



Research Article

Online ISSN (3219-2789)

CT-Detected Incidental Colorectal Wall Thickening: Biomarker-Augmented Triage and Accelerated Colonoscopy in a Prospective Controlled Study

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Received: 30 June 2026; Revised: 10 September 2026; Accepted: 15 September 2026

Abstract

Background: Colorectal wall thickening identified incidentally on imaging of the abdomen poses a clinical challenge because subsequent management is variable. Incorporation of biological markers may enhance triage allocation without the need for additional imaging. **Objective:** To evaluate whether biomarker-enhanced triage improves colonoscopy prioritization for patients with incidental colorectal wall thickening findings. **Methods:** A prospective, controlled pilot trial randomized 50 adult outpatients with CT-detected incidental colorectal wall thickening (1:1) with usual care vs. a biomarker-augmented triage pathway. Intervention includes fecal immunochemical testing, fecal calprotectin, C-reactive protein, complete blood counts, albumin, and symptom profiling to prioritize urgent, expedited, or routine endoscopic referral. **Results:** Biomarker-guided triage accelerated referral patterns overall, with 92.0% of study-arm patients assigned to urgent or expedited referrals vs. 60.0% in the control group. This pathway was associated with a decrease in the median time to colonoscopy (43 vs. 22 days, $p<0.01$) and a significant improvement in the proportion of colonoscopies performed within 30 days (68.0% vs. 20.0%; $p<0.01$). Patients with clinically significant disease had significantly higher fecal hemoglobin (83.84 ± 28.84 vs. 3.43 ± 1.88 $\mu\text{g Hb/g}$) and fecal calprotectin (467.51 ± 129.86 vs. 86.99 ± 40.72 $\mu\text{g/g}$). Radiologically, the most prominent association with patients having significant disease was with marked wall thickening ($\text{OR}=28.42$). **Conclusions:** A stool and blood biomarker profile based on routine radiology reports enables rapid appraisal with clinically relevant capabilities to inform subsequent endoscopy. This triage strategy provides a rapid non-imaging assessment of clinical severity and should be extended to a larger cohort for validation.

Keywords: Biomarker-augmented triage; Computed tomography; Colonoscopy; Fecal immunochemical test; Incidental colorectal wall thickening.

زيادة سمك جدار القولون والمستقيم العرضي التي تم اكتشافها بالأشعة المقطعية: الفرز المعزز بالمؤشر الحيوي وتنظير القولون المعجل في دراسة مستقبلية محكمة

الخلاصة

الخلفية: تتخذ جدار القولون والمستقيم الذي تم تحديده بالصدفة عند تصوير البطن بشكل تحديدا سريريا لأن الإدارة اللاحقة متغيرة. قد يعزز دمج العلامات البيولوجية توزيع الفرز دون الحاجة إلى تصوير إضافي. **الهدف:** تقييم ما إذا كان الفرز المعزز بالمؤشر يحسن أولوية تنظير القولون للمرضى الذين لديهم نتائج عرضية لزيادة كثيف جدار القولون والمستقيم. **الطرائق:** أجرت تجربة تجريبية محكمة مستقبلية عشوائية على 50 مريضا خارجيا بالغاً معرضين لزيادة سمك جدار القولون والمستقيم العرضية التي تم اكتشافها بالأشعة المقطعية (1:1) مع الرعاية المعتادة مقابل مسار الفرز المعزز بالمؤشر الحيوي. شمل التدخل اختبارات الكيمائية المناعية البرازية، كالبروتكتين البرازي، البروتين التفاعلي C، عد كامل للدم، الألبومين، وتحليل الأعراض لإعطاء الأولوية للإحالات العاجلة أو السريعة أو الروتينية بالمنظار. **النتائج:** سرع الفرز الموجه بالمؤشرات الحيوية أنماط الإحالة بشكل عام، حيث تم تعيين 92.0% من مرضى ذراع الدراسة إلى إحالات عاجلة أو معجلة مقابل 60.0% في مجموعة الضابطة. ارتبط هذا المسار بانخفاض في متوسط الوقت لرؤية تنظير القولون (43 مقابل 22 يوما، $p<0.01$) وتحسن كبير في نسبة تنظير القولون التي أجريت خلال 30 يوما (68.0% مقابل 20.0%; $p<0.01$). المرضى الذين يعانون من مرض ذو دلالة سريرية كان لديهم نسبة هيموغلوبين برازية أعلى بشكل ملحوظ (83.84 ± 28.84 مقابل 3.43 ± 1.88 ميكروغرام Hb/g) وكالبروتكتين البراز (467.51 ± 129.86 مقابل 86.99 ± 40.72 ميكروغرام/غ). من الناحية الإشعاعية، كان الارتباط الأكثر بروزا مع المرضى الذين يعانون من مرض كبير هو زيادة سمكة الجدران بشكل ملحوظ ($\text{OR}=28.42$). **الاستنتاجات:** يمكن ملف المؤشرات الحيوية للبراز والدم بناء على تقارير الأشعة الروتينية التقييم السريع مع قدرات ذات صلة سريرية لإبلاغ التنظير اللاحق. توفر هذه الاستراتيجية تقييما سريعا غير تصويري لشدة الحالة السريرية ويجب توسيعها لتشمل مجموعة أكبر للتحقق.

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Article citation: Mahmoud MM. CT-Detected Incidental Colorectal Wall Thickening: Biomarker-Augmented Triage and Accelerated Colonoscopy in a Prospective Controlled Study. *Al-Rafidain J Med Sci.* 2026;11(2):121-132. doi: <https://doi.org/10.54133/ajms.v11i2.3228>

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INTRODUCTION

Incidental colorectal wall thickening on routine abdominal computed tomography is a significant radiologic observation, since the growing mural thickness and the nodal enlargement of the nodal association strengthen the likelihood of clinically significant colorectal pathology [1]. A threshold of 8.5 mm has been linked to significantly increased rates of colon cancer and positive regional lymph nodes that facilitate organized downstream assessment once mural abnormality is recognized as routine [1-3]. Fecal immunochemical testing has become the focus of risk-based triage following lower gastrointestinal symptom recognition, as quantitative fecal

hemoglobin has a high negative predictive value and clinically useful discrimination in symptomatic populations at referral [4]. A large fast-tracked cohort resulted in an optimal threshold of 19 $\mu\text{g Hb/g}$ feces, which yielded 85.4% sensitivity, 85.2% specificity, and 99.5% negative predictive value for colorectal cancer, indicating that stool-based prioritization may have a significant role in determining the urgency and the nature of subsequent investigation [5]. The diagnostic value of fecal immunochemical testing can be extrapolated to patients with more dangerous bowel symptoms, such that the diagnostic test can still be used to support rule-out performance and prioritize a pathway rather than being limited to low-risk presentations only [6]. Big prospective symptomatic

