RESEARCH ARTICLE

Diagnostic Value of Rectal Bleeding in Predicting Colorectal Cancer: a Systematic Review

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Abstract

This study aimed at summarizing published study findings on the diagnostic value of rectal bleeding (RB) and informing clinical practice, preventive interventions and future research areas. We searched Medline and Embase for studies published by September 13, 2013 examining the risk of colorectal cancer in patients with RB using highly inclusive algorithms. Data for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and positive predictive value (PPV) of RB were extracted by two researchers and analyzed applying Meta-Disc (version 1.4) and Stata (version 11.0). Methodological quality of studies was assessed according to QUADAS. A total of 38 studies containing 5,626 colorectal cancer patients and 73,174 participants with RB were included. The pooled sensitivity and specificity were 0.47 (95% CI: 0.45-0.48) and 0.96 (95% CI: 0.96-0.96) respectively. The overall PPVs ranged from 0.01 to 0.21 with a pooled value of 0.06 (95% CI: 0.05-0.08). Being over the age of 60 years, change in bowel habit, weight loss, anaemia, colorectal cancer among first-degree relatives and feeling of incomplete evacuation of rectum appeared to increase the predictive value of RB. Although RB greatly increases the probability of diagnosing colorectal cancer, it alone may not be sufficient for proposing further sophisticated investigations. However, given the high specificity, subjects without RB may be ruled out of further investigations. Future studies should focus on strategies using RB as an "alarm" symptom and finding additional indications to justify whether there is a need for further investigations.

Keywords: Colorectal cancer - rectal bleeding - predictive - symptoms

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Introduction

Colorectal cancer is one of the most common cancers all over the world; GLOBOCAN 2008 reported that there were 1.2 million new cancer cases and 0.6 million cancer deaths worldwide (Jemal et al., 2011). According to Keane et al, the five year survival rate for colorectal cancer patients at different stages varied substantially, ranging from 93.2% for stage I (tumor invades mucosa or submucosa) patients to 6.6% for stage IV (distant spread) patients. Timely and efficient referral leading to early diagnosis of colorectal cancer may contribute to improved survival (Gondos et al., 2008); symptoms indicative of a high risk of colorectal cancer must be recognized by both patients and outpatient clinicians. The UK guidelines (National Institute for Health and Clinical Excellence) recommend that patients with ''alarm'' features, such as rectal bleeding, weight loss, change of bowel habit to looser or more frequent stools, a palpable right-sided abdominal mass or iron deficiency anaemia are required to be seen by a specialist for further investigation within 2 weeks of referral (Olde Bekkink et al., 2010). However, these symptoms are also common among people with benign conditions; clinicians have to select patients at higher risk for investigation to lower the false positives to the maximum extent.

Rectal bleeding (RB) is a relatively specific early symptom of colorectal cancer. Retrospective studies showed that 15.6-74.3% colorectal cancer patients have had the symptom before diagnosis (Hamilton et al., 2009; Schoppmeyer et al., 2009; Wang et al., 2010; Harmston et al., 2010; Thompson et al., 2011; Pedersen et al., 2013). Ford et al conducted a meta-analysis of 14 studies in 2008, the pooled sensitivity and specificity were 64% and 52% respectively, and the specificity reached 96% in patients with dark red RB. Olde Bekkink et al concluded that age ≥60 years (pooled positive likelihood ratio (PLR):2.79), severe anaemia (pooled PLR:3.67), weight loss (pooled PLR:1.89) and change in bowel habit (pooled PLR:1.92) raise the probability of colorectal cancer in patients with RB. Jellema et al found patients with dark blood or blood mixed with stool have significantly higher risk than those without the symptoms. A recent review examining the diagnostic value of symptoms for colorectal cancer in primary care by Astin et al showed positive predictive value (PPV) for RB ranged from 2.2% to 16% in the 13 included studies and the pooled PPV reached 8.1% in those aged ≥50 years, the paper also revealed higher risk when RB combined with other symptoms (e.g., weight loss and change in bowel habit, the pooled PLR were 1.9 and 1.8 respectively). Although these reviews summarized the evidences of diagnostic value of RB, some of them failed

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Table 1. Characteristics of Studies

