–69	1526 (48.5)
70–74	237 (7.5)
Sex	
Female	1525 (48.5)
Male	1619 (51.5)
BMI, kg/m^2	
<24.0	1531 (48.7)
24.0 to <28.0	1331 (42.3)
≥28.0	282 (9.0)
Smoking status	
Never	2182 (69.4)
Current	731 (23.3)
Ever	231 (7.3)
Alcohol drinking	
Never	1942 (61.8)
<4 times per week	714 (22.7)
≥4 times per week	488 (15.5)
NSAID or anticoagulant drugs use	
Never	2971 (94.5)
Current or ever	173 (5.5)
Family history of CRC among first-degree relatives	
No	2717 (86.4)
Yes	353 (11.2)
Unclear	74 (2.4)
Advanced findings at colonoscopy	
CRC	24 (0.8)
Advanced adenoma	230 (7.3)
Non-advanced adenoma	622 (19.8)
None of above	2268 (72.1)
Anatomical site of advanced neoplasm	
CRC	
Distal site	17 (70.8)
Proximal site	7 (29.2)
Advanced adenoma	
Distal site	129 (56.1)
Proximal site	70 (30.4)
Both	30 (13.0)
Missing	1 (0.4)
Size of advanced adenoma, mm	
<10	15 (6.5)
10 to <15	105 (45.7)
15 to <20	62 (27.0)
≥20	47 (20.4)
Missing	1 (0.4)

BMI: Body mass index; CRC: Colorectal cancer; NSAID: Non-steroidal anti-inflammatory drug.

14.6%), while disappearing for the comparison of qualitative FIT-2 or FIT-3 $vs.$ quantitative FIT, respectively (qualitative $vs.$ quantitative: 19.1% or 22.7% $vs.$ 14.6%). According to PPV, NPV, LR+, and LR−, identical test performances were present while comparing each qualitative FIT with the quantitative FIT. An exception was that the qualitative FIT-1 had varyingly lower PPVs for various colorectal neoplasms but slightly higher NPVs when compared with the quantitative FIT (all $P < 0.05$).

We further conducted subgroup analyses to explore the variation of the test performance for detecting site-specific neoplasms [Supplementary Figure 1, http://links.lww.com/CM9/A558] and size-specific advanced adenoma [Supplementary Figure 2, http://links.lww.com/CM9/A558]. Significantly higher sensitivities for distal or proximal advanced adenoma for the qualitative FIT-1 than the quantitative FIT at threshold preset by the manufacturers, respectively (distal: 31.1% $vs.$ 13.6%, $P = 0.001$; proximal: 33.3% $vs.$ 6.4%, $P < 0.001$). As for size-specific advanced adenoma, except for the qualitative FIT-2 and the qualitative FIT-3, only qualitative FIT-1 had higher sensitivities for 10 to <15 mm (23.8% $vs.$ 3.8%; $P < 0.001$), 15 to <20 mm (39.1% $vs.$ 17.2%; $P < 0.001$), and ≥ 20 mm (53.3% $vs.$ 22.2%; $P < 0.001$) than the quantitative FIT (all $P < 0.05$).

Test characteristics of the FITs at adjusted cut-offs

Featured by flexible adjustment of thresholds, quantitative FIT enables us to adjust the thresholds to ensure a fair comparison with the qualitative FITs under specific circumstances.

First, by adjusting the cut-offs of the quantitative FIT to yield the similar levels of 90%, 95%, and 97% specificities that qualitative FITs had, no difference in diagnostic performance assessed by various evaluation indicators was observed between each qualitative and quantitative FITs at the similar specificity [Table 3]. The equivalent sensitivities between each qualitative and quantitative FITs were observed for detecting CRC (qualitative $vs.$ quantitative: 70.8%–83.3% $vs.$ 58.3%–75.0%) and for advanced adenoma (qualitative $vs.$ quantitative: 17.0%–33.9% $vs.$ 14.8%–25.2%) at comparable specificities. Furthermore, the results were also consistent when stratified by anatomic site or lesion size. However, an exception was that the qualitative FIT-1 had higher sensitivities than the quantitative FIT for detecting advanced adenoma located at proximal site ($P = 0.027$) and with 10 to <15 mm in diameter ($P = 0.049$), respectively [Supplementary Figures 3 and 4, http://links.lww.com/CM9/A558].

Second, consistent test performance of detecting various colorectal neoplasms were also observed at comparable positivity rates (12.1% $vs.$ 12.1%, 6.6% $vs.$ 6.5%, and 4.5% $vs.$ 4.4%, respectively) [Table 4]. The sensitivity of each of the three qualitative FITs was equivalent to the quantitative FITs for the detection of CRC (qualitative $vs.$ quantitative: 70.8%–83.3% $vs.$ 62.5%–79.2%) and advanced adenoma (qualitative $vs.$ quantitative: 17.0%–33.9% $vs.$ 14.8%–26.5%) at comparable positivity rates, respectively. Identical levels of specificity, Youden index, PPV, NPV, LR+, and LR− for detecting various colorectal neoplasms were also achieved while comparing each qualitative FIT with the quantitative FITs at apparently very different positivity rates, respectively.