cohorts have thus strengthened the role of fecal hemoglobin as a useful triage variable in an urgent colorectal referral system even in the presence of an already worrying baseline symptom profile [7]. Immunochemical fecal occult blood testing of stool has been suggested as a stool protein biomarker to diagnose advanced colorectal neoplasia and has demonstrated the best overall diagnostic performance in comparative evidence synthesis [8]. This ranking helps to retain fecal hemoglobin as the fundamental biologic marker in symptomatic colorectal triage and permit other markers to serve as supplements and not substitutes [9]. Fecal calprotectin also provides another biologic aspect since it indicates intestinal inflammatory activity and is often increased in colorectal neoplasia, but its specificity is less than fecal hemoglobin [10]. Meta-analytic data have demonstrated that patients with colorectal cancer are approximately five-fold more likely than controls to have an elevated fecal calprotectin, which justifies its use as an adjunctive marker in case of inflammatory or infiltrative disease as part of the differential diagnosis [11]. Repeated fecal immunochemical testing can enhance cancer sensitivity in symptomatic patients compared to a single measurement. The rate of missed cancers is significantly lower with double-testing; paired results below 10 µg Hb/g indicate a very low-risk subgroup, while concordant positive results identify a highly enriched subpopulation of cancer, making repeat testing appealing when a single sample does not resolve clinical uncertainty. The importance of integrating complementary biologic signals in symptomatic colorectal assessment has also been highlighted by multi-marker fecal strategies. A point-of-care panel consisting of four integrated fecal markers had a negative predictive value of 94.8% for significant pathology and 100% for colorectal cancer or inflammatory bowel disease in cases where all four markers had a negative value, suggesting that combinations of biomarker architectures can help reduce unnecessary colonoscopy and refine prioritization of patients at higher risk [13]. The negative result of a FIT does not necessarily rule out clinically significant disease in symptomatic patients, particularly with the persistence of red-flag features. In a direct-to-test pathway, the vast majority of FIT-negative patients did not have significant pathology, and the colorectal cancer incidence was limited to 0.5%, but still the occurrence of FIT-negative cancers and the prevalence of iron-deficiency anemia among missed cases were noted, indicating that triage models that conserve clinical and blood-based escalation signals should be used instead of relying on FIT alone [14]. In addition to an easy-to-use positive-versus-negative scheme, the quantitative values of FIT may underpin risk stratification within the already-referred group of patients for diagnostic colonoscopy, since the degree of fecal hemoglobin is a dependent measure of graded risk in symptomatic groups. This facilitates more sophisticated prioritization models where stool-based risk is combined with other biologic and clinical factors to decide the urgency of definitive endoscopic examination [15]. The primary objective of this investigation was to determine if a biomarker-

enhanced triage method better identifies patients with incidental colorectal wall thickening reported in finalized routine reporting than clinical-only risk stratification. Specifically, this study sought to determine whether combining stool and blood biomarkers—fecal immunochemical testing, fecal calprotectin, C-reactive protein, white blood cell count, and serum albumin—with structured clinical assessment could create a more effective referral pathway than standard practice by evaluating whether this non-imaging approach accelerates colonoscopy access and appropriately triages patients at high risk for clinically significant colorectal disease (e.g., colon cancer or advanced adenoma). In summary, this research aimed to confirm a model of translation in which standard gastrointestinal radiology reporting serves as a direct entry point to a structured, biology-based outpatient triage pathway.

METHODS

Study Design and Setting

This trial was a two-arm, prospective, controlled pilot trial in adult outpatients whose finalized routine abdominal radiology reports already reported incidental colorectal wall thickening and whose further management was being arranged via conventional gastroenterology referral mechanisms. The methodological aim was to test a report-based, non-imaging triage model and was not to test a new radiologic acquisition protocol, so the radiology report text served as the point of entry into the study pathway, and all further prioritization was based on laboratory and clinical information received after report completion instead of on further CT or MRI studies. Each participant was subjected to a 90-day post-enrollment period to give enough time to the participants to be referred, to receive endoscopic workup when clinically necessary, and to have clinically significant colorectal disease ascertained.

Study population and report-based case identification

The study population comprised adults whose finalized routine radiology reports contained terminology consistent with newly described colorectal wall thickening—including focal wall thickening, segmental mural thickening, diffuse colorectal thickening, asymmetric thickening, circumferential thickening, or other structured or narrative descriptors employed by gastrointestinal radiologists in routine reporting. Case identification was performed through systematic review of finalized report text within the radiology information system after report release. Only incidental abnormality cases—those identified on imaging conducted for a reason not explicitly part of a known colorectal disease pathway—were retained. Study Data Report language was recorded verbatim into the study dataset, and each reported abnormality was coded based on the colonic segment to allow for later

comparison with colonoscopic and histopathologic findings.

Eligibility criteria

Eligible participants were defined as adult patients with a routine radiology report finalized within the last 6 months describing incidental colorectal wall thickening who were clinically stable and able to undergo diagnostic evaluation in an outpatient setting. Exclusion criteria included a previous diagnosis of colorectal cancer and an urgent need for inpatient surgery at the time of screening. We excluded participants with diagnosed active flare management of inflammatory bowel disease, overt gastrointestinal bleeding requiring an urgent visit preceding a colonoscopy within the last 6 months, inability to provide stool samples for biomarker testing, and any clinical condition that prohibited completion of the 90-day clinical follow-up pathway. These criteria were implemented before allocation to obtain a homogeneous pilot cohort defined by diagnostic uncertainty triggered by incidental reports instead of one entering an emergency or surveillance pathway on defined circumstances.

Sample size and group allocation

The final study sample comprised 50 participants. This number was selected a priori as a pilot sample size sufficient to evaluate feasibility, pathway coverage, biomarker coverage, signal detection for clinically significant disease, and the performance of the triage algorithm itself, prior to any subsequent confirmatory expansion. Participants were allocated 1:1, with 25 assigned to a control arm and 25 to a biomarker-enhanced triage arm. Allocation was performed following confirmation of eligibility and baseline registration, and the final analysis was conducted on an intention-to-follow basis, comprising all enrolled participants with available outcome tracking. Participants were randomized (1:1) to the study or control arm using a computer-generated random number sequence with permuted blocks. Allocation was concealed using sequentially numbered, opaque, sealed envelopes (SNOSE). An independent investigator generated the sequence and prepared the envelopes. Clinical staff enrolled participants, and envelopes were opened only after obtaining written informed consent and baseline assessments.

Recruitment and enrollment processes

Potentially eligible patients were identified after finalization of their radiology reports and screened against the predetermined criteria using the radiology report, referral information, and a brief chart review. Once eligibility was confirmed, patients were approached for participation, the study pathway was explained, and written informed consent was obtained prior to any study-specific sample collection. Registration recorded the enrollment date, report date, imaging indication, referring service, and first planned

gastroenterology or endoscopy contact. In the intervention arm, stool and blood testing was scheduled within seven days of enrollment to preserve temporal proximity between incidental report detection and triage assignment. In the control arm, enrollment did not alter standard care sequencing and served only for observational tracking of the diagnostic pathway.

