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Review Article

Efficacy of ColonFlag as a Complete Blood Count-Based Machine Learning Algorithm for Early Detection of Colorectal Cancer: A Systematic Review

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What's Known

- Detecting asymptomatic individuals for colorectal cancer (CRC) screening remains a challenging task. ColonFlag is a machine learning algorithm, incorporating age, gender, and 20 complete blood count (CBC) parameters from routine lab data.
- Machine learning techniques offer a valuable supplementary avenue, yet their feasibility for translation into clinical practice remains uncertain.

What's New

- ColonFlag demonstrated the ability to detect CRC in asymptomatic patients, yet it exhibited variability in performance across diverse populations.
- While ColonFlag is not intended to replace traditional screening programs, its potential to identify CRC before clinical diagnosis suggests an opportunity to detect more cases than regular screening alone.

Abstract

Background: Colorectal cancer (CRC) screening is essential to reduce incidence and mortality rates. However, participation in screening remains suboptimal. ColonFlag, a machine learning algorithm using complete blood count (CBC), identifies individuals at high CRC risk using routinely performed tests. This study aims to review the existing literature assessing the efficacy of ColonFlag across diverse populations in multiple countries.

Methods: The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) were followed in reporting this systematic review. Searches were conducted on PubMed, Cochrane, ScienceDirect, and Google Scholar for English articles, using keywords related to CBC, machine learning, ColonFlag, and CRC, covering the first development study from 2016 to August 2023. The Cochrane Prediction Model Risk of Bias Assessment Tool (PROBAST) was used to assess the risk of bias.

Results: A total of 949 articles were identified during the literature search. Ten studies were found to be eligible. ColonFlag yielded Area Under the Curve (AUC) values ranging from 0.736 to 0.82. The sensitivity and specificity ranged from 3.91% to 35.4% and 82.73% to 94%, respectively. The positive predictive values ranged between 2.6% and 9.1%, while the negative predictive values ranged from 97.6% to 99.9%. ColonFlag performed better in shorter time windows, tumors located more proximally, in advanced stages, and in cases of CRC compared to adenoma.

Conclusion: While ColonFlag exhibits low sensitivity compared to established screening methods such as the fecal immunochemical test (FIT) or colonoscopy, its potential to detect CRC before clinical diagnosis suggests an opportunity for identifying more cases than regular screening alone.

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Keywords ● Blood cell count ● Colorectal neoplasms ● Electronic health records ● Machine learning ● Mass screening

Introduction

Colorectal cancer (CRC) stands as the world's third most common cancer, with over 1.9 million new cases and 930,000 deaths in 2020 alone.[1-3] Developed countries witness 25-30% of CRC diagnoses in stage IV with distant metastases.[4] Effective

screening is crucial to lower CRC incidence and mortality.[5, 6] Current options include a decade-spanning colonoscopy or an annual fecal immunochemical test (FIT).[7] Despite recognized benefits, participation in CRC screening remains suboptimal.[8, 9]

Israel's cost-effective approach uses a machine learning algorithm called ColonFlag to scan routine lab tests for high-risk indicators.[10] Anemia, identified with a 9.7% positive predictive value, can signal high-risk CRC.[11] In individuals lacking apparent anemia, colorectal neoplasms can still induce subtle changes in lab profiles due to minor blood loss.[12, 13] The ColonFlag algorithm integrates demographic data and complete blood counts (CBC), predicting asymptomatic CRC, and has been validated in several countries.[6, 14-19] This study aims to review the existing literature assessing the efficacy of ColonFlag across diverse populations in multiple countries.

Materials and Methods

Data Sources and Search Strategy

We adhered to PRISMA guidelines for our systematic review, registered on PROSPERO (ID: CRD42023454992). Searching on databases and gateways such as PubMed, Cochrane, ScienceDirect, and Google Scholar from 2016 to August 2023, we focused on English articles using specific keywords related to CBC, machine learning, ColonFlag, and CRC (table 1). We specifically chose articles from 2016 as it marks the first development study of ColonFlag. The objective of this study was to specifically evaluate ColonFlag as one of the existing machine learning algorithms. Titles and abstracts were independently assessed by RDP and SAS, with disagreements resolved through discussion with TAS.