Third, while using the uniform Hb concentration thresholds (8.0, 14.4, and 20.8 μg Hb/g, respectively) [Table 5], three qualitative FITs performed differently for detecting colorectal neoplasms when compared with the quantitative FIT. There was no statistical difference in sensitivities for

Table 2: Comparison of diagnostic performance for different colorectal neoplasms between qualitative FITs (Pupu tube) *vs.* quantitative FIT (OC-Sensor) with the preset thresholds by the manufacturers.

Diagnostic performance	Qualitative FIT tests			Quantitative FIT test
	FIT-1	FIT-2	FIT-3	
Threshold, μg Hb/g	8.0	14.4	20.8	20.0
Positivity rate, %	12.1[*]	6.6[*]	4.5[*]	2.8
Sensitivity (95% CI), %				
CRC	83.3 (65.8–94.1)	79.2 (61.1–91.4)	70.8 (52.1–85.4)	58.3 (39.7–75.4)
Advanced adenoma	33.9 (28.7–39.4)[*]	22.2 (17.7–27.2)[*]	17.0 (13.0–21.6)	11.7 (8.4–15.8)
Non-advanced adenoma	12.9 (10.7–15.3)[*]	6.4 (4.9–8.3)[*]	4.5 (3.2–6.1)	1.9 (1.1–3.1)
Advanced neoplasm	38.6 (33.5–43.9)[*]	27.6 (23.0–32.5)[*]	22.0 (17.8–26.8)	16.1 (12.5–20.4)
Any neoplasm	20.3 (18.1–22.7)[*]	12.6 (10.8–14.5)[*]	9.6 (8.0–11.4)	6.1 (4.8–7.5)
Specificity (95% CI), %	90.2 (89.3–91.1)[*]	95.2 (94.5–95.8)[*]	97.1 (96.5–97.6)[*]	98.4 (98.0–98.8)
Youden index	28.8 (21.2–37.6)[*]	22.7 (15.8–30.1)	19.1 (12.3–26.4)	14.6 (8.3–20.8)
PPV (95% CI), %				
CRC	5.3 (3.5–7.6)[*]	9.1 (6.0–13.1)	12.1 (7.9–17.7)	16.1 (10.0–24.0)
Advanced adenoma	20.5 (17.2–24.2)[*]	24.4 (19.6–29.8)	27.9 (21.7–34.8)	31.0 (22.9–40.2)
Non-advanced adenoma	21.1 (17.7–24.8)	19.1 (14.8–24.2)	20.0 (14.6–26.4)	13.8 (8.2–21.4)
Advanced neoplasm	25.8 (22.1–29.7)[*]	33.5 (28.1–39.3)	40.0 (33.0–47.3)	47.1 (37.9–56.5)
Any neoplasm	46.8 (42.5–51.2)[*]	52.6 (46.7–58.5)	60.0 (52.7–67.0)	60.9 (51.6–69.7)
NPV (95% CI), %	94.4 (93.6–95.1)[*]	93.7 (92.9–94.5)	93.4 (92.6–94.1)	93.0 (92.2–93.8)
LR+ (95% CI)				
CRC	8.5 (6.8–10.7)	16.5 (12.4–21.9)	24.4 (16.8–35.4)	36.6 (21.6–62.1)
Advanced adenoma	3.5 (2.5–4.9)	4.6 (2.7–7.9)	5.8 (2.8–12)	7.4 (2.5–21.7)
Non-advanced adenoma	1.3 (0.7–2.3)	1.3 (0.4–4.3)	1.5 (0.3–8.4)	1.2 (0–68.5)
Advanced neoplasm	4.0 (3.0–5.3)	5.7 (3.8–8.6)	7.6 (4.4–13)	10.1 (4.7–21.5)
Any neoplasm	2.1 (1.5–2.9)	2.6 (1.5–4.4)	3.3 (1.7–6.6)	3.8 (1.3–11.4)
LR− (95% CI)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.8–1.0)

[*] Indicating *P* < 0.05 between qualitative FIT and the quantitative FIT (reference) using the Chi-square test. CRC: Colorectal cancer; FITs: Fecal immunochemical tests; Hb: Hemoglobin; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; NPV: Negative predictive value; PPV: Positive predictive value.

Table 3: Comparison of diagnostic performance for different colorectal neoplasms between qualitative FITs (Pupu tube) *vs.* quantitative FIT (OC-Sensor) with thresholds adjusted to comparable specificities.