Study groups

Control arm (usual report-based referral pathway). Participants in the control arm followed the standard referral route determined by the finalized radiology report and the treating clinician's judgment. No study-initiated biomarker package was applied to modify referral priority in this arm. Time to gastroenterology review, colonoscopy request, progression to urgent assessment, and any intervals introduced by cancellations or deferrals were recorded as they occurred in routine practice. This arm therefore served as the pragmatic comparator against which the added value of biomarker-guided prioritization was assessed. Study arm (Biomarker-enhanced triage pathway). A biomarker-enhanced triage package was conducted within 7 days of enrollment in the study arm. This pathway was a composite prioritization framework that integrated FIT, fecal calprotectin, serum CRP, CBC, serum albumin, and a structured symptom inventory. According to the study workflow, the result of the triage process was translated into one of three categories of urgency with respect to endoscopic referral: 1) Urgent, 2) Expedited, and 3) Routine, and passed to the clinical team responsible for communication. No further imaging was conducted to assist with triaging; instead, the interpretation of the radiology report was already complete and comprised the only input on imaging.

Stool and blood biomarker assessment

Stool specimens were collected using dedicated fecal collection devices suitable for quantitative automated analysis. Quantitative fecal hemoglobin was measured by fecal immunochemical assay on the Eiken OC-SENSOR platform, an automated FIT analyzer, with results expressed as micrograms of hemoglobin per gram of feces; fecal calprotectin was measured on the OC-SENSOR PLEDIA calprotectin system and reported in micrograms per gram. The calprotectin assay employed the OC-FCa reagent kit, comprising the OC-FCa Reagent (REF V-PH11), OC-FCa Calibrator (REF V-PH12), and the corresponding control materials (REF V-PH13, V-PH14, and V-PH15). The manufacturer specifies a measurable calprotectin range of 20 to 2720 µg/g. Within the same product family, the OC-Auto Sampling Bottle 3 (REF V-PZ25) is specified for stool sample handling. According to the manufacturer's specifications for the OC-SENSOR io FIT system, a quantitative working range of up to 1000 ng Hb/mL in sample buffer is defined, which the system converts to the reported fecal hemoglobin concentration in µg Hb/g feces. Serum C-reactive protein and albumin were measured

on the Roche Cobas C311 chemistry analyzer (catalog number 04826876001). Serum albumin was determined using the Bromocresol Purple assay (ALBP; catalog number 08056714190), and C-reactive protein using the high-sensitivity latex assay (CRPHS; catalog number 08057605190), an established automated quantitative assay on Cobas c systems (Diagnostics). The complete blood count was performed on an automated Sysmex XN-series hematology analyzer, with the XN-1000 as the standardized platform for hematologic measurement in this study; the system provides automated CBC and high-throughput differential analysis. Hemoglobin was reported in g/dL, total white blood cell counts in cells/ μ L, platelet count in cells/ μ L, hematocrit as a percentage, and mean corpuscular volume in fL. Standard adult reference ranges used for interpretive flagging were hemoglobin 13–18 g/dL (men) and 12–16 g/dL (women), white blood cells 4,500–11,000/ μ L, mean corpuscular volume 80–100 fL, and serum albumin approximately 3.5–5.0 g/dL; for CRP, healthy adults typically show very low values, with many laboratories regarding concentrations below approximately 8–10 mg/L as within the normal range (Sysmex).

Structured symptom inventory and clinical data collection

A standardized symptom inventory, completed at enrollment, was used to capture clinical data before referral priority was assigned. The inventory recorded rectal bleeding, change in bowel habit, persistent diarrhea, new-onset constipation, abdominal pain, tenesmus, mucus per rectum, unintentional weight loss, anorexia, fatigue suggestive of anemia, fever, nocturnal symptoms, personal history of colorectal polyps, first-degree family history of colorectal cancer, recent antibiotic exposure, recent nonsteroidal anti-inflammatory drug use, and major comorbid illness. Symptom duration was recorded in weeks and symptom severity on a simple ordinal scale. At the time of assessment, the case-record form also captured demographic data, the indication for the index imaging study, the report date, the location of the reported thickening, and the referring specialty.

Biomarker-enhanced triage algorithm and referral priority classification

Referral-urgency categories were derived from a clinically interpretable, pre-specified triage algorithm that combined stool, blood, and symptom data. Participants were classified as urgent when any major high-risk feature was present: fecal hemoglobin at or above 10 μ g Hb/g feces, fecal calprotectin at or above 250 μ g/g, a substantial inflammatory signal (elevated CRP with hypoalbuminemia), iron-deficiency or otherwise unexplained anemia on CBC, or alarm symptoms strongly suggestive of clinically significant colorectal disease. The 10 μ g Hb/g feces threshold for FIT positivity was adopted in accordance with current principles of symptomatic colorectal assessment, which support this limit for urgent referral decision-

making (ACPGBI). Participants were classified as expedited when urgent features were absent but an intermediate-risk profile was present, including fecal calprotectin of 100–249 μ g/g, persistent lower gastrointestinal symptoms with mildly positive inflammatory blood markers or borderline elevations in stool biomarkers, or an anatomically concerning reporting pattern without urgent alarm features. Participants were classified as routine when stool biomarkers were non-alarming, blood inflammatory and nutritional markers were not materially abnormal, and the symptom inventory did not yield an alarm profile. The calprotectin cut-points aligned with commonly used clinical thresholds, whereby values below 50 μ g/g are generally regarded as indicating a low likelihood of inflammatory bowel disease, values of 100–249 μ g/g as borderline or intermediate-risk, and values at or above 250 μ g/g as warranting urgent specialist assessment (Darmzentrum Bern). The overall decision pathway, from incidental CT detection through referral-priority classification, is summarized in Figure 1.

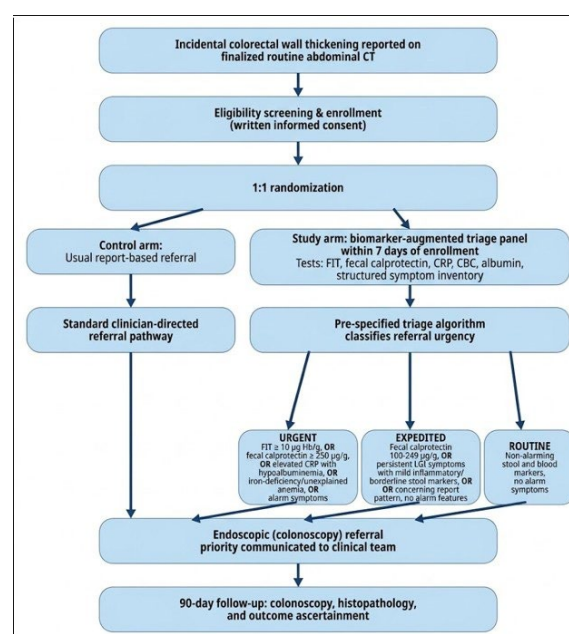


Figure 1: Proposed decision-making flowchart for the biomarker-augmented triage pathway, from incidental CT detection of colorectal wall thickening through randomization, biomarker-based classification of referral urgency, and 90-day outcome ascertainment.