First author	Year of publication	Country	Setting	Age of participants	Further investigation used
Farrands	1985	UK	Primary care	>=30	Barium enema, colonoscopy
Tate	1988	UK	Primary care	Median age: 65	Colonoscopy
Mant	1989	Australia	Primary care	Mean age: 57.7	Colonoscopy, sigmoidoscopy, barium enema
Brenna	1990	Norway	Primary care	-	Colonoscopy
Zarchy	1991	US	Primary care	Mean age: 57	Sigmoidoscopy, barium enema
Berkowitz	1993	South Africa	Secondary care	Median age: 67	Colonoscopy
Neugut	1993	US	Population-based	>=35	Colonoscopy
Steine	1994	Norway	Primary care	Mean age: 54	Barium enema
Fijten	1995	Netherland	Primary care	Mean age: 42	Sigmoidoscopy, barium enema, colonoscopy
Metcalf	1996	UK	Primary care	Median age: 58	Colonoscopy
Norrelund S1	1996	Denmark	Primary care	>=40	Barium enema, colonoscopy
Norrelund S2	1996	Denmark	Primary care	>=40	Barium enema, colonoscopy
Helfand	1997	Portland	Primary care	Mean age: 55.3	Rigid sigmoidoscopy, barium enema
Cheong	2000	Malaysia	Secondary care	Mean age: 51.7	Colonoscopy
Wauters	2000	Brussels	Primary care	-	-
Morini	2001	Italy	Population-based	Mean age: 56	Colonoscopy
Selvachandran	2002	UK	Primary care	-	Endoscopy
Tan	2002	Malaysia	Secondary care	Mean age: 55.7	Colonoscopy
Pepin	2002	US	Secondary care	Mean age: 61	Sigmoidoscopy, colonoscopy
de Bosset	2002	Switzerland	Secondary care	Mean age: 58	Colonoscopy
Panzuto	2003	Italy	Primary care	Median age: 61	Colonoscopy, barium enema
Ahmed	2005	UK	Primary care	>=50	Colonoscopy
Ellis	2005	UK	Primary care	>34	Flexible sigmoidoscopy
Heintze	2005	Germany	Primary care	-	Colonoscopy, rectoscopy, sigmoidoscopy
Sánchez	2005	Spain	Primary care	Mean age: 49.2	Colonoscopy
du Toit	2006	UK	Primary care	>=45	Sigmoidoscopy, barium enema, colonoscopy
Robertson	2006	UK	Primary care	Mean age: 52	Sigmoidoscopy
Thompson	2007	UK	Secondary care	-	Sigmoidoscopy, barium enema, colonoscopy
Bjerregaard	2007	Denmark	Primary care	Median age: 61	Colonoscopy, flexible sigmoidoscopy
Jones	2007	UK	Primary care	-	-
Thompson	2008	UK	Primary care	Median age: 61	Sigmoidoscopy, whole colonic imaging
Bafandeh	2008	Iran	Secondary care	Mean age: 42.7	Colonoscopy
Nikpour	2008	Iran	Secondary care	Mean age: 43.6	Flexible sigmoidoscopy, colonoscopy
Meng	2009	China	Population-based	>=40	Colonoscopy
Navarro	2009	Spain	Population-based	>=50	Colonoscopy
Koning	2010	Netherlands	Secondary care	Mean age: 67.3	Endoscopy
Rajasekhar	2012	UK	Population-based	-	Colonoscopy
Hippisley-Cox	2012	UK	Primary care	>=30	Colonoscopy, barium enema

to take all the then existing qualified studies into analysis (Rubin et al., 2009); besides, several new and large sample size studies conducted in UK, Spain, Iran and China have been published recently. Thus, an updated comprehensive assessment may provide more accurate and detailed information on relationship between colorectal cancer and RB and its most common co-occurring symptoms.

Materials and Methods

Data sources and search strategy

We utilized two approaches to locate as many relevant papers as possible. First, we searched the literatures in Medline and Embase available by September 13, 2013 using the following search terms "(Colorectal or rectal or colon) and (cancer or carcinoma or tumor) and (rectal bleeding or hemafecia or hematochezia or blood in the stool or blood in stool)". Second, we searched the references of relevant review papers for additional articles. This process was conducted iteratively until no new papers were identified.

Inclusion criteria

The inclusion criteria were as follows: 1) articles written in English; 2) studies investigating the relationships between symptoms and colorectal cancer that include RB; 3) studies using prospective cohort or cross-sectional designs and 4) studies providing at least the numbers of patients with RB and colorectal cancer.