Diagnostic performance	Thresholds adjusted to comparable specificity					
	Qualitative FIT-1	Quantitative FIT	Qualitative FIT-2	Quantitative FIT	Qualitative FIT-3	Quantitative FIT
Threshold, μg Hb/g	8.0	3.2	14.4	5.0	20.8	8.0
Positivity rate, %	12.1	10.9	6.6	6.1	4.5	4.2
Sensitivity (95% CI), %						
CRC	83.3 (65.8–94.1)	75.0 (56.5–88.5)	79.2 (61.1–91.4)	66.7 (47.9–82.2)	70.8 (52.1–85.4)	58.3 (39.7–75.4)
Advanced adenoma	33.9 (28.7–39.4)	25.2 (20.5–30.4)	22.2 (17.7–27.2)	17.4 (13.4–22)	17.0 (13–21.6)	14.8 (11.1–19.2)
Non-advanced adenoma	12.9 (10.7–15.3)	10.9 (8.9–13.2)	6.4 (4.9–8.3)	5.8 (4.3–7.6)	4.5 (3.2–6.1)	3.9 (2.7–5.4)
Advanced neoplasm	38.6 (33.5–43.9)	29.9 (25.2–35.0)	27.6 (23.0–32.5)	22.0 (17.8–26.8)	22.0 (17.8–26.8)	18.9 (14.9–23.4)
Any neoplasm	20.3 (18.1–22.7)[*]	16.4 (14.4–18.6)	12.6 (10.8–14.5)	10.5 (8.8–12.4)	9.6 (8.0–11.4)	8.2 (6.7–9.9)
Specificity (95% CI), %	90.2 (89.3–91.1)	90.8 (89.8–91.6)	95.2 (94.5–95.8)	95.3 (94.6–95.9)	97.1 (96.5–97.6)	97.1 (96.5–97.6)
Youden index	28.8 (21.7–36.6)	20.7 (13.8–29.2)	22.7 (17.1–30.2)	17.3 (10.3–24.1)	19.1 (11.9–25.7)	16.0 (9.5–21.6)
PPV (95% CI), %						
CRC	5.3 (3.5–7.6)	5.2 (3.4–7.7)	9.1 (6.0–13.1)	8.3 (5.3–12.4)	12.1 (7.9–17.7)	10.5 (6.5–16.0)
Advanced adenoma	20.5 (17.2–24.2)	16.9 (13.7–20.6)	24.4 (19.6–29.8)	20.8 (16.1–26.2)	27.9 (21.7–34.8)	25.6 (19.4–32.5)
Non-advanced adenoma	21.1 (17.7–24.8)	19.8 (16.3–23.7)	19.1 (14.8–24.2)	18.8 (14.2–24.0)	20.0 (14.6–26.4)	18.0 (12.8–24.4)
Advanced neoplasm	25.8 (22.1–29.7)	22.2 (18.5–26.2)	33.5 (28.1–39.3)	29.2 (23.8–35.0)	40.0 (33.0–47.3)	36.1 (29.2–43.5)
Any neoplasm	46.8 (42.5–51.2)	42.0 (37.5–46.6)	52.6 (46.7–58.5)	47.9 (41.8–54.1)	60.0 (52.7–67.0)	54.1 (46.6–61.5)
NPV (95% CI), %	94.4 (93.6–95.1)	93.6 (92.8–94.4)	93.7 (92.9–94.5)	93.3 (92.5–94.0)	93.4 (92.6–94.1)	93.2 (92.4–93.9)
LR+ (95% CI)						
CRC	8.5 (6.8–10.7)	8.1 (6.0–10.9)	16.5 (12.4–21.9)	14.2 (9.7–20.9)	24.4 (16.8–35.4)	19.8 (12.1–32.4)
Advanced adenoma	3.5 (2.5–4.9)	2.7 (1.7–4.3)	4.6 (2.7–7.9)	3.7 (1.8–7.4)	5.8 (2.8–12.0)	5.0 (2.2–11.5)
Non-advanced adenoma	1.3 (0.7–2.3)	1.2 (0.6–2.4)	1.3 (0.4–4.3)	1.2 (0.3–4.5)	1.5 (0.3–8.4)	1.3 (0.2–9.7)
Advanced neoplasm	4.0 (3.0–5.3)	3.2 (2.2–4.6)	5.7 (3.8–8.6)	4.7 (2.8–7.9)	7.6 (4.4–13.0)	6.4 (3.4–11.9)
Any neoplasm	2.1 (1.5–2.9)	1.8 (1.2–2.7)	2.6 (1.5–4.4)	2.2 (1.2–4.1)	3.3 (1.7–6.6)	2.8 (1.3–6.2)
LR− (95% CI)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)

[*] Indicating *P* < 0.05 between qualitative FIT and the quantitative FIT (reference) using the Chi-square test. FITs: Fecal immunochemical tests; Hb: Hemoglobin; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; NPV: Negative predictive value; PPV: Positive predictive value.

Table 4: Comparison of diagnostic performance for different colorectal neoplasms between qualitative FITs (Pupu tube) *vs.* quantitative FIT (OC-Sensor) with thresholds adjusted to comparable positivity rates.