Inclusion and Exclusion Criteria

English-language primary research articles

Table 1: Detailed description of the search strategy used for systematic review

	No	Query	Results
PubMed	1.	(Blood count* OR "full blood count*" OR "complete blood count*" OR "blood work")	408,201
	2.	(((ColonFlag OR "machine learning" OR "Models, Statistical"[Mesh] OR "ROC Curve"[MESH] OR "predict* tool*"[tw] OR nomogram*[tw] OR "predict* model*"[tw] OR decision*[tw] OR scor*[tw] OR algorithm*[tw] OR "risk scor*"[tw] OR "sensitivity and specificity*"[tw] OR sensitivity[tw] OR specificity[tw] OR "predictive value of tests"[tw] OR prediction*[tw] OR "receiver operating characteristic curve*"[tw] OR "ROC curve*"[tw] OR "area under curve*"[tw] OR "area under curve"[tw] OR "area under the curve*"[tw] OR AUC[tw] OR "C statistic*"[tw] OR discriminat*[tw] OR classif*[tw] OR "absolute risk*"[tw] OR indices[tw] OR stratify*[tw] OR "c-statistic"[tw] OR "C statistic"[tw] OR "statistical learning"[tw] OR "statistical-learning"[tw] OR "positive predictive value*"[tw] OR "negative predictive value*")))	6,181,583
	3.	(("Colorectal Neoplasms"[Mesh] OR ((colorectal[tw] OR colorect*[tw]) AND (tumo*[tw] OR cancer[tw] OR carcinom*[tw] OR neoplas*[tw] OR malignan*[tw]))) OR ("Colonic Neoplasms"[Mesh] OR ((colon[tw] OR bowel[tw] OR colon*[tw]) AND (neoplas*[tw] OR tumo*[tw] OR cancer[tw] OR carcinom*[tw] OR malignan*[tw]))))	449,967
	4.	#1 AND #2 AND #3	2,039
	5.	#4 NOT ("case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "guideline"[Publication Type] OR "introductory journal article"[Publication Type] OR "meta analysis"[Publication Type] OR "news"[Publication Type] OR "retracted publication"[Publication Type] OR "review"[Publication Type] OR "systematic review"[Publication Type])	1,829
	6.	#5; filter English, Adult 19+ years	1,089
	7.	#6; filter 2016-2023	467
Cochrane	1.	colorectal cancer OR colon cancer OR colorectal neoplasm* OR colon neoplasm*	24,087
	2.	"Full blood count" OR "complete blood count"	2,452
	3.	ColonFlag OR machine learning OR predict* model OR algorithm	39,149
	4.	#1 AND #2 AND #3	2
ScienceDirect	1.	"colorectal cancer" OR "colorectal neoplasm" OR "colon cancer" OR "colon neoplasm"	262,063
	2.	ColonFlag OR machine learning	264,400
	3.	"Complete blood count" OR "full blood count"	80,689
	4.	#1 AND #2 AND #3	133
	5.	#4; filter 2016-2023	137
Google Scholar	1.	"colorectal cancer" OR "colorectal neoplasm*" OR "colon cancer" OR "colon neoplasm*"	18,100
	2.	ColonFlag OR "machine learning"	18,600
	3.	"Full blood count" OR "complete blood count"	17,200
	4.	#1 AND #2 AND #3	823
	5.	#4; filter 2016-2023	632
	6.	#5 NOT "systematic review*"	347

evaluating ColonFlag's performance in CRC risk detection were included. Abstracts, conference proceedings, previously published systematic reviews, correspondence, and case studies were excluded.

Data Extraction

Three reviewers (RDP, SAS, NNH) independently assessed study eligibility and collected data using tailored extraction forms. Validation occurred through subsequent discussions, resolving disagreements until consensus. Extracted data included publication year, design, location, patient details (setting, type, population), sample size, data source, baseline patient characteristics, and model performance measures: Area Under the ROC Curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and odds ratio (OR).

Risk of Bias

The PROBAST was used to assess bias in studies developing or validating prediction models. PROBAST includes signaling questions in four domains: 1) Participants: How well the study population represents the target group, how missing data is managed, and how participants are chosen for model development or validation. 2) Predictors: The selection and measurement of variables used in the model, including how missing data, categorization, and interactions are handled. 3) Outcome: How the outcome (what the model predicts) is measured and managed, considering blinding, completeness of data, and appropriate outcome definitions. 4) Analysis: Evaluation of model development aspects, the type of selected model, management of missing data, and methods used for validation.[20] Three reviewers independently performed the risk of bias evaluation, which was confirmed by subsequent discussion. Any discrepancies that arose were discussed for resolution.

Results

Study Selection

From 949 initially identified articles, 591 underwent screening after removing duplicates. Figure 1 outlines the selection process following PRISMA guidelines. Initially, 14 articles were eligible based on titles and abstracts. During the full-text assessment, four articles were excluded as they did not use ColonFlag as the intended index test. Two studies did not use artificial intelligence (AI), instead, they compared blood count parameters in two groups (n=1) and assessed the enhancement of FIT with blood test values (n=1). The other two studies employed a deep neural network for various parameters such as tumor marker and blood chemistry, not merely blood count (n=1), and evaluated AI models based on colonoscopy images and diverse datasets (n=1).