Data extraction and analysis

Descriptive data about the included studies were extracted from the articles identified using a data-extracting form, including first author, year of publication, country of study conducted, settings of participants, age of subjects, investigations used to diagnose cancer, true positive (TP), false positive (FP), false negative (FN), true negative (TN). All data extraction was performed by two researchers independently and discrepancies were solved by consensus. Sensitivity, specificity, PLR and NLR were calculated by Meta-Disc (version 1.4), Stata (version 11.0) was used to estimate the PPV (PPV here represents the probability of colorectal cancer in patients with RB). Methodological quality of studies was assessed according to QUADAS.

Results

Studies selected

A total of 7594 articles were retrieved from Medline

Table 2. Sensitivity, Specificity and Positive Likelihood Ratios of Rectal Bleeding

First author & year of publication	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	+ LR (95% CI)	- LR (95% CI)
Farrands 1985	5	62	8	64	0.38 (0.14-0.68)	0.51 (0.42-0.60)	0.78 (0.38-1.59)	1.21 (0.76-1.92)
Tate 1988	9	40	5	76	0.64 (0.35-0.87)	0.66 (0.56-0.74)	1.86 (1.17-2.97)	0.55 (0.27-1.11)
Mant 1989	16	129	-	-	-	-	-	-
Brenna 1990	23	171	22	617	0.51 (0.36-0.66)	0.78 (0.75-0.81)	2.36 (1.72-3.23)	0.62 (0.46-0.84)
Zarchy 1991	8	222	15	549	0.35 (0.16-0.57)	0.71 (0.68-0.74)	1.21 (0.68-2.14)	0.92 (0.68-1.24)
Berkowitz 1993	11	112	3	275	0.79 (0.49-0.95)	0.71 (0.66-0.76)	2.71 (1.98-3.72)	0.30 (1.11-0.82)
Neugut 1993	74	787	17	1155	0.81 (0.72-0.89)	0.59 (0.57-0.62)	2.01 (1.79-2.24)	0.31 (0.20-0.48)
Steine 1994	17	271	37	1498	0.31 (0.20-0.46)	0.85 (0.83-0.86)	2.06 (1.37-3.09)	0.81 (0.67-0.97)
Fijten 1995	9	260	-	-	-	-	-	-
Metcalf 1996	8	91	-	-	-	-	-	-
Norrelund S1 1996	32	176	-	-	-	-	-	-
Norrelund S2 1996	13	95	12	89	0.52 (0.31-0.72)	0.48 (0.41-0.56)	1.01 (0.67-1.51)	0.99 (0.64-1.53)
Helfand 1997	13	188	-	-	-	-	-	-
Cheong 2000	11	77	11	276	0.50 (0.28-0.72)	0.78 (0.74-0.82)	2.29 (1.44-3.64)	0.64 (0.42-0.97)
Wauters 2000	27	359	79	83425	0.25 (0.18-0.35)	1.00 (1.00-1.00)	59.45 (42.24-83.65)	0.75 (0.67-0.84)
Morini 2001	28	208	21	429	0.57 (0.42-0.71)	0.67 (0.64-0.71)	1.75 (1.34-2.29)	0.64 (0.46-0.88)
Selvachandran 2002	82	1505	13	668	0.86 (0.78-0.93)	0.31 (0.29-0.33)	1.25 (1.14-1.36)	0.45 (0.27-0.74)
Tan 2002	33	121	25	306	0.57 (0.43-0.70)	0.72 (0.67-0.76)	2.01 (1.53-2.63)	0.60 (0.44-0.81)
Pepin 2002	2	66	6	489	0.25 (0.03-0.65)	0.88 (0.85-0.91)	2.10 (0.62-7.13)	0.85 (0.57-1.27)
de Bosset 2002	25	231	26	862	0.49 (0.35-0.63)	0.79 (0.76-0.81)	2.32 (1.71-3.14)	0.65 (0.49-0.85)
Panzuto 2003	18	96	23	143	0.44 (0.28-0.60)	0.60 (0.53-0.66)	1.09 (0.75-1.60)	0.94 (0.70-1.25)
Ahmed 2005	44	281	42	196	0.51 (0.40-0.62)	0.41 (0.37-0.46)	0.87 (0.70-1.08)	1.19 (0.93-1.51)
Ellis 2005	11	308	-	-	-	-	-	-
Heintze 2005	17	405	-	-	-	-	-	-
Sánchez 2005	6	120	-	-	-	-	-	-
du Toit 2006	15	250	23	2601	0.39 (0.24-0.57)	0.91 (0.90-0.92)	4.50 (2.98-6.79)	0.66 (0.51-0.86)
Robertson 2006	22	582	-	-	-	-	-	-
Thompson 2007	333	5079	134	2983	0.71 (0.67-0.75)	0.37 (0.36-0.38)	1.13 (1.07-1.20)	0.78 (0.67-0.90)
Bjerregaard 2007	83	1090	39	960	0.68 (0.59-0.76)	0.47 (0.45-0.49)	1.28 (1.13-1.45)	0.68 (0.52-0.89)
Jones 2007	338	14951	-	-	-	-	-	-
Thompson 2008	624	9841	322	5646	0.66 (0.63-0.69)	0.36 (0.36-0.37)	1.04 (0.99-1.09)	0.93 (0.85-1.02)
Bafandeh 2008	4	138	12	326	0.25 (0.07-0.52)	0.70 (0.66-0.74)	0.84 (0.36-1.99)	1.07 (0.80-1.43)
Nikpour 2008	26	376	-	-	-	-	-	-
Meng 2009	5	130	16	709	0.24 (0.08-0.47)	0.85 (0.82-0.87)	1.54 (0.70-3.36)	0.90 (0.71-1.15)
Navarro 2009	18	2834	10	6987	0.64 (0.44-0.81)	0.71 (0.70-0.72)	2.23 (1.69-2.94)	0.50 (0.31-0.83)
Koning 2010	5	156	-	-	-	-	-	-
Rajasekhar 2012	48	351	39	318	0.55 (0.44-0.66)	0.48 (0.44-0.51)	1.05 (0.86-1.29)	0.94 (0.74-1.21)
Hippisley-Cox 2012	841	28111	1762	1204833	0.32 (0.31-0.34)	0.98 (0.98-0.98)	14.17 (13.39-15.00)	0.69 (0.67-0.71)
Pooled value	2904	70270	2722	1316480	0.47 (0.45-0.48)	0.96 (0.96-0.96)	1.97 (1.24-3.12)	0.76 (0.70-0.83)