Diagnostic performance	Thresholds adjusted to comparable positivity rate					
	Qualitative FIT-1	Quantitative FIT	Qualitative FIT-2	Quantitative FIT	Qualitative FIT-3	Quantitative FIT
Threshold, μg Hb/g	8.0	3.0	14.4	4.8	20.8	7.2
Positivity rate, %	12.1	12.1	6.6	6.5	4.5	4.4
Sensitivity (95% CI), %						
CRC	83.3 (65.8–94.1)	79.2 (61.1–91.4)	79.2 (61.1–91.4)	66.7 (47.9–82.2)	70.8 (52.1–85.4)	62.5 (43.7–78.8)
Advanced adenoma	33.9 (28.7–39.4)	26.5 (21.8–31.7)	22.2 (17.7–27.2)	17.4 (13.4–22.0)	17.0 (13.0–21.6)	14.8 (11.1–19.2)
Non-advanced adenoma	12.9 (10.7–15.3)	11.9 (9.8–14.2)	6.4 (4.9–8.3)	5.9 (4.5–7.8)	4.5 (3.2–6.1)	3.9 (2.7–5.4)
Advanced neoplasm	38.6 (33.5–43.9)	31.5 (26.7–36.6)	27.6 (23.0–32.5)	22.0 (17.8–26.8)	22.0 (17.8–26.8)	19.3 (15.3–23.8)
Any neoplasm	20.3 (18.1–22.7)	17.6 (15.5–19.8)	12.6 (10.8–14.5)	10.6 (8.9–12.5)	9.6 (8.0–11.4)	8.3 (6.8–10.0)
Specificity (95% CI), %	90.2 (89.3–91.1)	89.6 (88.6–90.5)	95.2 (94.5–95.8)	94.9 (94.2–95.5)	97.1 (96.5–97.6)	96.9 (96.3–97.4)
Youden index	28.8 (20.7–37.7)	21.1 (13.8–27.9)	22.7 (17.2–30.8)	16.9 (11–24)	19.1 (14.1–25.2)	16.2 (8.4–22.4)
PPV (95% CI), %						
CRC	5.3 (3.5–7.6)	5.0 (3.3–7.2)	9.1 (6.0–13.1)	7.8 (5.0–11.7)	12.1 (7.9–17.7)	10.8 (6.8–16.1)
Advanced adenoma	20.5 (17.2–24.2)	16.0 (13.0–19.4)	24.4 (19.6–29.8)	19.6 (15.1–24.7)	27.9 (21.7–34.8)	24.5 (18.6–31.2)
Non-advanced adenoma	21.1 (17.7–24.8)	19.4 (16.1–23.1)	19.1 (14.8–24.2)	18.1 (13.8–23.2)	20.0 (14.6–26.4)	17.3 (12.2–23.4)
Advanced neoplasm	25.8 (22.1–29.7)	21.0 (17.6–24.7)	33.5 (28.1–39.3)	27.5 (22.3–33.1)	40.0 (33.0–47.3)	35.3 (28.5–42.5)
Any neoplasm	46.8 (42.5–51.2)	40.4 (36.2–44.7)	52.6 (46.7–58.5)	45.6 (39.7–51.6)	60.0 (52.7–67.0)	52.5 (45.2–59.8)
NPV (95% CI), %	94.4 (93.6–95.1)	93.7 (92.9–94.4)	93.7 (92.9–94.5)	93.3 (92.5–94.0)	93.4 (92.6–94.1)	93.2 (92.4–93.9)
LR+ (95% CI)						
CRC	8.5 (6.8–10.7)	7.6 (5.9–9.8)	16.5 (12.4–21.9)	13.0 (8.9–19.0)	24.4 (16.8–35.4)	20.1 (12.9–31.3)
Advanced adenoma	3.5 (2.5–4.9)	2.5 (1.6–3.9)	4.6 (2.7–7.9)	3.4 (1.7–6.8)	5.8 (2.8–12)	4.7 (2–10.8)
Non-advanced adenoma	1.3 (0.7–2.3)	1.1 (0.6–2.1)	1.3 (0.4–4.3)	1.2 (0.3–4.4)	1.5 (0.3–8.4)	1.2 (0.2–8.9)
Advanced neoplasm	4.0 (3.0–5.3)	3.0 (2.1–4.2)	5.7 (3.8–8.6)	4.3 (2.6–7.2)	7.6 (4.4–13)	6.2 (3.4–11.4)
Any neoplasm	2.1 (1.5–2.9)	1.7 (1.2–2.4)	2.6 (1.5–4.4)	2.1 (1.1–3.9)	3.3 (1.7–6.6)	2.7 (1.2–5.9)
LR− (95% CI)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)

CRC: Colorectal cancer; FITs: Fecal immunochemical tests; Hb: Hemoglobin; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; NPV: Negative predictive value; PPV: Positive predictive value.

