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An Exploratory Analysis of Fecal Immunochemical Test Performance for Colorectal Cancer Screening in Nigeria

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Abstract

Introduction The fecal immunochemical test (FIT) for hemoglobin is recommended for colorectal cancer (CRC) screening in resource-limited environments. However, there are several unique variables that may alter FIT performance in this setting, including endemic intestinal parasites and high ambient temperature. This prospective study evaluated the performance of FIT in asymptomatic, average-risk individuals of screening age in rural Nigeria.

Methods Three hundred and twenty-four community volunteers completed a questionnaire and provided stool specimens for parasitology and microbiome analysis. Specimens were frozen and stored at −80 °C. Of 324 subjects, 139 met criteria for average-risk CRC screening and had a stool sample for analysis. These were thawed and tested with a qualitative FIT. Specimens positive for occult blood were retested every two days to evaluate the impact of time and temperature on test performance.

Results Of 139 individuals, 69 (49.6%) were positive for intestinal parasites and 10 (7.2%) were positive for occult blood. The most common pathogen was Cryptosporidium (40.6%). Among patients with intestinal parasites, 10.1% (7/69) had a positive FIT. Only 4.3% (3/70) of patients without parasites had a positive FIT ($p = 0.208$). On bivariate analysis, sociodemographic variables were not associated with a positive FIT result. Thirty percent (3/10) of the FIT-positive specimens became FIT-negative with routine storage.

Conclusion Although a positive FIT result was more common in those with parasitic infection, the relationship was not significant in this small cohort. The impact of high ambient temperature on test positivity may necessitate shorter processing time guidelines for equatorial countries. Additional prospective studies are needed to validate FIT performance in Nigeria.

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Introduction

Colorectal cancer (CRC) is the third most common cancer globally, and the number of new cases is predicted to increase by 77% between 2008 and 2030. The majority of that growth (62%) is projected to occur in low-and middle-income countries (LMICs) such as Nigeria [1]. Across sub-Saharan Africa (SSA), CRC screening has not been a health system priority [2–4]. However, recent evidence suggesting a rising incidence has made prevention and early detection increasingly relevant to Nigerian clinicians and policymakers [5–7].

The fecal immunochemical test (FIT) uses an antibody against human globin, a component of hemoglobin, to detect occult blood in the stool [8]. For countries considering CRC screening, several organizations recommend FIT in settings with limited endoscopic resources [9–11]. This is based on an extensive body of peer-reviewed literature that supports the efficacy of FIT for average-risk, asymptomatic CRC screening from high-income countries (HIC) [8, 12–14]. However, there are numerous potential barriers to effective FIT-based screening in a limited-resource country like Nigeria. These barriers include insufficient data on disease incidence, risk-factor assessment and health system capacity. To address some of these challenges, the African Organization for Research and Training in Cancer (AORTIC) recommends a highly targeted approached [10]. Risk stratification, even among high-risk individuals, has been studied in Nigeria and will likely be required for FIT-based screening, while endoscopy capacity remains limited [15].

Uncertainty exists regarding the performance of FIT in equatorial SSA. The impact of the region's high ambient temperature on test performance is potentially confounding. A study of over 200,000 quantitative FIT results in northern Italy demonstrated an inverse relationship between temperature and fecal Hgb concentration, with a 17% lower probability (OR 0.83, 95% CI 0.76–0.9) of a positive result in the summer months [16]. In prospective trials, the rate of Hgb degradation may be as high as 18% per day at an ambient temperature of 30 °C [17]. However, at a population-level small temperature-dependent differences in test positivity may not significantly alter the tests overall sensitivity and specificity [18].

Across the region, a double-burden of overlapping communicable and non-communicable disease still exists. In Nigeria, intestinal parasitic infection remains endemic [19–22]. However, the relationship between asymptomatic infection and FIT positivity is unclear, and there is no literature specific to FIT performance as a CRC screening tool in an endemic environment [23–26]. This exploratory analysis evaluates the relationship between parasitic infection, high ambient temperature and FIT performance in asymptomatic, average-risk individuals of screening age in rural Nigeria.