Follow-up and clinical pathway tracking

Follow-up was for a period of 90 days from enrollment for all participants. Follow-up data were captured using electronic medical records, endoscopy scheduling systems, laboratory records, histopathology reports, and direct contact when needed to verify whether colonoscopy had occurred elsewhere. The gastroenterology consultation date, endoscopy request date, colonoscopy appointment date, colonoscopy completion date, biopsy receipt date, and final clinical disposition date were documented. Pathway fidelity was assessed by comparing the referral category assigned in the study arm with the actual time to colonoscopy and the

identification of a clinically significant lesion. Pathway events, including failed appointments, failure to return samples, cancellation of procedures, admission to hospital, and crossover to emergency evaluation, were also recorded.

Colonoscopy, histopathology, and outcome validation

Findings of colonoscopy represented the main procedural gold standard for the reported triage route. We reviewed endoscopic reports for lesion location, lesion morphology, esophageal involvement, strictures, ischemic changes, infiltrative abnormalities, polyp burden, and completeness of examination. Histopathology—when tissue sampling was undertaken as routine care—was used as the reference standard for classification of final lesions. Outcome validation stressed either congruence of the colonic segment described in the radiology report with the segment involved at colonoscopy or on pathology, with clinically justifiable proximity between long or overlapping segments. A negative colonoscopy was maintained as a confirmed negative endoscopic result if no additional, potentially treatable diagnosis developed over the follow-up period. All colonoscopy and histopathology findings were evaluated independently by two experienced assessors (endoscopists and pathologists, respectively) who were blinded to study-arm assignments and baseline participant data. Any discrepancies in outcome classification or histological diagnoses were resolved through consensus or adjudication by a third senior reviewer.

Outcomes and endpoint definitions

The main endpoint was clinically significant colorectal histopathology within 90 days. Clinically significant disease was defined as palpable colorectal adenocarcinoma, advanced adenoma, significant active colitis, ischemic colitis, infiltrative pathology, or any other sign of a colorectal lesion requiring definitive therapy. Secondary endpoints included time to colonoscopy (days from randomization), urgent-referral yield (the proportion of urgent-priority patients in whom clinically significant disease was diagnosed), the proportion of negative colonoscopies, and the ability of the combined-biomarker triage score to rank-order clinically significant disease. Advanced adenoma was defined by clinical criteria commonly used in practice based on standard pathology, and final endpoint adjudication was done after review of the endoscopy and histopathology reports.

Data management and variable coding

All data were stored in a dedicated study database under coded participant identifiers rather than identifiable personal information. Radiology report wording was stored in a structured text field, while segment location, biomarker values, symptom variables, referral categories, and endoscopic findings were stored as analyzable coded variables. Continuous

variables included age, fecal hemoglobin concentration, fecal calprotectin concentration, CRP, albumin, hemoglobin, white blood cell count, platelet count, and time to colonoscopy in days. Categorical variables included sex, report segment, symptom presence, referral category, colonoscopy completion status, and final disease classification. Entered data underwent validation to detect impossible dates, out-of-range numeric values, and inconsistent coding between referral category and follow-up events.

Ethical considerations

This study was approved by the Ethics Committee in the College of Medicine, Tikrit University, Iraq (Approval No. COM/TU/2024/147, approved on 15 May 2024), and was conducted in accordance with the ethical principles of the Declaration of Helsinki [16]. Written informed consent was obtained from all participants prior to enrollment and any study-specific sample collection.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 31.0.2.0, with a two-sided *p*-value below 0.05 considered statistically significant. Continuous variables were reported as mean $\pm$ standard deviation, or as median with interquartile range for skewed time-to-event data, and categorical variables as counts and percentages. Age and biomarker variables were compared using Welch's independent-samples *t*-test, with effect estimates expressed as mean differences with 95% confidence intervals, and comorbidity count and time to colonoscopy using the Mann–Whitney *U* test. Binary categorical variables and associations between high-risk radiologic features, pathway outcomes, and clinically significant disease were assessed by Fisher's exact test, with odds ratios and 95% confidence intervals; radiologic extent and severity distributions and referral-priority categories were compared by chi-square test. The discriminative ability of the biomarker-enhanced triage model was evaluated by receiver operating characteristic (ROC) curve analysis, with estimation of the area under the curve and threshold-based sensitivity, specificity, and predictive values. No formal a priori sample-size or power calculation was performed, consistent with the exploratory, pilot nature of this trial; the sample size of 50 participants was instead determined on pragmatic and feasibility grounds, as detailed above. Because the limited number of outcome events relative to the number of candidate predictors precluded stable multivariable modelling, multivariable logistic regression was not performed in this pilot cohort and is planned for a larger, confirmatory study; *p*-values for the multiple biomarker and radiologic comparisons reported here were not adjusted for multiplicity, and these comparisons should be interpreted as hypothesis-generating rather than confirmatory.

RESULTS

We enrolled 50 patients with incidental thickening of the colonic wall and randomized them 1:1 to control (n= 25) and biomarker-enhanced triage (n= 25) arms.

Table 1: Baseline characteristics of the population studied

Variable	Control (n=25)	Study (n=25)	Effect estimate	p-value
Age (year)	58.56±10.27	57.56±12.46	Mean difference 1.0 (95% CI -5.5 to 7.5)	0.758
Male sex	13(52)	12(48)	OR 1.17 (95% CI 0.39 to 3.56)	1.0
Comorbidity count	1.64±1.11	1.40±1.15	Mean difference 0.24 (95% CI -0.41 to 0.89)	0.45
Alarm symptoms at enrollment	9(36)	10(40)	OR 0.84 (95% CI 0.27 to 2.65)	1.0

Results are presented as frequency, percentage, and mean ± SD. Age was compared by Welch's independent-samples t test. Comorbidity count was compared by Mann–Whitney U test. Categorical variables were compared by Fisher's exact test. Odds ratios are shown for binary variables. A two-sided *p*-value < 0.05 was considered statistically significant.