Table 5: Comparison of diagnostic performance for different colorectal neoplasms between qualitative fecal immunochemical tests (FITs; Pupu tube) *vs.* quantitative FIT (OC-Sensor) with thresholds adjusted to comparable Hb concentration.

Items	Thresholds adjusted to same Hb concentration					
	Qualitative FIT-1	Quantitative FIT	Qualitative FIT-2	Quantitative FIT	Qualitative FIT-3	Quantitative FIT
Threshold, μg Hb/g	8.0	8.0	14.4	14.4	20.8	20.8
Positivity rate, %	12.1[*]	4.2	6.6[*]	3.1	4.5[*]	2.7
Sensitivity (95% CI), %						
CRC	83.3 (65.8–94.1)	58.3 (39.7–75.4)	79.2 (61.1–91.4)	58.3 (39.7–75.4)	70.8 (52.1–85.4)	58.3 (39.7–75.4)
Advanced adenoma	33.9 (28.7–39.4)[*]	14.8 (11.1–19.2)	22.2 (17.7–27.2)[*]	12.2 (8.8–16.3)	17.0 (13.0–21.6)	11.3 (8.0–15.3)
Non-advanced adenoma	12.9 (10.7–15.3)[*]	3.9 (2.7–5.4)	6.4 (4.9–8.3)[*]	2.3 (1.4–3.5)	4.5 (3.2–6.1)[*]	1.9 (1.1–3.1)
Advanced neoplasm	38.6 (33.5–43.9)[*]	18.9 (14.9–23.4)	27.6 (23.0–32.5)[*]	16.5 (12.8–20.9)	22.0 (17.8–26.8)	15.7 (12.1–20.0)
Any neoplasm	20.3 (18.1–22.7)[*]	8.2 (6.7–9.9)	12.6 (10.8–14.5)[*]	6.4 (5.1–7.9)	9.6 (8.0–11.4)[*]	5.9 (4.7–7.4)
Specificity (95% CI), %	90.2 (89.3–91.1)[*]	97.1 (96.5–97.6)	95.2 (94.5–95.8)[*]	98.1 (97.6–98.5)	97.1 (96.5–97.6)[*]	98.4 (98.0–98.8)
Youden index	28.8 (22.5–36.5)	16.0 (11.1–23.6)	22.7 (16.5–30.8)	14.6 (9.1–21.9)	19.1 (12.0–26.8)	14.2 (8.2–20.0)
PPV (95% CI), %						
CRC	5.3 (3.5–7.6)	10.5 (6.5–16.0)	9.1 (6.0–13.1)	14.3 (8.8–21.4)	12.1 (7.9–17.7)	16.5 (10.2–24.5)
Advanced adenoma	20.5 (17.2–24.2)	25.6 (19.4–32.5)	24.4 (19.6–29.8)	28.6 (21.1–37.0)	27.9 (21.7–34.8)	30.6 (22.4–39.8)
Non-advanced adenoma	21.1 (17.7–24.8)	18.0 (12.8–24.4)	19.1 (14.8–24.2)	14.3 (8.8–21.4)	20.0 (14.6–26.4)	14.1 (8.4–21.9)
Advanced neoplasm	25.8 (22.1–29.7)[*]	36.1 (29.2–43.5)	33.5 (28.1–39.3)	42.9 (34.4–51.7)	40.0 (33.0–47.3)	47.1 (37.8–56.5)
Any neoplasm	46.8 (42.5–51.2)	54.1 (46.6–61.5)	52.6 (46.7–58.5)	57.1 (48.3–65.6)	60.0 (52.7–67.0)	61.2 (51.7–70.1)
NPV (95% CI), %	94.4 (93.6–95.1)	93.2 (92.4–93.9)	93.7 (92.9–94.5)	93.0 (92.2–93.8)	93.4 (92.6–94.1)	93.0 (92.2–93.7)
LR+ (95% CI)						
CRC	8.5 (6.8–10.7)	19.8 (12.1–32.4)	16.5 (12.4–21.9)	30.1 (18.0–50.3)	24.4 (16.8–35.4)	37.5 (22.1–63.7)
Advanced adenoma	3.5 (2.5–4.9)	5.0 (2.2–11.5)	4.6 (2.7–7.9)	6.3 (2.3–17.6)	5.8 (2.8–12.0)	7.3 (2.4–22.3)
Non-advanced adenoma	1.3 (0.7–2.3)	1.3 (0.2–9.7)	1.3 (0.4–4.3)	1.2 (0–38.3)	1.5 (0.3–8.4)	1.2 (0–68.5)
Advanced neoplasm	4.0 (3.0–5.3)	6.4 (3.4–11.9)	5.7 (3.8–8.6)	8.5 (4.1–17.6)	7.6 (4.4–13)	10.1 (4.7–21.9)
Any neoplasm	2.1 (1.5–2.9)	2.8 (1.3–6.2)	2.6 (1.5–4.4)	3.3 (1.2–9.3)	3.3 (1.7–6.6)	3.8 (1.2–11.7)
LR− (95% CI)	0.7 (0.6–0.8)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.8–1.0)	0.8 (0.7–0.9)	0.9 (0.8–1.0)

[*] Indicating $P < 0.05$ between each of the qualitative FIT and quantitative FIT (reference) using the Chi-square test. CRC: Colorectal cancer; FITs: Fecal immunochemical tests; Hb: Hemoglobin; LR+: Positive likelihood ratio; LR−: Negative likelihood ratio; NPV: Negative predictive value; PPV: Positive predictive value.