Methods

This study was part of a larger prospective evaluation of the gastrointestinal microbiome of adults in rural Nigeria. Institutional research board approval from Obafemi Awolowo University (OAU) in Ile-Ife, Nigeria was granted for both aspects of this study, including the processing of anonymized stool for fecal occult blood. Between May and June 2018, adult volunteers over the age of 18 from the community of Ijebu-Jesa and Ere-Ijesa in South West Nigeria were prospectively enrolled. Participants completed a detailed questionnaire to elicit sociodemographic as well as clinical, dietary, and lifestyle information relevant to the analysis of the gastrointestinal microbiome.

Sample collection

Each participant provided one fresh stool specimen for intestinal microbiome characterization and three specimens for parasite analysis. The specimen for microbiome analysis was returned to study personnel within 24 h of evacuation. This specimen was then divided into three cryogenic vials for preservation at −80 °C at OAU. Three separate stool specimens from consecutive bowel movements were returned in dedicated, formalin containing vials for parasite analysis.

Parasitology

The color, consistency, and presence of parasites, mucus, and blood in the sample were noted and documented. Direct smear samples were made with both saline and iodine mounts on clean grease-free slides. These were examined at 10× and 40× power with light microscopy for ova and parasite cysts. The stool samples were concentrated using the formol-ether concentration method. The worm burden was determined by counting the number of eggs per gram of feces using the Stoll egg counting technique. The infection intensity was reported as eggs per gram (epg) of feces. Detection of Cryptosporidium oocysts and other intestinal coccidian parasites, such as *Isospora* sp., and *Cyclospora* sp., in the concentrated stool was done using Modified Ziehl–Neelson staining. All individuals infected with intestinal parasites were provided treatment.

Study population

For this analysis, we retrospectively used the enrollment questionnaire to identify individuals appropriate for average-risk CRC screening with FIT. Study participants between 40 and 75 years of age were identified. The lower end of this age range is approximately 10 years younger than the median age of CRC diagnosis (i.e., 50–53) in Nigeria [7, 15]. It is also in keeping with forth coming CRC screening guidelines from the Society of Gastroenterology and Hepatology in Nigeria. Patients with a colonoscopy within the last 10 years or a family history (i.e., first degree) of CRC were excluded, as were patients with a diagnosis of HIV or recent diagnosis or treatment of Typhoid, Cholera, Hemorrhoids or hematochezia.

Fecal immunochemical test

A sample of fresh-frozen stool was thawed for every individual meeting study inclusion criterion. The spiral applicator was removed from the sodium-azide-containing buffer solution and inserted into the stool until covered. The applicator was returned to the buffer solution and agitated until the stool dissolved. Three drops of stool–buffer solution were then placed in the well of the test cassette impregnated with human globin antibody. In this manner, each specimen was tested for occult blood with the Medline iFOB (Medline Industries Inc. Northfield Il., Lot nom. 768L11). Stool was exposed to ambient temperature for no longer than 48 h between evacuation and processing, including the time taken to thaw prior to testing. The Medline iFOB is a Clinical Laboratory Improvement Act (CLIA)-waived, qualitative fecal immunochemistry product with a manufacturer-set, lower limit of hemoglobin detection of 50 μg/g.

Each specimen was processed as per the manufacturer's instructions, including verification of activated internal control. The result for each test was interpreted by two members of the research team blinded to the results of the parasite testing. As per the manufacturer's instructions, even the faintest discoloration at the test line was interpreted as a positive result. A third blinded member of the research team was used to settle any disagreement in test result.

The impact of ambient temperature and sample processing time on FIT performance was also evaluated. After all of the specimens were tested, the negative tests were discarded and the positive tests were stored at room temperature. Each positive test included residual stool–buffer solution that was retested for occult blood every 2 days for 8 days. The result (i.e., positive vs. negative) was recorded, and negative tests were discarded. Each result was confirmed by two members of the research team. The average ambient temperature was recorded during each testing period.

Statistical analysis

Descriptive statistics were performed on the sociodemographic and parasite results. The Fisher Exact test was used to determine whether a significant relationship existed between intestinal parasite infection and FIT result. A two-tailed p value level of 0.05 was used to denote significance. A bivariate analysis was performed to test for factors associated with FIT positivity.