Study Characteristics

This review included 10 studies outlined in table 2, providing details on the studies and subject characteristics. One study introduced ColonFlag as a novel algorithm,[10] seven studies[6, 14-19] validated it across diverse populations, and two studies[21, 22] compared ColonFlag's performance with FIT. Sample sizes varied from 17,000 to 2.5 million individuals, drawn from asymptomatic subjects, electronic medical records (EMR), or primary care databases. Ayling and others focused on symptomatic individuals in a prospective study with approximately 500 subjects.[21, 22] Goshen and others conducted a 14-month prospective study using ColonFlag to detect asymptomatic CRCs in a population at risk.[17] The remaining seven studies collected data retrospectively, and the majority of them additionally conducted a case-control analysis. Data, primarily from general practice records, was collected nationwide, with some studies including hospital records. Kinar and others expanded their dataset by incorporating records from Israel and the United Kingdom.[10]

ColonFlag Performance Test

Most studies focused on the AUC as the primary outcome, with secondary outcomes including sensitivity, specificity, PPV, NPV, and OR. AUC values across diverse populations ranged from 0.736 to 0.82.[10, 15, 16, 18, 19] Excluding Ayling's prospective studies,[21, 22] the sensitivity and specificity ranged from 3.91% to 35.4% and 82.73% to 94%, respectively. Ayling's studies had higher sensitivity (52.4% and 88.24%) and lower specificity (71.3% and 71.07%). PPV varied between 2.6% and 9.1%, and NPV ranged from 97.6% to 99.9%. Table 3 shows the outcome of the included studies. Among the studies providing ColonFlag scores,[6, 14, 16, 19] two[16, 19] indicated higher scores in CRC-diagnosed individuals ($\bar{x}$=79-83.8) than those without a diagnosis ($\bar{x}$=51.5-56.3). In the development study,[10] an AUC of 0.826±0.01 was achieved, further validated on an external THIN database in the UK with an AUC of 0.81, OR of 40, and specificity of 94%. Figure 2 compares studies, revealing AUC ranging from 0.736 to 0.82.

An age-only detection algorithm achieved an AUC of 0.73.[15] In a case-control sensitivity analysis with age matching, the resulting AUC dropped to 0.583.[16] Notably, a comprehensive

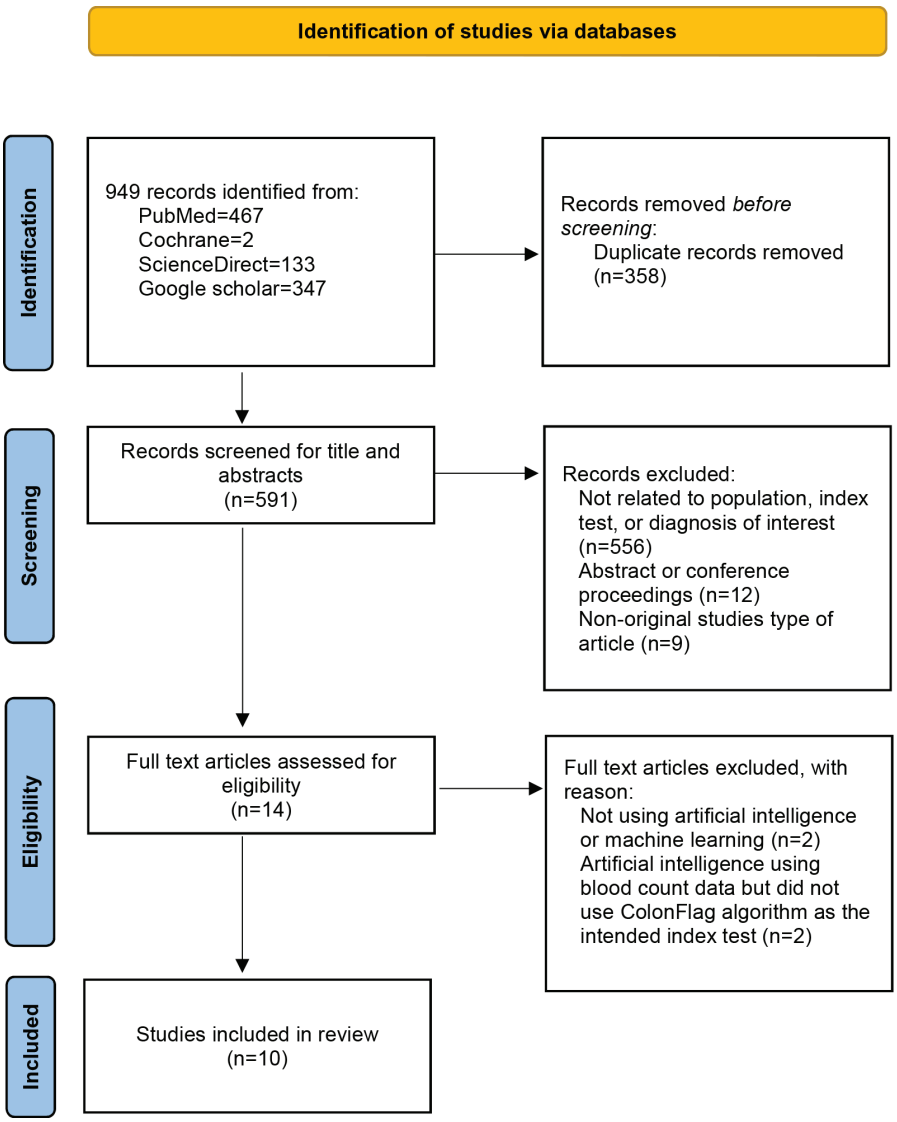

Figure 1: The flow diagram shows the study selection process following the PRISMA 2020 statement. We identified 949 records via online databases, of which 591 underwent screening based on title and abstract. Subsequently, 14 studies were evaluated for eligibility, with four studies excluded for not employing machine learning (n=2) or not utilizing ColonFlag (n=2). Finally, 10 studies were deemed suitable for inclusion in this systematic review.