CRC detection between the qualitative and the quantitative FITs (70.8%–83.3% *vs.* 58.3%). However, only the qualitative FIT-1 and the qualitative FIT-2 had higher sensitivities than the quantitative FIT for advanced adenoma (qualitative FIT-1 *vs.* quantitative FIT: 33.9% [95% CI: 28.7%–39.4%] *vs.* 14.8% [95% CI: 11.1%–19.2%], *P* < 0.001; qualitative FIT-2 *vs.* quantitative FIT: 22.2% [95% CI: 17.7%–27.2%] *vs.* 12.2% [95% CI: 8.8%–16.3%]; *P* = 0.007), respectively, whereas the qualitative FIT-3 and the quantitative FIT performed almost equally (17.0% [95% CI: 13.0%–21.6%] *vs.* 11.3% [95% CI: 8.0%–15.3%]; *P* = 0.108). The test performances of various colorectal neoplasms detection between the qualitative and the quantitative FITs were almost consistent with identical levels of specificity, Youden index, PPV, NPV, LR+, and LR−, respectively.

When stratified by sex, age, and among the average-risk population, the results from subgroup and overall analyses were generally consistent. Detailed results of test accuracy of qualitative *vs.* quantitative FIT stratified by sex, age, and among the average-risk population were shown in Supplementary Tables 1 to 9, http://links.lww.com/CM9/A558, respectively.

ROC analysis

Figure 1 presents the comparison of ROC curves of the quantitative FIT regarding the detection of various CRC and pairs of sensitivity and specificity of three qualitative FITs. The AUCs of the quantitative FIT were 0.900 (95% CI: 0.823–0.977) for detecting CRC, 0.662 (95% CI: 0.624–0.699) for advanced adenoma, 0.668 (95% CI: 0.652–0.724) for advanced neoplasm, and 0.562 (95% CI: 0.539–0.584) for any neoplasm, respectively. Pairs of sensitivity and specificity were very closed to the ROC curves in each subgroup, which means similar sensitivities of the qualitative FIT were observed when compared with the quantitative FIT at the same levels of specificity.
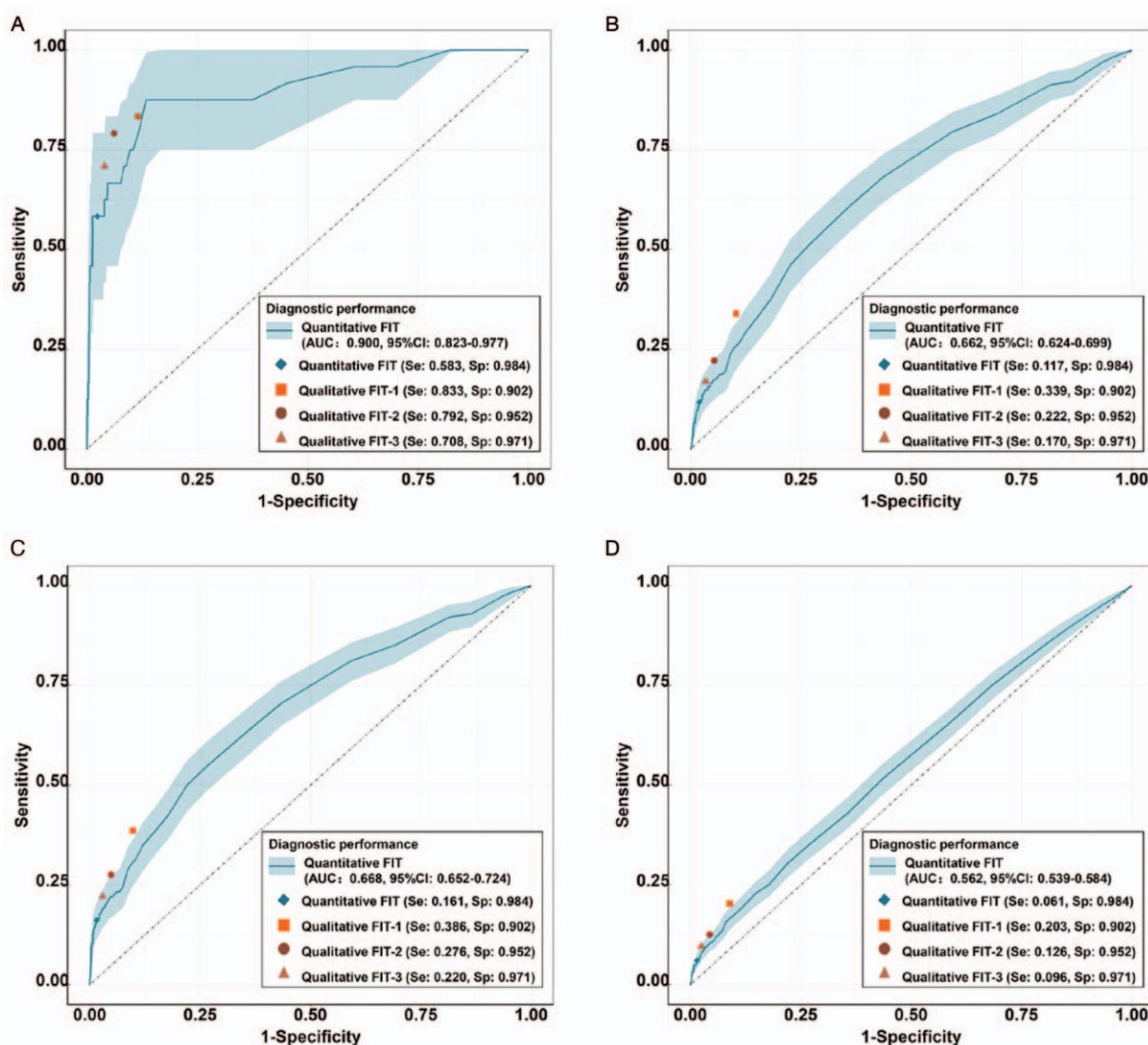
Figure 1: ROC curves of a quantitative and qualitative FIT for detecting colorectal cancers (A), advanced adenoma (B), advanced neoplasm (C), any neoplasm (D). AUC: Area under the curve; FIT: Fecal immunochemical test; Hb: Hemoglobin; ROC: Receiver operating characteristic; Se: Sensitivity; Sp: Specificity.