Results

From 324 individuals who completed the questionnaire and stool collection as part of the microbiome evaluation, 154 (47.5%) met inclusion criteria for this study. Individuals were excluded based on age (114/324), recent typhoid infection (40/324), cholera (8/324), HIV positivity (1/324), colonoscopy within the last 10 years (3/324), hematochezia

Table 1 Sociodemographic characteristics

Characteristics	*n*	%
Age		
40–45	15	10.8
45–54	34	24.5
55–64	44	31.7
65–75	46	33.1
Gender		
Male	27	19.4
Female	112	80.6
Formal education		
None	39	28.1
Primary	47	33.8
Secondary	29	20.9
Technical training	16	11.5
University	6	4.3
Graduate school	2	1.4
Monthly household income		
< 10,000 N ($28USD)	46	33.1
10,000–49,999 N ($28–139USD)	61	43.9
50,000–99,999 N ($139–277USD)	12	8.6
100,000–249,999 N ($139–692USD)	11	7.9
250,000–499,999 ($692–1386USD)	4	2.9
> 500,000 ($1386USD)	5	3.6
Health insurance		
Yes	7	5
No	132	95

Table 2 Breakdown of parasitic pathology

Parasite	*n*	%
Cryptosporidium	28	40.6
E. hist	25	36.2
E. coli	18	26.1
Cyclospora	4	5.8
Hookworm	4	5.8
Ascaris	3	4.3

Table 3 FIT result in parasite positive and negative individuals

FIT result	Parasitic infection		*p* value
	Positive *n* (%)	Negative *n* (%)	
FIT+	7 (10.1)	3 (4.3)	0.208
FIT−	62 (89.9)	67 (95.7)	

(3/324), or positive family history of CRC (1/324). Of the 154, fresh-frozen stool was not available for 11 subjects and another four subjects had insufficient specimen for FIT processing. Thus, FIT was performed on 139 of 154 eligible subjects. Sociodemographic variables of this cohort are presented in Table 1. Of the 139 individuals, 49.6% (69/139) were positive for intestinal parasites. The most common pathogen was *Cryptosporidium* (40.6%), followed by *Entamoeba histolytica* (36.2%) and *Entamoeba coli* (26.1%). The distribution of parasitic pathology is listed in Table 2. *Cryptosporidium*, *Entamoeba histolytica* and *Entamoeba coli* were seen in individuals with a positive FIT. The intensity of infection was only available for seven subjects, all of whom were FIT-negative. Infection with *Ascaris* ranged from 300 to 3600 epg and was not associated with FIT positivity. Hookworm infection with an intensity of 200–600 epg was also not associated with FIT positivity.

The overall test positivity for occult blood with fecal immunochemistry was 7.2% (10/139). The difference in FIT positivity between those with intestinal parasites (10.1%) and those without (4.3%) was not significant ($p = 0.208$). This is outlined in Table 3. On bivariate analysis, age 40–45 (6.7%) versus 45–54 (5.9%) versus 55–64 (9.1%) versus 65–75 (11.1%) was not associated with FIT result ($p = 0.93$). Similarly, gender (male 11.1% vs. female 6.3%, $p = 0.41$), education level (≤primary 7% vs. ≥secondary 7.5%, $p = 0.1$) and household income ($p = 0.4$) were not associated with FIT result. Finally, type of parasite infection did not appear to have an impact on FIT result ($p = 0.31$). These results are presented in Table 4.

Table 4 Bivariate analysis for factors associated with FIT positivity

Covariate	FIT+ *n* (%)	*p* value
Age		
40–45	1 (6.7)	0.9
45–54	2 (5.9)	
55–64	4 (9.1)	
65–75	3 (11.1)	
Gender		
Male	3 (11.1)	0.4
Female	7 (6.3)	
Formal education		
≤ Primary	6 (7.0)	1
≥ Secondary	4 (7.5)	
Monthly household income		
≤ 49,999 N ($139USD)	10 (9.3)	0.4
50,000–99,999 N ($139–277USD)	0 (0.0)	
≥ 100,000 ($139USD)	0 (0.0)	
Health insurance		
Yes	0 (0.0)	1.0
No	10 (7.6)	
Parasite		
No parasites	3 (4.3)	0.3
Cryptosporidium + *E. hist* + *E. coli* + cyclospora	7 (10.9)	
Ascaris + Hookworm	0 (0.0)	

The 10 stool specimens positive for occult blood were retested every two days. The relationship between time (evacuation to analysis) and FIT result is presented in Fig. 1. At 4 days from evacuation, inclusive of thaw time, the first positive FIT became negative. Of the initially positive FIT results, 30% (3/10) were negative at 10 days from evacuation with a mean ambient temperature of 27 °C.