TP, true positive; FP, false positive; FN, false negative; TN, true negative; +LR, positive likelihood ratio; -LR, negative likelihood ratio

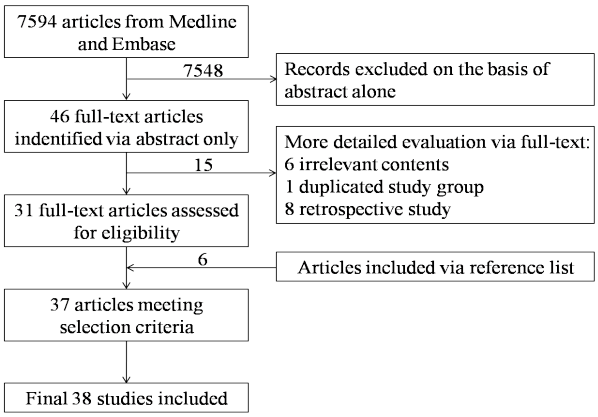

Figure 1. Flow Diagram of Study Selection Process

and Embase, 7548 records were excluded on the basis of abstract alone. The full texts of the remaining 46 articles were retrieved for more detailed evaluation. Of these, 6 articles were excluded for irrelevant contents, 1 was excluded for duplicated study group and 8 were excluded for study design (i.e., retrospective study). Additional 6 articles were incorporated via reference lists and finally 37 articles containing 38 studies were included (Figure 1).