Mean age was comparable in the control and study arms (58.56 ± 10.27 *versus* 57.56 ± 12.46 years; mean difference = 1.00, 95% CI = −5.50 to 7.50; *p* = 0.7583), with a confidence interval containing zero and indicating no clinically meaningful difference. Sex distribution was also well balanced across treatment arms, with 52.0% of male control arm patients (n= 13) and 48.0% of male enrolments in the study arm (n= 12; OR = 1.17; 95% CI = 0.39 to 3.56; *p* = 1.0). Baseline comorbidity burden did not differ significantly between groups (1.64 ± 1.11 *versus* 1.4 ± 1.15; mean difference 0.24, 95% CI = −0.41 to 0.89; *p* = 0.4501), and alarm symptoms at enrollment were present at comparable frequencies (36.0% *versus* 40.0%; OR = 0.84, 95% CI = 0.27 to 2.65; *p* = 1.0). The absence of material between-group differences in demographic, clinical, and symptom-related characteristics provides a middle-level baseline, which enhances the internal validity of later comparisons of referral performance and diagnostic outcomes. Radiologic report features were equally distributed between the control and study arms (Table 2).

Table 2: Radiology report features and distribution of incidental colorectal wall thickening

Variable	Control (n=25)	Study (n=25)	p-value
Extent: focal	10(40)	11(44)	0.945
Extent: segmental	8(32)	7(28)	
Extent: diffuse	7(28)	7(28)	
Severity: mild	8(32)	7(28)	0.931
Severity: moderate	11(44)	11(44)	
Severity: marked	6(24)	7(28)	
Symmetry: symmetric	14(56)	13(52)	1.0
Symmetry: asymmetric	11(44)	12(48)	

Values are presented as frequency and percentage.

Table 3: High-risk radiologic features and clinically significant disease (full cohort, n=50)

Feature	Disease present (n=17)	Disease absent (n=33)	Effect estimate	p-value
Focal extent	12(70.6)	9(27.3)	OR 6.4 (95% CI 1.75 to 23.35)	0.006
Marked thickening	11(64.7)	2(6.1)	OR 28.42 (95% CI 4.98 to 162.2)	<0.0001
Asymmetric thickening	12(70.6)	11(33.3)	OR 4.8 (95% CI 1.35 to 17.09)	0.018

Group-wise radiologic distributions were compared by chi-square test for extent and severity, and by Fisher's exact test for symmetry. Associations between high-risk radiologic features and clinically significant disease in the full cohort were tested by Fisher's exact test, with odds ratios and 95% confidence intervals reported. A two-sided *p*-value < 0.05 was considered statistically significant.

Within the biomarker-augmented arm, all measured biomarkers differed significantly according to final disease status (Table 4). Patients with clinically significant colorectal disease had markedly higher fecal hemoglobin (83.84 ± 28.84 *vs.* 3.43 ± 1.88 µg

Group assignments confirmed appropriate pre-allocation balance (Table 1), as baseline characteristics were similar.

The amount of thickening was similar with focal involvement seen in 40.0% *vs.* 44.0% (control *vs.* study group), segmental in 32.0% *vs.* 28.0%, and diffuse in 28.0% *vs.* 28.0% (*p* = 0.9445) of the control and study groups, respectively. Severity distribution showed no significant between-group difference, with mild thickening in 32.0% *versus* 28.0%, moderate thickening in 44.0% *versus* 44.0%, and marked thickening in 24.0% *versus* 28.0% (*p* = 0.9307). Symmetry of thickening was likewise balanced, with symmetric involvement in 56.0% *versus* 52.0% and asymmetric involvement in 44.0% *versus* 48.0% of the control and study arms (*p* = 1.0). This equivalence was expected, as radiologic morphology was determined prior to, and independent of, subsequent triage-arm allocation. In contrast, analysis of high-risk radiologic features across the full cohort (n= 50) revealed a clear concentration of clinically significant disease among patients with morphologically suspicious thickening (Table 3). Marked thickening showed the strongest association with clinically significant disease, present in 64.7% of affected patients *versus* 6.1% of unaffected patients (OR = 28.42, 95% CI = 4.98 to 162.20; *p* < 0.0001). Focal extent (70.6% *vs.* 27.3%; OR = 6.40, 95% CI = 1.75 to 23.35; *p* = 0.0059) and asymmetric thickening (70.6% *vs.* 33.3%; OR = 4.80, 95% CI = 1.35 to 17.09; *p* = 0.0175) were similarly associated with clinically significant disease. These findings support the biological plausibility of the cohort and confirm that morphologically suspicious wall thickening—particularly marked, focal, and asymmetric patterns—corresponds to a substantially higher likelihood of clinically significant colorectal pathology.

Hb/g; mean difference 80.41, 95% CI = 58.24 to 102.59; *p* < 0.0001) and fecal calprotectin (467.51 ± 129.86 *vs.* 86.99 ± 40.72 µg/g; mean difference 380.52, 95% CI = 279.75 to 481.30; *p* < 0.0001) than those without significant disease. C-reactive protein

was likewise elevated in patients with significant disease (15.53 ± 6.18 vs. 5.97 ± 3.28 mg/L; mean difference 9.56, 95% CI= 4.65 to 14.46; $p= 0.0013$), while hemoglobin (10.78 ± 1.32 vs. 13.45 ± 0.56 g/dL;

mean difference -2.67 , 95% CI= -3.71 to -1.64 ; $p= 0.0002$) and albumin (3.37 ± 0.33 versus 4.09 ± 0.18 g/dL; mean difference -0.73 , 95% CI= -0.99 to -0.47 ; $p< 0.0001$) were significantly lower.

Table 4: Biomarker profile by disease status in the biomarker-augmented arm

Variable	Significant disease (n=9)	No significant disease (n=16)	Effect estimate	p-value
Fecal Hb (μg Hb/g)	83.84±28.84	3.43±1.88	Mean difference 80.41 (95% CI 58.24 to 102.59)	<0.0001
Fecal calprotectin (μg/g)	467.51±129.86	86.99±40.72	Mean difference 380.52 (95% CI 279.75 to 481.30)	<0.0001
C-reactive protein (mg/L)	15.53±6.18	5.97±3.28	Mean difference 9.56 (95% CI 4.65 to 14.46)	0.0013
Hemoglobin (g/dL)	10.78±1.32	13.45±0.56	Mean difference -2.67 (95% CI -3.71 to -1.64)	0.0002
Albumin (g/dL)	3.37±0.33	4.09±0.18	Mean difference -0.73 (95% CI -0.99 to -0.47)	<0.0001

Values are presented as mean ± SD. Comparisons between patients with and without clinically significant disease in the biomarker-augmented arm were performed using Welch's independent-samples t test. Effect estimates are expressed as mean differences with 95% confidence intervals. A two-sided p -value < 0.05 was considered statistically significant.

Largest effect sizes and smallest P values were seen for the fecal hemoglobin and fecal calprotectin, demonstrating that the stool-based markers provided the best separation, while CRP, hemoglobin, and albumin provided complementary but markedly less pronounced separation. These results as a whole provide supportive evidence for the expected pattern

that biomarker-based triage identifies a higher risk subgroup defined by biologically and clinically logical laboratory abnormalities. Referral priority classification differed significantly between the two arms ($p= 0.0299$), with the study arm showing a marked shift toward higher-urgency categories (Table 5).