model with an AUC of 0.78 outperformed the AUC of 0.65 from an age-only model. Gender-specific age-alone models yielded AUCs of 0.61 for men and 0.60 for women, considerably lower than the comprehensive model's AUC of 0.78.[18] Another study, initially showing an AUC of 0.736, dropped to 0.536 when age was excluded in case-control matching. Substituting any symptom for the ColonFlag score resulted in an AUC of 0.725.[19]

ColonFlag Score Cut-off and Odds Ratio

Birks and others used a ColonFlag risk score cutoff of 99.84, yielding an OR of 26.5 for CRC diagnosis.[16] Kinar and others reported a similar value (99.38, top one percentile), resulting in an OR of 21.8.[14] Goshen and others used a cutoff score of 99.6, yielding an OR of 33.3.[17] Schneider and others assessed ColonFlag with a cutoff score of ≥96, corresponding to a specificity of 97%, resulting in an OR of 17.7.[18] Holt and others demonstrated a PPV of 10% at a ColonFlag score cutoff >99.8.[19]

ColonFlag Performance Test Based on Various Subgroups Analysis

The studies analyzed various aspects, consistently reporting four: time window to CRC diagnosis (n=5), tumor location (n=4), CRC stage (n=3), and histopathological findings (n=4). ColonFlag performs better in shorter time windows, proximal tumor locations, advanced stages, and CRC compared to adenoma.

Time Window: Sensitivity during the initial 6 months surpassed the subsequent period for both the top one and three percentile groups across age groups.[14-16, 18]

Table 2: Characteristics of the studies included in the systematic review

Study	Study Design	Patient setting	Patient type	Patient population	Geographic location	Timing of data collection	Source of data	Number of subjects			Time window (months)	Mean Age (years)	Gender	
								Total	Cases	Control			Male (%)	Female (%)
Kinar, 2016[10]	Retrospective cohort+case-control	Primary care	Anyone	Inclusion: Age 50-75. Exclusion: Diagnosed with cancers other than CRC.	Israel and UK	Israel: January 2003-June 2011 UK: January 2003-May 2012	Maccabi Healthcare Services (MHS) and the UK Health Improvement Network (THIN)	Israel: 606,403 UK: 30,674	Israel: 3,315 UK: 5,061	UK: 25,613	3-6	Israel: 58.7 UK: 67.4	Israel: 46.4 UK: 49.2	Israel: 53.6 UK: 50.8
Kinar, 2017[14]	Retrospective cohort	Primary care	Anyone	Inclusion: Aged 50-75 on January 1, 2008, with≥1 FBC in the MHS during the six-month testing period. Exclusion: Cancer diagnosis before January 1, 2008, or no blood test during the testing period.	Israel	July 2007-December 2007	MHS and Israeli Cancer Registry	112,584	133	97	6	60.9	44	56
Birks, 2017[16]	Case-control+ retrospective cohort	Primary care	Anyone	Inclusion: Patients >40 years old with≥1 FBC in their record. Exclusion: <12 months registered, <2 years follow-up, prior CRC or precursors, hemoglobin gene defects.	UK	January 2000-April 2015	Clinical Practice Research Datalink (CPRD)	2,550,119	25, 430	NA	18-24	No CRC= 60.5±14.0 CRC=72.7± 10.5	NA	NA
Hornbrook, 2017[15]	Retrospective case-control	Unclear	Asymptomatic	Inclusion: Eligible CRC cases with CBC before diagnosis.	United States	1998-2013	Kaiser Permanente Northwest Region's Tumor Registry	17,095	900	16,195	0-6 and 6-12	58.0±11.8	44.1	55.9
Ayling, 2018[21]	Prospective (PGC) and Retrospective cohort (RLH)	Secondary care	Symptomatic	Inclusion: IDA patients referred to Plymouth Gastroenterology Clinic for FIT evaluation; IDA patients referred to Royal London Hospital for colonoscopy. Exclusion: Patients with non-anemia causes.	UK	March 2014-March 2017	Gastroenterology Clinic in Derriford Hospital, Plymouth, and Royal London Hospital medical records	592	NA	NA	NA	Plymouth Male: 70.9 Female: 69.1 London Male: 66 Female: 60	48.14	51.86
Goshen, 2018[17]	Cohort prospective	Secondary care	Anyone	Inclusion: Ages 50-75 in MHS with CBC recorded between October 2015 and December 2016, without a colonoscopy in the past 10 years, and no FIT in the 18 months before the index CBC.	Israel	October 2015-December 2016	MHS EMR and Israel Cancer Registry	79671	NA	NA	1-6 and 7-12	NA	NA	NA