Study characteristics

The 37 articles documented 35 prospective cohort and 3 cross-sectional studies containing 5626 colorectal cancer patients and 73174 participants with RB from 16 countries including UK (n=13), US (n=3), Denmark (n=3), Netherland (n=2), Malaysia (n=2), Spain (n=2), Italy (n=2), Norway (n=2), Iran (n=2), Australia (n=1), South Africa (n=1), China (n=1), Brussels (n=1), Portland (n=1), Germany (n=1) and Switzerland (n=1). The sample size of the studies ranged from 99 to 1235547. Twenty four studies recruited participants at primary care settings, 9 at secondary hospitals and 5 from communities. The mean/median age of participants ranged from 40 to 67.3. Eighteen studies utilized single verification tests

Table 3. Diagnostic Value of Rectal Bleeding Combined with 2 Additional Symptoms

First author & year of publication	Symptoms	No. with symptoms	No. with colorectal cancer	Sensitivity (%)	Specificity (%)	PPV (%)
Ellis and Thompson 2005	RB+A+C	67	6	55	44	9
Thompson 2007	RB+A+C	1169	101	21.6	86.8	8.6
Thompson 2007	RB+C+PS	1301	101	21.6	85.1	7.8
Thompson 2008	RB+A+C	2687	181	19	83.8	6.7

A, abdominal pain; C, change in bowel habit; PS, perianal symptoms

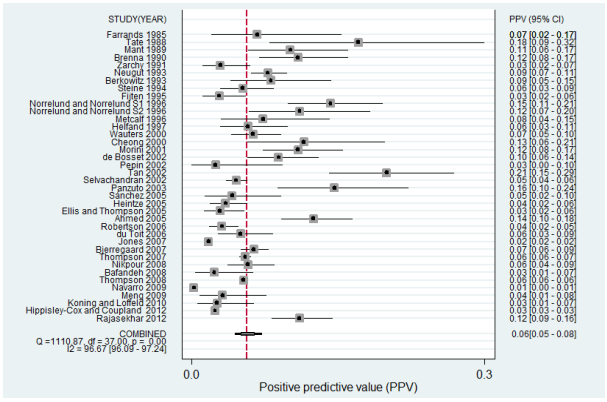

Figure 2. Overall PPVs of Patients with Rectal Bleeding

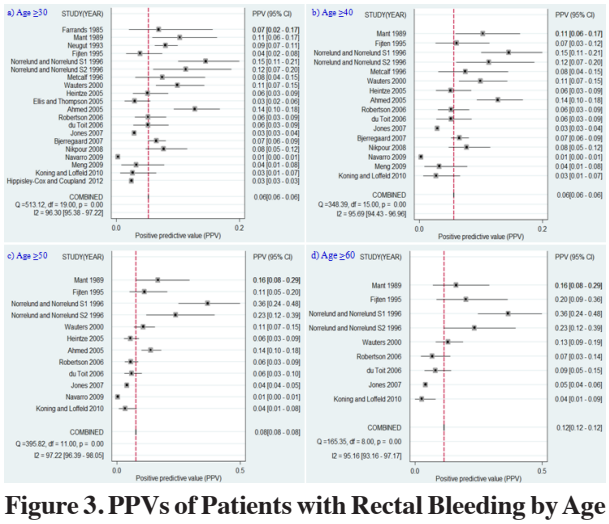

Figure 3. PPVs of Patients with Rectal Bleeding by Age

and others employed different tests across study sites. The most commonly used reference standards were colonoscopy (n=30), flexible/rigid sigmoidoscopy (n=15) and barium enema (n=12). Summary characteristics of studies are presented in Table 1 and 2.

Diagnostic value of RB

In the 26 studies with data enabling the construction of 2 × 2 tables, sensitivity ranged from 0.24 to 0.86, specificity from 0.31 to 1.00, PLRs from 0.78 to 59.45 and NLRs from 0.30 to 1.21; The pooled values of the above indicators were 0.47 (95% CI: 0.45-0.48), 0.96 (95% CI: 0.96-0.96), 1.97 (95% CI: 1.24-3.12) and 0.76 (95% CI: 0.70-0.83) respectively (Table 2). The overall PPVs ranged from 0.01 to 0.21 with a pooled value of 0.06 (95% CI: 0.05-0.08). When stratified by age, pooled PPVs were relatively low in patients over 30 and 40 years (only 0.06) and rose substantially in patients aged over 50 and 60 subjects, reached 0.08 and 0.12 respectively (Figure 2). Seven study showed modest evidence of male