Associations between sensitivity and several risk factors

We conducted multivariate regression analyses to explore the potential factors associated with the sensitivity. As displayed in Supplementary Table 5, http://links.lww.com/CM9/A558, sensitivities of detecting advanced neoplasm did not significantly vary for each qualitative FIT or quantitative FIT according to several risk variables including sex, age, BMI, smoking status, alcohol drinking, medical history of NSAID or anticoagulant drugs, and family history of CRC among first-degree relatives, respectively. All P values were >0.05.

Discussion

In this study, we conducted a head-to-head comparison of the diagnostic performance between the qualitative and the quantitative FITs based on stool samples collected from a prospective CRC screening cohort. Using either threshold preset by the manufacturer or uniform thresholds, our findings demonstrated that there were obvious discrepancies in the test performance for detecting colorectal neoplasms such as sensitivity and specificity between the self-administered qualitative and the laboratory-based quantitative FIT. However, diagnostic performances became similar when thresholds were adjusted to yield comparable specificities and comparable positive rates, respectively. Furthermore, the sensitivities of FITs for detecting advanced neoplasms were performed with consistency across the variation of several risk variables. Based on the comprehensive evaluation of the diagnostic performance indicators, our findings concerning the diagnostic value of the qualitative and the quantitative FITs are of public health significance in CRC screening.

In the current study, we chose the OC-Sensor representing the quantitative FIT because of its widespread use in the current CRC screening programs. Our ROC analyses of the overall test performance of the quantitative FIT for advanced neoplasms were consistent with previous studies that reported AUCs ranging from 0.62 to 0.73.[20-23] We found that there was no difference in sensitivities in CRC detection between the qualitative and the quantitative FITs. This result was in line with a meta-analysis that reported similar pooled sensitivities, with 93% (95% CI: 83%–97%) for qualitative FIT and 86% (95% CI: 68%–95%) for quantitative FIT, respectively.[10] However, at a lower threshold of 8.0 or 14.4 μg Hb/g, the qualitative FIT yielded higher sensitivities than the quantitative FIT for detecting advanced adenoma. It could be explained that the sensitivities of advanced adenoma could be enhanced while using low FIT thresholds.[11,24]

Based on the continuous results of quantitative FIT, the positivity thresholds could be adjusted flexibly in this analysis. Sensitivities of advanced adenoma varied between the qualitative and the quantitative FITs even using the same cutoff values of Hb concentration. This phenomenon could be partly attributed to the disparity in the antigen-antibody binding reaction and detection mechanism. However, there was no considerable difference in performance characteristics between the qualitative and the quantitative FITs at similar levels of specificities

and positivity rates, respectively. Furthermore, our ROC analyses also showed that pairs of sensitivity and specificity of the qualitative FIT for various colorectal neoplasms were almost located on the ROC curves and the corresponding 95% CI zones of the quantitative FIT, which were consistent with the findings from Tao et al.[25] Therefore, the qualitative and the quantitative FITs perform equally well regarding their potential to detect colorectal neoplasms after adjusting to similar specificities and positivity rates.