				Exclusion: Referred for FIT in the last 3 months but not completed, and prior cancer diagnosis.										
Hilsden, 2018[6]	Retrospective cohort and case-control	Secondary care	Asymptomatic	Inclusion: Asymptomatic individuals, 50-75, had a screening colonoscopy from January 2013 to Jun 2015, with a CBC within a year, average CRC risk, and personal/family history of polyps/CRC. Exclusion: Positive FOBT, prior CRC, genetic predisposition, or no CBC within a year before colonoscopy.	Canada	January 2013-June 2015	Alberta Health Services Forzani and MacPhail Colon Cancer Screening	17676	NA	NA	NA	NA	46.6	53.4
Schneider, 2020[18]	Retrospective cohort+case-control	Unclear	Anyone	Inclusion: KPNC Health Plan members (1996-2015), aged ≥37, with ≥1 outpatient CBC. Cases: Ages 50-75, CBC, no prior/current CRC diagnosis, later diagnosed with CRC. Controls: Ages 50-75, randomly selected CBC, no CRC diagnosis. Both require a 6-month health plan membership and CBC before colonoscopy.	United States	January 199-December 2015	Kaiser Permanente Northern California Health Plan	308,721	6,019	302,702	0-6 and 6-12	58.5±7.7	48	52
Ayling, 2021[22]	Prospective cohort	Secondary care	Symptomatic	Inclusion: Patients over 40, on urgent pathway for suspected CRC on May 1, 2020. Exclusion: No final diagnosis, declined investigations, inaccessible, overseas, unable to attend, awaiting definitive investigations, and invalid FIT.	UK	May-October 2020	Barts Health NHS Trust	532	NA	NA	6	63	50.81	49.82
Holt, 2023[19]	Case-control+ retrospective cohort	Primary care	Anyone	Inclusion: Individuals >40 years, with one FBC in CPRD record (01/2000-28/04/2015) and associated ColonFlag score. Exclusion: <2 years follow-up, <12 months registered, or hemoglobin gene defect.	UK	January 2000-April 2015	CPRD and National Cancer Registry	1,893,641	18,130	270,750	18-24	NA	NA	NA

Table 3: Overall performance test of ColonFlag across the studies included in the systematic review

Study	Mean ColonFlag score	AUC (95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%)	NPV (%)	OR (95% CI)
Kinar, 2016[10] (Israel)		0.82±0.01*		88±2*			26±5*
Kinar, 2016 (UK)[10]		0.81		94±1			40±6
Kinar, 2017[14]	Female=59.3 Male=46.8		17.3				21.8 (13.8, 34.2)
Birks, 2017[16]	No CRC=51.5±29.0 CRC=79.1±19.5	0.776 (0.771, 0.781)	3.91 (3.40, 4.48)	82.73 (82.68, 82.78)	8.8	99.6	26.5 (23.3, 30.2)
Hornbrook, 2017[15]		0.8 (0.79, 0.82)					34.7 (28.9, 40.4)
Ayling, 2018[21]			52.4	71.3	6.3	97.6	
Goshen, 2018[17]			21.7				33.3 (22.6, 49.1)
Hilsden, 2018[6]	56.8±18.5		8.1 (6.4, 9.8)				5.1 (2.3, 8.9)
Schneider, 2020[18]		0.78 (0.77, 0.78)	35.4 (33.8, 36.7)				17.7 (16.5, 18.7)
Ayling, 2021[22]			88.24 (63.56, 98.54)	71.07 (66.94, 74.94)	9.1 (95% CI, 7.47, 11.15)	99.45 (95% CI, 98.03, 99.85)	
Holt, 2023[19]	No CRC=56.3 CRC=83.8	0.736 (0.715, 0.759)	10		2.6	99.9	1.05 (1.047, 1.053)**

AUC: Area Under the Curve; PPV: Positive predictive value; NPV: Negative predictive value; OR: Odds ratio; *Standard Deviation (SD value); **OR for a ColonFlag/unit increase

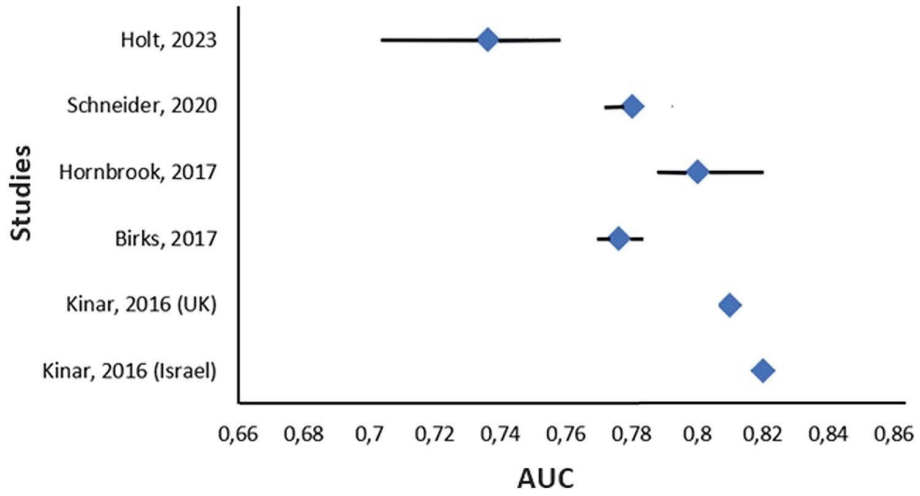

Figure 2: The AUC reported by five studies in six populations. AUC values ranged from 0.736 to 0.82 (blue diamonds) with their respective 95% confidence intervals (black horizontal lines).