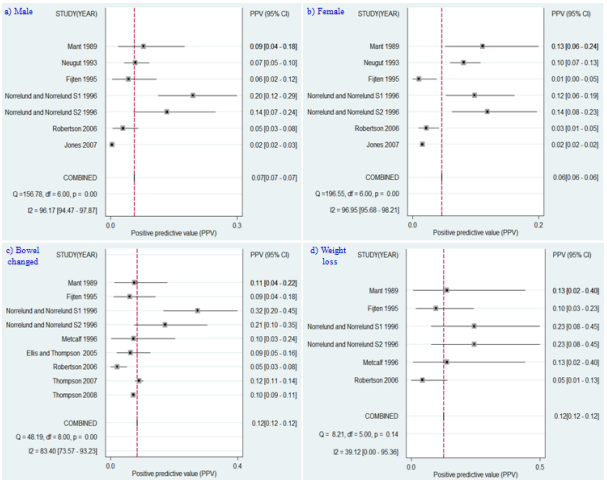

Figure 4. PPVs of Patients with Rectal Bleeding by Gender and Combined Symptoms

predominance with the pooled PPVs of 0.07 versus 0.06 (Figure 3).

Some single symptoms or history seemed to raise the PPV of RB. When combined with abdominal pain (9 studies), change in bowel habit (9 studies) and weight loss (6 studies), the pooled PPVs were 0.07, 0.12 and 0.12 respectively (Figure 4). Mant found that combined with diagnosis of colorectal cancer among first-degree relative(s) and feeling of incomplete evacuation of rectum, the PPVs were 0.1 and 0.12 respectively. Fijten et al even reported a PPV as high as 0.21 when combined with anaemia. However, in 3 studies with data on diagnosed number of colorectal cancer cases among patients with RB and perianal symptoms, the pooled PPV was only 3.6%. Other less studied symptoms including nausea, decreased appetite, pain on defecation, etc. did not show any combined effect in improving the diagnostic value of RB.

Three studies examined the diagnostic value of RB in combination with 2 additional symptoms. In 2005, Ellis and Thompson performed a study at primary care settings and documented 9% prevalence of colorectal cancer among patients with RB as well as change in bowel habit and abdominal pain. In 2007, Thompson et al conducted a study at single surgical outpatient clinic and reported that 7.8% of the patients with RB, change in bowel habit and perianal symptoms were diagnosed with colorectal cancer; and 8.6%, among patients with RB, change in bowel habit and abdominal pain. In 2008, Thompson's group carried out a study at tertiary hospitals and found 181 (6.7%) colorectal cancer patients among 2697 subjects with RB, change in bowel habit and abdominal pain (Table3). These studies also enable comparison between PPVs of single symptom (RB by its own), 2 symptoms (RB combined

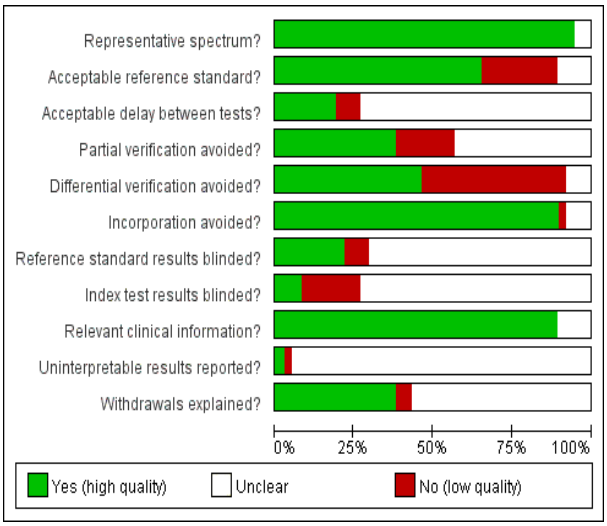

Figure 5. Quality of Studies

with another common symptom) and 3 symptoms (RB combined with 2 additional common symptoms). For the 2005 study, the highest 3-symptom PPV was 9.0%; while the 2-symptom PPV, 9.2% and the single-symptom PPV, 4.1%. For the 2007 study, the highest 3-symptom PPV was 8.6%; while the 2-symptom PPV, 12.1% and the single-symptom PPV, 6.2%. For the 2008 study, the highest 3-symptom PPV was 6.7%; while the 2-symptom PPV, 10.2% and the single-symptom PPV, 6.0%.

Quality of studies

As shown in Figure 5, included studies scored differently on the QUADAS quality indicators. They performed relatively better on representative spectrum of patients, reference standard independent of RB and compatible clinical data for test interpretation as well as utilization; but poor on patients receiving the same reference standard. For example, only 18 studies applied the same reference standard to all participants. Commonly missing information key to result interpretation and quality assessment included time period between RB and diagnosis tests, blinding of outcome assessment and reporting of uninterpretable test results.