Table 5: Referral priority and endoscopic pathway progression by study arm

Variable	Control (n=25)	Study (n=25)	Effect estimate	p-value
Urgent priority	6(24)	9(36)	—	0.0299
Expedited priority	9(36)	14(56)	—	
Routine priority	10(40)	2(8.0)	—	
Urgent or expedited combined	15 (60.0%)	23(92)	OR 7.67 (95% CI 1.44 to 40.83)	0.0181
Time to colonoscopy (day)	42(32–58)	22(17–33)	—	<0.0001
Colonoscopy within 30 days	5(20)	17(68)	OR 8.50 (95% CI 2.34 to 30.91)	0.0014
Urgent-referral yield	4/6(66.7)	9/9(100)	OR 8.33 (95% CI 0.34 to 202.34)	0.1429

Overall referral-priority distribution was compared by chi-square test. Urgent-or-expedited referral and colonoscopy within 30 days were compared by Fisher's exact test with odds ratios and 95% confidence intervals. Time to colonoscopy is presented as median (interquartile range) and was compared by Mann–Whitney U test. A two-sided $p< 0.05$ was considered statistically significant.

Urgent priority was assigned to 36.0% of study-arm patients compared with 24.0% of control-arm patients, expedited priority to 56.0% vs. 36.0%, and routine priority to only 8.0% versus 40.0%. When urgent and expedited categories were combined, 92.0% of study-arm patients received accelerated referrals compared with 60.0% of control-arm patients (OR= 7.67, 95% CI= 1.44 to 40.83; $p= 0.0181$). This translated into faster pathway progression: median time to colonoscopy was reduced from 42 days (IQR= 32.0–58.0) in the control arm to 22.0 days (IQR= 17.0–33.0) in the study arm ($p< 0.0001$), and colonoscopy within 30 days was achieved in 68.0% of study-arm patients versus 20.0% of control-arm patients (OR= 8.50, 95% CI= 2.34 to 30.91; $p= 0.0014$). Urgent-referral yield, the proportion of urgent-priority patients in whom clinically significant disease was ultimately confirmed, was numerically higher in the study arm (100% [9/9] versus 66.7% [4/6]), although this difference did not reach statistical significance (OR= 8.33, 95% CI= 0.34 to 202.34; $p= 0.1429$), most likely reflecting the small number of urgent cases in this pilot cohort. Taken together, these findings demonstrate that biomarker-guided triage produced a more clinically appropriate distribution of referral

urgency and meaningfully accelerated access to diagnostic colonoscopy relative to usual care. The final validated diagnostic spectrum and key outcome metrics by study group are presented in Figure 2.

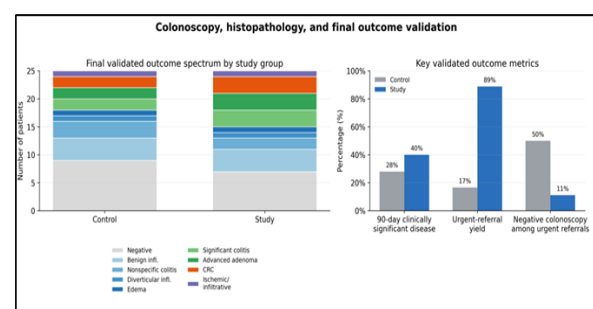


Figure 2: Validated colonoscopy, histopathology, and final 90-day outcome spectrum by study group.

The overall 90-day rate of clinically significant colorectal disease was numerically higher in the study arm than in the control arm (40% versus 28%), though this difference remained modest and is consistent with an underpowered pilot comparison. In contrast, urgent-referral yield was substantially greater in the study arm than in the control arm (89% versus 17%),

while the proportion of negative colonoscopies among urgently prioritized patients was correspondingly lower in the study arm (11% *versus* 50%). The validated pathology spectrum remained heterogeneous in both groups, with benign inflammatory and nonspecific findings persisting alongside clinically significant diagnoses such as advanced adenoma, significant colitis, colorectal cancer, and ischemic or infiltrative disease. Together, these findings indicate that although the overall burden of significant disease was similar in magnitude between arms, biomarker-guided triage more effectively concentrated urgent referrals among patients who truly harbored clinically significant pathology. Discriminative performance of each biomarker-augmented triage model *vs.* the report-only approach for the identification of clinically significant colorectal disease is shown in Figure 3. Receiver Operating Characteristic (ROC) Curve analysis revealed that the biomarker-augmented model has significantly better overall AUC performance (0.929, 95% CI 0.840–1.000) versus (0.747, 95% CI 0.595–0.899) for the report-only model (Figure 3A). The biomarker-augmented strategy had improved sensitivity at the prespecified operating thresholds (88.2%, 95% CI 65.7–96.7% *vs.* 70.6%, 95% CI 46.9–86.7%) and higher negative predictive value (92.3%, 95% CI 75.9–97.9% *vs.* 84.8%, 95% CI 69.1–93.4%), but modestly lower specificity relative to the report-only model (72.7%, 95% CI 55.8–84.9% *vs.* 84.8%, 95% CI 69.1–93.4%) (Figure 3B).

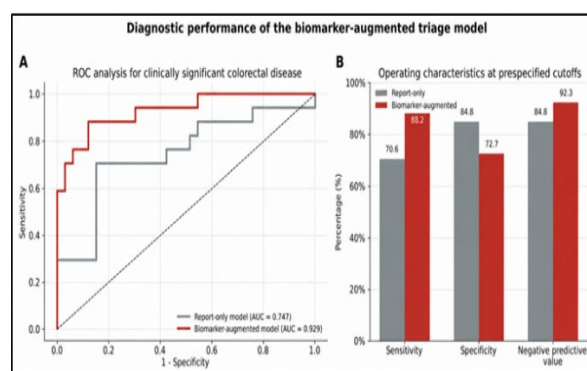


Figure 3: A) ROC-based diagnostic performance of the biomarker-augmented triage model for clinically significant colorectal disease; B) Operating characteristics at prespecified cutoffs.