Discussion

In Nigeria, intestinal parasite infection remains endemic [19–21]. The results from our analysis demonstrate a parasite infection rate in about half of asymptomatic, average-risk individuals from two communities in rural South West Nigeria. This high rate underscores the importance of identifying any confounding effects of parasitic infection on CRC screening using FIT. The high proportion of individuals with a parasitic infection in this cohort also reflects the rural environment, lack of higher education and the degree of poverty, all of which have been previously

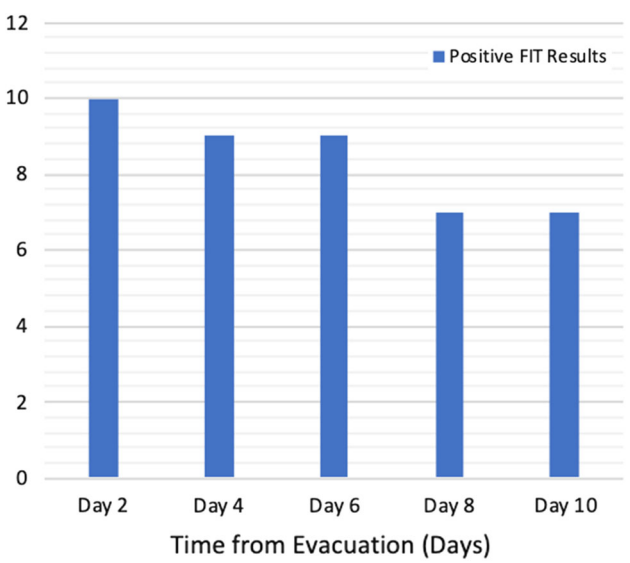

Fig. 1 Impact of stool sample processing time on FIT performance in Nigeria

associated with intestinal parasites in Nigeria [21, 22]. It is interesting to note the high rate of parasitic infection among older individuals.

Asymptomatic parasite infection can be associated with occult blood loss that is sufficient to trigger a positive result on FIT [27]. However, a heterogeneous group of studies have reported mixed findings regarding the association between intestinal parasite infection and a positive result on stool-based occult blood tests. Betson et al. (2010) and others have demonstrated a correlation between schistosomiasis and positive guaiac fecal occult blood test (gFOBT) [23–25, 28]. However, in a study of 1238 male subjects from Saudi Arabia, there was no difference in gFOBT positivity between those with or without intestinal parasites, including *S. mansoni* and *E. histolytica* [26]. In southern Nigeria, the rate of parasitic infection among 225 individuals at a private clinic between the ages of 15–70 was 13.3%. The species included *Ascaris lumbricoides*, *E. histolytica* and hookworm. In this study, 93% of those infected were under the age of 50 and there was no correlation between positive gFOBT and intestinal parasites [29]. In many of these studies, patients with active symptoms were not excluded, which potentially limits the generalizability of their findings to an asymptomatic screening population.

In asymptomatic patients, the impact of parasite infection on the performance of FIT for the purposes of CRC screening remains unknown. To our knowledge, our study is the first to examine this relationship. We used FIT rather than gFOBT in order to maximize the relevance of our findings. CRC screening with FIT is associated with higher compliance rates, superior advanced adenoma, and CRC detection and dominant cost-effectiveness [12, 13]. Globally, FIT has replaced gFOBT as the most common population-based CRC screening tool and is recommended for use in resource-limited environments for both organized and opportunistic screening [9, 11, 30].

Despite the high burden of parasitic disease in our cohort (49.6%), infection was not associated with FIT result. This is in keeping with the work by Ugwuoke et al. [29] using gFOBT in rural Nigeria. This is an important finding, as a strong correlation between FIT positivity and enteric parasites would potentially reduce the test's utility and cost-effectiveness in an endemic region. In Nigeria, a high number of false positive results would quickly overwhelm the limited endoscopy capacity. This is a valuable building block for future research into CRC screening with FIT in Nigeria.