Birks and others focused on the 18-24 month period in their primary analysis, with secondary analyses at intervals of 3-6, 6-12, 12-18, and 24-36 months before diagnosis, revealing declining AUC, sensitivity, and specificity with extended time windows.[16] Holt and others identified the 'pre-symptomatic' phase, indicating ColonFlag scores began rising around 3-4 years before diagnosis. Effective discrimination occurred in the 18-24 months preceding CRC diagnosis[19] (table 4).

Tumor Location: Three studies revealed the ColonFlag's capacity to detect CRC throughout the entire colon, especially excelling in proximal sites (table 5).[10, 15, 18] Its efficacy peaked in identifying cecal and ascending colon tumors, diminished in the transverse colon, and reached its lowest in the sigmoid colon and rectum. The OR in table 4 is the OR of the ColonFlag model for detecting tumors based on various locations in the colon. At a specificity of 99%, the OR for detecting cecal tumors was 93.4, significantly higher than the 10.2 OR for detecting rectal tumors.[15]

Stage: ColonFlag demonstrated higher sensitivity and OR in detecting advanced-stage CRC compared to early-stage cases (table 6).[6, 15, 18] The performance difference between the two groups: early-stage (0, 1, 2) and advanced stages (SEER 3, 4, 7) was statistically significant.[18]

Table 4: ColonFlag performance based on different time windows or time intervals from the blood count examination to the time of diagnosis

Study	AUC[a]	Sensitivity[b]	Others
Kinar, 2017[14]		0-6 months 1% percentile=25% 3% percentile=29% 6-12 months 1% percentile=9.5% 3% percentile=20%	
Birks, 2017[16]	3-6 months=0.844 6-12 months=0.813 12-24 months=0.791 18-24 months=0.776 24-36 months=0.751	3-6 months=14.2% 6-12 months=9.3% 12-24 months=6.2% 18-24 months=3.91% 24-36 months=2.5%	Specificity[b] 3-6 months=92.50% 6-12 months=86.98% 12-24 months=84.98% 18-24 months=82.73% 24-36 months=79.41%
Hornbrook, 2017[15]		0 - 180 days: 50-75 age group=34.5% 40-89 age group=39.9% 181-360 days: 50-75 age group=18.8% 40-89 age group=27.4%	
Schneider, 2020[18]		0-182 days=40.5% 183-365 days=25.0%	OR[c] 0-182 days=12.9 183-365 days=6.3
Holt, 2023[19]	Males 0-6 months=0.624 6-12 months=0.605 12-18 months=0.557 18-24 months=0.536 Females 0-6 months=0.624 6-12 months=0.624 12-18 months=0.567 18-24 months=0.536		

AUC: Area Under the Curve; OR: Odds Ratio; [a]Computed by plotting a Receiver Operating Characteristics (ROC) curve based on model predictions and true labels, then calculating the area under this curve. [b]Using the predicted outcomes from a binary classification model and comparing them to the true outcomes of the instances. [c]Calculated by comparing the odds of the event in the exposed group to the odds of the event in the unexposed group using data.

Table 5: ColonFlag performance based on different tumor locations across the colon and rectum

Study	Sensitivity[a]	OR[b]	Others
Kinar, 2016[10]			Specificity[a] Rectum=85.9% Left colon=87.4% Transverse colon=93.6% Right colon=96.1%
Hornbrook, 2017[15]		Cecum=93.4 Ascending=90.0 Transverse=51.1 Sigmoid=13.8 Rectum=10.2	
Hilsden, 2018[6]	Ascending/cecum=10.8% Other=13.2%	Ascending/cecum=2.6 Other=3	
Schneider, 2020[18]	Distal=27.3% Proximal=51.8%	Distal=12.1 Proximal=34.7	AUC[c] Distal=0.74 Proximal=0.86

AUC: Area Under the Curve; OR: Odds Ratio; [a]Using the predicted outcomes from a binary classification model and comparing them to the true outcomes of the instances. [b]Calculated by comparing the odds of the event in the exposed group to the odds of the event in the unexposed group using data. [c]Computed by plotting a Receiver Operating Characteristics (ROC) curve based on model predictions and true labels, then calculating the area under this curve.