Our previous study based on the TARGET-C trial showed that the positivity rates of the qualitative FIT-1 with preset 8.0 μg Hb/g (equal to 100 ng/mL) cutoff were 14.7% and 13.4% in the average-risk and low-risk population, respectively.[14] In the present study, although including part of the overlapped samples, the positivity rate of the qualitative FIT-1 was 12.1%, which was slightly lower than those in the previous study. The following underlying reasons may explain. First, the stool samples used in the current and previous study were from different bowel movements. For the present study, we used frozen fecal samples for a laboratory test. The fecal Hb might be degraded in a long storage period. Second, the FITs conducted in the present study were tested in a laboratory setting that had higher standards ensuring the consistency of the results. However, in the screening setting as conducted in our previous study, the test results were provided by the participants which may lead to strong heterogeneity due to the lack of a timely central review of the results.

In the established FIT-based CRC screening program, colonoscopy was conducted only in those participants with positive FIT results. However, the thresholds of qualitative FITs of the current study and available on the market seem to be low, which leads to a large number of unnecessary colonoscopies.[12] The current and previous findings showed that qualitative FIT had generally higher positive rates but lower specificity and PPV than quantitative FIT did.[26,27] One cohort study that included 1,181,904 participants in Korea showed that although the positivity rate of the qualitative FIT was three times as high as the quantitative one (8.1% vs. 2.5%), the qualitative FIT had greatly decreased PPV for CRC (14.4% vs. 5.2%).[26] Huang et al[27] also found that compared with a quantitative FIT, a qualitative one had inferior PPV for advanced neoplasms. Therefore, to decrease the colonoscopy load and to avoid unnecessary examinations, manufacturers need to increase the positivity thresholds of qualitative FITs that had low PPVs. In practice, determining a threshold of FIT according to positivity rates may be a practical and straightforward method that could directly reflect the colonoscopy load.

Although the two types of FITs had comparable test performance in specific conditions, a few considerations regarding FIT selection still need to be discussed. The self-administered qualitative FITs need visual interpretation and can be developed and interpreted individually, facilitating the on-site implementation or testing in the clinic or at home. In contrast, the laboratory-based quantitative FITs enable to offer batch-processed testing

leading to advantage in ensuring the consistency of diagnostic performance for advanced neoplasm. Recently, there is growing consensus that quantitative FITs may be preferred for organized, high-volume screening programs where FITs are processed centrally.[28-30] Given the similar test performance but different application characteristics, appropriate types of FITs should be selected by the health providers to meet the specific demand in the actual screening setting. However, the cost-effectiveness study of the two types of FIT in the CRC screening is sparse and needed to be further investigated.

For either the qualitative FIT or the quantitative FIT, our finding showed that the sensitivity would not be affected by sex and age for detecting advanced neoplasm, supporting it acting as a relatively objective indicator. Nonetheless, findings were discrepant concerning sex and age difference of sensitivity for detecting advanced neoplasms. To our knowledge, two studies conducted by Brenner et al[31,32] found that two of six studied FITs have statistical sex difference (men vs. women, immoCARE-C: 32.9% vs. 20.5%, P = 0.039; QuickVue iFOB: 59.6% vs. 43.0%, P = 0.014) and age difference (50–64 vs. 65–79 years, 34.7% vs. 51.2%; P = 0.004) in sensitivities for advanced neoplasm. However, multivariate regression analyses in our study and a study conducted by Stegeman et al[33] showed that the sensitivity was not affected by age (odds ratio = 0.99, 95% CI: 0.92–1.06). Therefore, whether the sex and age may affect the sensitivity of FIT for detecting advanced neoplasm deserves further exploration.

There are some strengths in our study. First, the stool samples were prospectively collected from a large-scale, multicentered population-based CRC screening program with screening colonoscopy results as the golden standard, which allowed evaluation of test performance in screening settings. Second, three levels of thresholds were preset by the manufacturer for qualitative FIT to offer comprehensive head-to-head comparisons with quantitative FIT concerning test performance at varying thresholds.

There are also some limitations to which needed to be paid attention when interpreting our results. First, FIT test results in this study were based on frozen fecal samples rather than fresh fecal samples, which differed from the actual screening setting. However, a previous study suggested that with the use of frozen or fresh stool samples, little influence on the test performance of FITs was observed.[34] Second, due to the low prevalence of CRC in a screening program, the numbers of CRC samples were limited, which yield rather wide CIs of the sensitivities. A further enlarged sample set to validate the findings is required.

To conclude, differences in the diagnostic performance of the self-administered qualitative and the laboratory-based quantitative FITs were observed while using threshold preset by the manufacturers or the same thresholds. However, such heterogeneity could be overcome by the adjustment of thresholds to yield comparable specificities and positivity rates. In population-based CRC screening programs, appropriate types of FITs and cutoffs needed to be determined carefully based on intended levels of specificity and manageable positivity rates.

Conflicts of interest

None.

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