Unfortunately, there is little additional evidence to support the efficacy of FIT in Nigeria or other LMICs. In our study, the overall FIT positivity rate was 7.2%, at a 50 µg/g cutoff. This is higher than would be expected in an environment felt to have a low polyp burden and comparatively low age-standardized incidence rate (ASR) of CRC (4.1–6.9/100,000) [31–34]. In comparison, in Germany, with an overall age-standardized incidence rate of CRC that exceeds 50/100,000, a 50 µg/g cutoff yields a test positivity rate of just 4.3% [35]. Similar to Nigeria, the prevalence of CRC neoplasia in Thailand is low (i.e., ASR of CRC of 9.2–12.9/100,000) compared to HICs [36]. In this environment, a CRC screening pilot program was launched using a qualitative FIT with a 40 µg/g cutoff. The results demonstrated a positivity rate of just 1.1% [36]. Although no correlation was seen between FIT and parasitic infection in this study, the sample size was small and the trend was suggestive. Based on the results from this study (i.e., 10.1% FIT positivity in parasite positive individuals vs. 4.3% in parasite negative), future trials should seek to enroll at least 264 participants (i.e., 132 per arm) to have 80% power to detect a difference with an alpha level of 0.05. Further prospective evaluation is needed with endoscopic follow-up to fully validate the performance of this stool-based screening tool in Nigeria.

The impact of temperature on FIT performance is particularly relevant in the Nigerian context. Numerous large prospective studies have demonstrated a time and temperature-dependent degradation of stool-based hemoglobin that is salient to FIT performance [16, 17, 37]. In our study, stool samples that triggered a positive result on FIT started to become negative four days after evacuation. Specimens were stored in an environment with a high ambient temperature (overall mean of 27 °C)—in keeping with the reality of many private homes, businesses, and healthcare facilities. The US Multi-Society Task Force on CRC

endorses an outer limit sample return time of less than 10 days and suggests a rapid return of 24 h is preferable [8]. Given our results, the safe window for specimen return may be even shorter than 10 days in Nigeria and needs to be further evaluated to help guide quality-assurance in any future FIT-based screening program.

There are several limitations and potential criticisms of this study. Seventy percent (7/10) of the positive FIT results were in patients with intestinal parasites. This may be statistically significant in a larger cohort of patients. Our sample size was limited by the retrospective design of this exploratory analysis, which also necessitated the use of frozen stool. It has been documented that repeated freeze–thaw cycles can affect hemoglobin integrity [38]. However, this relationship was evaluated in a prospective study involving over 3000 asymptomatic adults. In this study, frozen stool subjected to a single thaw produced reliable results compared to unfrozen, buffer-preserved stool [39]. A large number of participants in this study were female (80%), which may have artificially lowered the true positivity rate given the lower incidence of colorectal neoplasia in Nigerian women vs. men [34]. A component of the study design included free treatment. This may have artificially enriched our cohort for individuals with intestinal parasites. It may have also enriched our cohort for individuals with subtle bowel-related symptoms, which were not captured in the questionnaire and screened out in our subsequent analysis. Intensity of infection was only captured for 10% of infected subjects. Although a range of intensity was seen across Ascaries and Hookworm infections without a positive FIT, the small numbers preclude a more robust conclusion regarding the relationship between the intensity of parasite infection and test performance.

Organized screening is a complex, multisectoral process that involves the coordination of the entire health system. The overall effectiveness of FIT-based CRC screening is dependent on numerous variables well beyond the scope of this exploratory analysis. However, as larger prospective trials are designed, practical issues such as target population identification/enrollment, stool capture without effective waste management, timely sample return and follow-up need to be evaluated. The logistical opportunities and challenges of FIT screening in Nigeria need to be more thoroughly studied in larger prospective trials.

Conclusion

FIT is widely recommended as the most appropriate screening strategy for environments with limited resources. However, there is little evidence to support the efficacy of FIT in lower-income countries with a unique set of potentially confounding variables. This study demonstrates that parasitic infection is still endemic in rural Nigeria, even among those at risk of CRC that may benefit from screening. In this small study, the impact of asymptomatic parasitic infection on FIT positivity was not significant. The finding that positive FIT results start to become negative 4 days after specimen evacuation suggests that the high ambient temperature in Nigeria may require shorter turn-around times than currently endorsed in HICs. These findings are critical building blocks for the design of larger prospective studies that are needed to validate FIT performance in Nigeria and SSA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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