Histopathological Findings: ColonFlag excelled in detecting CRC compared to its performance in identifying both CRC and high-risk adenomas.[21, 22] Two studies demonstrated its ability to identify high-risk precancerous conditions, including advanced adenomatous polyps (table 7). However, ColonFlag exhibited lower performance in identifying any adenomatous polyps than its CRC detection performance.[6, 18]

Table 6: ColonFlag performance based on CRC stage

Study	Sensitivity[a]	OR[b]	AUC[c]
Hornbrook, 2017[15]		In situ=12.1 I=16.7 II=54.1 III=57.3 IV=40.4	
Hilsden, 2018[6]	I/II=10.7% III/IV=18.3%	I/II=2.3% III/IV=4.6%	
Schneider, 2020[18]	Early stage (0, I, II)=28.8% Advanced stage (III, IV, VII)=43.4%		Early stage (0, I, II)=0.75 Advanced stage (III, IV, VII)=0.82

[a]Using the predicted outcomes from a binary classification model and comparing them to the true outcomes of the instances. [b]Calculated by comparing the odds of the event in the exposed group to the odds of the event in the unexposed group using data. [c]Computed by plotting a Receiver Operating Characteristics (ROC) curve based on model predictions and true labels, then calculating the area under this curve.

Table 7: ColonFlag performance based on histopathology findings

Study	Sensitivity[a]	Specificity[a]	PPV[b]	NPV[b]	OR[c]	AUC[d]
Ayling, 2018	CRC=52.4% CRC+HRA=46.9%	CRC=71.3% CRC+HRA=72%	CRC=6.3% CRC+HRA=13.1%	CRC=97.6% CRC+HRA=93.8%		
Hilsden, 2018					CRC=5.1 Advanced adenoma/SSP=2.0 Non-advanced adenoma/SSP=1.7 Non-neoplastic polyp=1.2	
Schneider, 2020	CRC=35.4% Adenoma=3.8%				CRC=17.7% Adenoma=1.3%	CRC=0.78 Adenoma=0.57
Ayling, 2021	CRC=81.8% CRC+HRA=42.8%	CRC=73.5% CRC+HRA=73.4%	CRC=8.3% CRC+HRA=13.7%		CRC=99.3% CRC+HRA=92.8%	

HRA: High-risk adenoma; OR: Odds ratio; SSP: Sessile serrated polyp; [a]Using the predicted outcomes from a binary classification model and comparing them to the true outcomes of the instances. [b]Using the predicted outcomes from ColonFlag and comparing them to the true outcomes of the instances. [c]Calculated by comparing the odds of the event in the exposed group to the odds of the event in the unexposed group using data. [d]Computed by plotting a Receiver Operating Characteristics (ROC) curve based on model predictions and true labels, then calculating the area under this curve.

Table 8: Risk of bias assessment

No	Study	Risk of Bias (ROB)				Applicability			Overall	
		Participants	Predictors	Outcome	Analysis	Participants	Predictors	Outcome	ROB	Applicability
1	Kinar, 2016[10]	Low	Low	Low	High	Low	Low	Low	High	Low
2	Kinar, 2017[14]	Low	Low	Low	Unclear	Low	Low	Low	Unclear	Low
3	Birks, 2017[16]	Low	Low	Low	Low	Low	Low	Low	Low	Low
4	Hornbrook, 2017[15]	Low	Low	Low	Low	Low	Low	Low	Low	Low
5	Ayling, 2018[21]	Low	Low	Low	Low	Low	Low	Low	Low	Low
6	Goshen, 2018[17]	Low	Low	Low	High	Low	Low	Low	High	Low
7	Hilsden, 2018[6]	Low	Low	Low	High	Low	Low	Low	High	Low
8	Schneider, 2020[18]	Low	Low	Low	Low	Low	Low	Low	Low	Low
9	Ayling, 2021[22]	Unclear	Low	Low	High	Low	Low	Low	High	Low
10	Holt, 2023[19]	Low	Low	Low	Low	Low	Low	Low	Low	Low

Risk of Bias: Four studies were deemed high-risk, and one had unclear bias (table 8). Three studies inadequately addressed missing data, omitting many participants due to incomplete datasets.[6, 10, 14] Another study lacked information on handling missing data appropriately.[14] Most studies used retrospective cohort and case-control designs, with only two using a prospective cohort approach with a limited number of subjects.[21, 22]

Discussion

ColonFlag utilizes a machine learning algorithm, employing a random forest model with decision trees and cross-validation, incorporating age, gender, and 20 CBC parameters.[10] It generates scores on a 1 to 100 scale, reflecting CRC risk based on fluctuations in the CBC levels.[14] The algorithm identified red blood cell (RBC) and Hb-related factors as crucial for case identification, with platelet-related factors also significant, and white blood cell-related factors having a smaller impact.[23] ColonFlag was able to identify CRC in asymptomatic patients, even without anemia.[24] However, the reported sensitivity of ColonFlag exhibits considerable variation, spanning from 3.91% to 35.4%. This broad range, especially when considering the lower limit, suggests a significant risk of overlooking individuals at a high risk of CRC. The notable decrease in sensitivity poses a concern, markedly reducing the tool's practical efficacy in clinical settings. The majority of the studies used a retrospective design, an absence of comparable diagnostic data (e.g., colonoscopy) for all cancer controls, and an inability to discern specific reasons for blood testing.