Taken together, these findings indicate that integrating fecal hemoglobin, fecal calprotectin, inflammatory markers, and blood indices with report-based triage substantially improved diagnostic discrimination for clinically significant colorectal disease, particularly by reducing missed cases, and support the clinical utility of the combined model for downstream referral prioritization. These 95% confidence intervals were derived using the Hanley—McNeil method for the area under the curve and the Wilson score method for sensitivity, specificity, and negative predictive value, based on 17 patients with and 33 without clinically significant disease in the full cohort (Table 3). Figure 4A–C present representative hematoxylin and eosin (H&E)-stained histopathology images illustrating the spectrum of clinically significant colorectal disease

confirmed among validated cases in this study. Figure 4A shows colorectal adenocarcinoma, characterized by irregular, crowded glandular structures with a cribriform, back-to-back architectural pattern, columnar cells with hyperchromatic, pleomorphic nuclei, and loss of normal glandular polarity infiltrating the surrounding stroma. Figure 4B shows advanced colorectal adenoma with high-grade dysplasia, demonstrating elongated, crowded villiform glands lined by columnar epithelium with nuclear stratification, hyperchromasia, and architectural complexity, without evidence of invasion beyond the basement membrane. Figure 4C shows active chronic colitis requiring treatment, with distorted crypt architecture, crypt branching, and a dense mixed inflammatory infiltrate within the lamina propria, together with focal cryptitis and mucosal hemorrhage, consistent with an active inflammatory process. Together, these images span the principal categories of clinically significant colorectal pathology identified through the biomarker-augmented triage pathway—malignant, premalignant, and inflammatory—and provide morphologic confirmation supporting the endoscopic and biomarker findings reported for these cases. As with other descriptive histopathology images in this study, Figure 3 is presented for illustrative and validation purposes only and not subjected to statistical analysis.

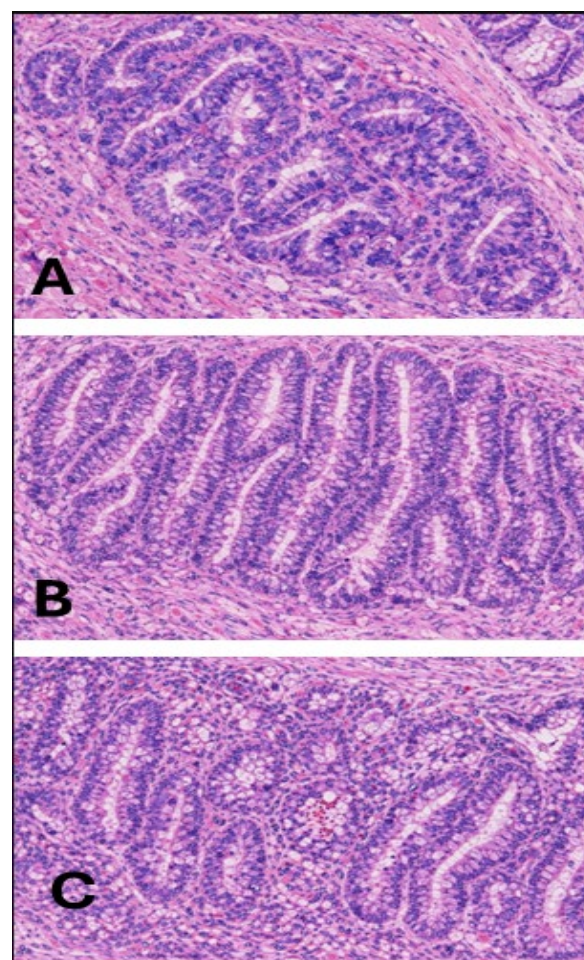


Figure 4: A) Histopathology image shows the output of colorectal adenocarcinoma from a validated significant case; B) Histopathology image shows the output of advanced colorectal adenoma with a high-grade dysplasia; C) Histopathology image shows the output of active chronic colitis requiring treatment.

DISCUSSION

The current research revealed that the basic radiologic distribution of incidental colorectal wall thickening was comparable in both the control and biomarker-triage cohorts, which is methodologically reassuring since the imaging appearances preceded downstream triage choices. More importantly, the present research discovered that focal extent, marked thickening, and asymmetric thickening were strongly correlated with clinically significant disease, and marked thickening was the variable with the greatest effect estimate [17]. The results of the present study seem quite consistent with the report conducted by Bas and Pakoz, who discovered that colonic wall thickening, as revealed by CT, was often associated with significant endoscopic pathology and that older age and low hemoglobin levels were associated with a higher probability of the abnormal finding during colonoscopy. Simultaneously, Bas and Pakoz highlighted that not every patient with thickening had cancer, and this finding also applies to the current study, where suspicious morphology increased risk but was not universal [18]. Only moderate inter-observer reliability of bowel wall thickening on CT and imperfect correlation with endoscopy were reported by Daniel and colleagues, adding a valuable counterpoint to the present study. The more robust associations in the present study can be explained by the fact that the study was conducted on finalized radiology reports that were already considered clinically interesting enough to include explicit thickening language in them, and inter-observer studies involve more borderline interpretations, which weaken predictive power [19]. The current study is also supported by Karabay and colleagues, who demonstrated that the growing colonic wall thickness on CT was correlated with colon cancer and that a threshold of more than 8.5 mm had a discriminatory value [2]. Somuncu and coworkers discovered that incidentally detected gastrointestinal wall thickening on abdominal CT often resulted in significant endoscopic findings; nevertheless, they also presented evidence that a non-negligible proportion of patients had benign or non-specific outcomes. The strong odds ratios in the current study thus seem clinically significant, though they should still be treated as signals of enrichment that should be given priority rather than being viewed as evidence of pathology in themselves [20]. Xu *et al.*, in a PET/CT setting, discovered that an integration of focal metabolic abnormalities with localized colonic wall-thickening parameters enhanced detection of high-risk colorectal lesions [21]. The recent work is not completely supportive. Wahlig and colleagues demonstrated that routine abdomen/pelvis CT has only moderate sensitivity in the detection of colorectal cancer, and smaller lesions are especially susceptible to being overlooked. That is, the current paper is on the topic of risk stratification following report-detected thickening, and Wahlig is on the topic of the detection performance of routine CT per se; both may be valid at the same time without contradiction [22]. Ergin and Kivrakoglu provide a balanced comparison as well.