Discussion

Although this review did not show high sensitivity of RB for the diagnosis of colorectal cancer (only 47 out of 100 colorectal cancer patients could be rightly identified), the specificity of this symptom reached 0.96. This suggests that RB alone may not be adequate for proposing further sophisticated investigations; clinicians should take other symptoms/history into consideration. However, given the high specificity, subjects without RB may be ruled out of further investigations. The overall PPV of RB was 0.6 meaning 6 out of 100 patients with RB were true colorectal cancer patients. This is over a hundred times the risk of colorectal cancer among general population. So clinicians should be sufficiently alerted to seek further indications, when encountered with RB, to rule out the possibility of colorectal cancer. Age is perhaps one of such indications. RB patients aged more than 60 years had a 0.12 probability of identifying colorectal cancer, nearly two-folds the possibility of all-age patients. Gender seemed to have only modest diagnostic value; male patients with RB were only 1% more likely to be diagnosed with colorectal cancer compared with female patients. The PPVs of RB co-presented with other symptoms varied widely. Change in bowel habit, weight loss, anaemia, first-degree relative(s) with colorectal cancer and feeling of incomplete evacuation of rectum seem to be the most important symptoms. Other conventionally stated alarm symptoms, such as abdominal pain, have modest diagnostic value. Unfortunately, symptom combinations may not necessarily increase the diagnostic values, the PPVs of some 2-symptom combinations were lower than that of single symptoms (e.g., 3.6% for RB combined with perianal symptoms versus 6% for RB alone) and the PPVs of some 3-symptom combinations were lower than that of 2-symptom combinations (e.g., 8.6% for RB combined with change in bowel habit and abdominal pain versus 12% for RB combined with change in bowel habit). These findings suggest that clinicians should be careful in interpreting and using combinations of symptoms especially combinations with relatively less specific symptoms.

Compared with previous reviews, our pooled analysis revealed moderately lower sensitivity and much higher specificity than that by Ford and colleagues (47% and 96% versus 64% and 52%), moderately higher sensitivity and similar specificity than that by Astin's group (47% and 96% versus 17% and 98%) and similar sensitivity, much higher specificity by Jellema et al (47% and 96% versus 44% and 66%). These may due mainly to the differences in the subjects included in the studies between the reviews. In our review, 63.2% of studies were performed at primary care settings; and 23.7%, at secondary hospitals; 13.2%, in communities. Whereas 73.3% studies included in Ford and colleagues' review were conducted at secondary hospitals. In terms of PPVs of RB alone and RB combined with other symptoms among discernable subgroups of subjects, our estimation was generally consistent with previous reviews. In particular, our review confirmed previous findings that patients presenting RB and a change in bowel habit without perianal symptoms are at highest risk of colorectal cancer and that excluding change in bowel habit from RB combined with perianal symptoms decreases the risk of colorectal cancer (Olde Bekkink et al., 2010).

The diagnostic value of RB and its usage is far from clear though great efforts had been invested on the issue. Given that RB alone substantially increases the probability of diagnosing colorectal cancer yet not sensitive enough to propose definitive diagnosis tests, future studies should focus on strategies using RB as an alarm symptom and finding additional indications to justify or rule out further investigations. For example, we may extend the variables to be observed simultaneously beyond the symptoms and signs commonly used in contemporary studies to family and diseases (e.g., diabetes, adiposity) histories, dietary habits (e.g., intake of vegetable, red meat, spicy food, beef, tobacco, alcohol, fish, sugar) and psycho-behavioral factors (e.g., depression, anxiety, sedentary work, exercise, anal sex) etc (Goldman et al., 2009; Nayak et al., 2009;

Arafa et al., 2011; Boyle et al., 2011; Aleksandrova et al., 2013; Di Maso et al., 2013; De Bruijnet al., 2013; Everatt et al., 2013; Tong et al., 2013). and perform more sophisticated analysis of the PPVs of multi-symptoms or build multi-variable models (e.g., score systems, regression models). Future efforts should also invest more on improving study quality with added attention being paid to using consistent reference standards, blinding of outcome assessment, reporting of uninterpretable test results and time period between RB and diagnosis tests.

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