Age was the primary predictive factor, evident in decreased AUC when age was matched in a case-control sensitivity analysis.[15, 16, 18] Despite the value of age in assessing CRC risk, combining ColonFlag score or symptoms with age and gender did not significantly enhance predictive capability compared to using age and gender alone. This implies ColonFlag's discriminative performance heavily relies on age rather than CBC changes.[19] Many studies use a >99 cutoff for a positive ColonFlag test, yielding notable OR for CRC detection, supporting further evaluation for scores exceeding this threshold.[25] Implementing one percentile cutoffs semiannually or three percentile cutoffs annually could offer comparable benefits.[14]

The included studies span across various countries and populations, revealing variations in ColonFlag's performance across these diverse demographic groups. The studies exhibit diverse study designs, ranging from retrospective, prospective cohort to case-control studies. They involved populations with different eligibility criteria and characteristics, some with limitations related to the quality and completeness of data, comparable diagnostic data, and potential inaccuracies in datasets. These diversities may introduce methodological variations and affect the synthesis of results.

The predictive performance of ColonFlag improves with a shorter time interval between CBC and diagnosis. It effectively discriminates between CRC patients and controls 18-24 months before diagnosis, without evident symptoms except for rectal bleeding.[19] This highlights the importance of investigating rectal bleeding for swift referral. The ColonFlag score shows an upward trend, diverging 3-4 years before diagnosis, within the pre-symptomatic phase. One-third of individuals with thrombocytosis and cancer had no documented cancer-related symptoms.[26] Early CRC detection is emphasized by monitoring CBC indices before symptoms appear.[23]

ColonFlag identifies CRC across the entire colon, excelling in proximal areas, and enhancing noninvasive screening tools for right-sided colon cancer such as FOBT or FIT.[27] The varying specificity in different colonic regions aligns with reduced anemia prevalence toward the rectum, underscoring the clinical significance of ColonFlag, especially for right-sided CRC detection.[28, 29] Lower Hb levels correlate with tumors closer to the colon's proximal region.[30] Studies noted a significant Hb decrease in patients with proximal colon tumors compared to distal colon and rectum tumors.[30-32] Disparities between proximal and distal CRC may be due to bleeding mechanisms, but other factors such as immunological processes should also be considered.[30]

Blood loss leading to iron deficiency is a primary cause of anemia in CRC patients.[33] Anemia in CRC often presents as microcytic, especially in advanced stages.[32] ColonFlag showed better performance in CRC cases than adenoma cases. Evaluating pre-cancerous lesions, the highest test performance was seen in advanced adenoma, while non-neoplastic polyps had the least robust performance. Iron deficiency and ferritin significantly decreased in CRC,[34] reinforcing the link between CRC and anemia. Prior studies found notable differences in 16 out of 23 blood cell parameters for CRC compared to adenoma and polyp,[35] consistent with a meta-analysis of CBC tests in CRC detection.[23] All eight indicators related to RBC displayed significant distinctions between CRC, adenoma, and polyp cases.[35] These outcomes align with a recent study where Hb, MCV, and serum ferritin levels decreased before a CRC diagnosis.[36]

Inflammation plays a crucial role in carcinogenesis,[37, 38] with chronic inflammation influencing every tumor development phase. Studies demonstrate the diagnostic potential of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV),[39-42] achieving an AUC of 0.904.[43] These parameters could potentially enhance the ColonFlag algorithm's performance, enabling it to identify subtle patterns, correlations, and trends that might have otherwise gone unnoticed.

To the best of our knowledge, this systematic review is the first to evaluate ColonFlag's efficacy comprehensively. The limitation of the study was its reliance on published data, which could introduce bias due to unreported outcomes. Additionally, the exclusion of articles in languages other than English was a limitation. Since the study was not a meta-analysis and lacked a comprehensive summary, no data analysis was undertaken to evaluate publication bias.

Conclusion

While ColonFlag exhibits low sensitivity compared to established screening methods such as the FIT or colonoscopy, its potential in detecting CRC before clinical diagnosis suggests an opportunity for identifying more cases than regular screening alone. The ColonFlag model does not serve as a substitute for traditional screening programs. Further prospective evaluation is warranted to assess the algorithm's feasibility, efficiency, and accuracy across diverse clinical settings. Moreover, studies are needed to evaluate how additional medical records or routine laboratory data influence test performance.

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Authors' Contribution

RD.P: Study concept, study design, project administration, data curation, drafting, and reviewing the manuscript; SA.S: Study concept, study design, project administration, data curation, drafting, and reviewing the manuscript; NN.H: Study concept, study design, data curation, drafting, and reviewing the manuscript; TA.S: Study concept, study design, data curation, drafting, and reviewing the manuscript; M.A; Study concept, study design, data curation, drafting, and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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