They discovered that radiologic imaging of gastrointestinal wall thickening was frequently associated with clinically significant endoscopic abnormalities, but a significant number of patients had normal or lower-risk results. This is exactly why the biomarkers included in the present study later are of clinical interest [23]. In the present study, it was established that patients with clinically significant disease were characterized by significantly increased levels of fecal hemoglobin, fecal calprotectin, and CRP, along with reduced levels of hemoglobin and albumin, and the separation of the stool biomarkers was most evident. The greatest signal of fecal hemoglobin and calprotectin indicates that lesion-proximal biomarkers are more effective than more indirect systemic measures [5]. The positive fecal hemoglobin signal of the present study is in line with the findings of Turvill and colleagues, whose Fast Track FIT study revealed that fecal immunochemical testing is highly diagnostic in patients with symptoms of colorectal cancer. The present paper goes on that reasoning to imply that when incidental mural thickening has already turned into a cause of concern, a significant increase in fecal hemoglobin could be used to distinguish between patients who should be promptly subjected to endoscopic clarification and those who could withstand less aggressive prioritization [5]. Lué and colleagues concluded that a combination of fecal occult blood testing and fecal calprotectin would be more accurate in diagnosing symptomatic patients than either method alone or would decrease the number of unnecessary colonoscopies [24]. Zhu and colleagues also determined that fecal hemoglobin and fecal calprotectin were effective in the detection of meaningful bowel disease in a prospective symptomatic cohort. Nonetheless, the current study seems to indicate a greater division between disease and no-disease groups compared to several mixed symptomatic cohorts. A probable reason is spectrum enrichment: incidental radiologic thickening had already preselected a higher pretest probability group than unselected lower-GI symptom cohorts [25]. Lanas and colleagues found that fecal hemoglobin and calprotectin could be used to prioritize primary care patients for colonoscopy referrals when there is a high risk of colorectal cancer, which once again is a strong support of the current study. The same practical endpoint is reached in the current study, but with a different entry point: instead of symptoms, finalized radiology reports that report incidental colorectal wall thickening. Such convergence will augment belief in the translational value of this biomarker strategy [26]. One of the most informative comparisons, which is partially contradictory, is given by Limsrivilai and colleagues. They discovered that FIT and fecal calprotectin could be effective in chronic lower gastrointestinal symptoms, although CRP addition had no significant effect on diagnostic accuracy. CRP could be a measure of biologic burden in the current study in a pre-selected imaging-abnormal cohort but remains a lesser measure when creating a practical prioritization instrument than stool tests [27]. Yamakawa *et al.* demonstrated that fecal calprotectin,

lactoferrin, and hemoglobin are both clinically informative of activity in inflammatory diseases as well as colorectal tumors, which corroborates the strong fecal calprotectin and fecal hemoglobin results in the current study. That is applicable to the present study, in which the endpoint was not just cancer and advanced adenoma but also significant inflammatory and ischemic pathology that needed treatment [28]. Ball and colleagues indicated that in symptomatic primary care, FIT had a good diagnostic accuracy, and later Barlow and colleagues demonstrated excellent FIT performance in early detection of colorectal cancer, particularly in the age group of 40–49 years but also found age-related variation in predictive performance [29,30]. The current research revealed that biomarker-based triage shifted a higher number of patients to urgent or expedited triage, significantly reduced the time to colonoscopy, and increased the number of patients who received a colonoscopy within 30 days. The lack of a significant difference in urgent-referral yield should not be over-interpreted in terms of efficacy, as the absolute yield still favored the study arm, and the confidence interval was necessarily broad due to the pilot sample consisting of only 50 patients [31]. Loveday and colleagues simulated the prioritization of FIT in response to COVID-related pathway disruption and found that the impact of delayed colorectal referrals could be alleviated by FIT-based prioritization. The most important common theme is that in situations where there is a finite endoscopy capacity, prioritization tools are important not because they result in more cancers being biologically present, but because they can be used to make sure that the most at-risk patients reach colonoscopy first [31]. D'Souza and colleagues demonstrated that FIT was superior in predicting meaningful colorectal pathology when compared to symptoms alone in patients referred on a 2-week-wait pathway [32]. Booth and colleagues summarized the symptomatic literature on the use of FIT and concluded that FIT could be used in numerous risk-stratified referral pathways and assist in the identification of individuals who would receive greatest priority in colorectal investigation [33]. Pin-Vieito and colleagues discovered that FIT thresholds have a material effect on sensitivity, specificity, and the percentage of patients who are forwarded to investigation [34]. Bailey and colleagues found that FIT works fine when used in low-risk symptomatic primary care groups, which justifies its use in the prioritization of investigations, but their study also cautions us that predictive values are heavily dependent on underlying disease prevalence [35]. More recent service studies also support the current study. Boulbadaoui and colleagues discovered that the use of FIT-value-based algorithms can enhance the performance of triage in symptomatic colorectal referrals, and Falvey and colleagues found that an algorithm based on FIT can be used to prioritize new symptomatic colorectal referrals to be investigated [36,37]. The findings of the present study are also supported by Saw and colleagues, who demonstrated that FIT is feasible to triage patients with possible colorectal cancer symptoms in a pilot group in New

Zealand. Practically, speed and prioritization can be enhanced before statistical certainty around yield is achieved [38].

Study Limitations

The study has several limitations. First, the sample size was small ($n=50$), in keeping with a pilot design, which limited the statistical power for secondary endpoints such as urgent-referral yield. Second, the biomarker cut-offs and disease outcomes were derived from a single-center pathway, limiting the generalizability of other populations and imaging practices. Third, blinding referring clinicians to biomarker results was not possible, which introduces the possibility of ascertainment bias in referral decisions. Fourth, the 90-day follow-up window may have been too short to detect indolent or slowly progressive pathology, leading to an underestimation of the true yield of clinically significant disease in both arms. Fifth, no formal a priori power calculation was performed; the sample size was determined pragmatically for feasibility rather than to achieve a pre-specified statistical power, and the multiple comparisons performed were not adjusted for multiplicity, so all p-values should be interpreted as hypothesis-generating. Sixth, the limited number of events relative to candidate predictors precluded multivariable regression to identify independent predictors of clinically significant disease; this should be addressed in a larger, adequately powered confirmatory trial.

Conclusion

The proposed pilot study suggests that incidental colorectal wall thickening that has already been reported in finalized routine radiology reports can be better addressed using a structured biomarker-enhanced triage pathway than conventional report-based referral. Despite comparable baseline clinical features and radiologic distribution in the two groups, the biomarker-directed model resulted in a more articulate prioritization pattern, a significantly larger proportion of urgent or expedited referral assignment, and a reduced time to colonoscopy. In the intervention arm, biologically coherent separation between patients with and without clinically significant colorectal disease was observed in fecal hemoglobin, fecal calprotectin, C-reactive protein, hemoglobin, and albumin, which lends credence to the clinical relevance of the combined triage framework. Focal, marked, and asymmetric thickening, also linked with clinically significant disease, were also found to be important in the full cohort, supporting the concept of combining radiologic pattern recognition with downstream laboratory and symptom-based evaluation as opposed to solely using report wording. The research also suggests that an outpatient workflow triggered by a report can be realized without extra imaging exposure and still enhance endoscopic prioritization while maintaining a lower ratio of uninformative urgent investigations. Since the study was a small pilot study, the results can only be

regarded as proof-of-concept and not definitive evidence of effectiveness. However, the identified gains in referral efficiency, the timeliness of colonoscopic examination, and the favorable diagnostic discrimination are encouraging and should be confirmed in larger multicenter cohorts. Should these findings be substantiated, the strategy would offer a viable translational approach to transform incidental radiologic detection of colorectal wall thickening into a more consistent, risk-stratified, and clinically useful referral pathway.

Conflict of interests

The authors declared no conflict of interest.

Funding source

The authors did not receive any source of funds.

Data sharing statement

The data that supports the findings of this study are available from the corresponding author upon a reasonable request.

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