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META-ANALYSIS

Patients with inflammatory bowel disease and post-inflammatory polyps have an increased risk of colorectal neoplasia: A meta-analysis

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Abstract

BACKGROUND

Longstanding intestinal inflammation increases the risk of colorectal neoplasia in patients with inflammatory bowel disease (IBD). Accurately predicting the risk of colorectal neoplasia in the early stage is still challenging. Therefore, identifying visible warning markers of colorectal neoplasia in IBD patients is the focus of the current research. Post-inflammatory polyps (PIPs) are visible markers of severe inflammation under endoscopy. To date, there is controversy regarding the necessity of strengthened surveillance strategies for IBD patients with PIPs.

AIM

To determine whether IBD patients with PIPs carryan increased risk of colorectal neoplasia.

METHODS

Researchers searched the following databases up to July 31, 2021: MEDLINE (PubMed), MEDLINE (Ovid), EMBASE, Cochrane Library, China National Knowledge Infrastructure, Wan-Fang Data, China Science and Technology Journal Database and Chinese BioMedical Literature Database. Cohort and case-control studies that compared the risk of colorectal neoplasia between IBD patients with or without PIPs and published in English or Chinese were included. Methodological quality was assessed using the Risk of Bias in Nonrandomized Studies-of Interventions assessment tool. The outcomes of interest were the rates of various grades of colorectal neoplasia. The pooled risk ratio (RR) and 95% confidence interval (95%CI) were calculated using the random-effects model. Begg's test and Egger's test were used to calculate the publication bias. Sensitivity and subgroup analyses were performed to verify the robustness of the results. The Grading of Recommendations, Assessment, Development and Evaluation

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approach was used to assess the overall quality of evidence supporting the outcomes of interest.

RESULTS

Nine studies involving 5424 IBD patients (1944 with PIPs *vs* 3480 without PIPs) were included. The overall bias in each included study ranged from moderate to serious. Compared with nonconcurrent PIPs, patients with PIPs had a higher risk of colorectal neoplasia (RR = 1.74, 95%CI: 1.35-2.24, $P < 0.001$, $I2 = 81.4\%$; aHR = 1.31, 95%CI: 1.01-1.70, $P = 0.04$, $I^2 = 26.2\%$; aOR = 2.62, 95%CI: 1.77-3.88, $P < 0.001$, $I^2 = 0\%$), advanced colorectal neoplasia (RR = 2.07, 95%CI: 1.49-2.87, $P < 0.001$, $I^2 = 77.4\%$; aHR = 1.63, 95%CI: 1.05-2.53, $P = 0.03$, $I^2 = 10.1\%$) and colorectal cancer (RR = 1.93, 95%CI: 1.32-2.82, $P = 0.001$, $I^2 = 83.0\%$). Publication bias was not observed in Begg's test or Egger's test. Sensitivity and subgroup analyses showed that the results are robust. The overall quality of evidence was assessed as moderate to low.

CONCLUSION

IBD patients with PIPs may have an increased incidence of colorectal neoplasia.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Pseudopolyps; Inflammatory polyps; Colorectal cancer; Colorectal neoplasia

Core Tip: This study is the first systematic review and meta-analysis to separately evaluate the potential risk between post-inflammatory polyps (PIPs) and colorectal neoplasia, advanced colorectal neoplasia, and colorectal cancer. Interestingly, we found that although malignant transformation from PIPs is rare, inflammatory bowel disease (IBD) patients with PIPs still bear an increased incidence of various grades of colorectal neoplasia. As an early warning of the increasing risk of colorectal neoplasia, IBD patients with PIPs should undergo strengthened surveillance to detect early dysplastic changes to allow for appropriate management so that there are improvements in both quality of life and survival rates.

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INTRODUCTION

Longstanding intestinal inflammation increases the risk of colorectal neoplasia in patients with inflammatory bowel disease (IBD)[1,2]. Unlike sporadic colorectal neoplasms, IBD-related colorectal neoplasms are usually characterized by a younger onset age, more malignant behavior and a poorer prognosis[3-5]. Therefore, clinical guidelines recommend regular endoscopic surveillance for IBD patients to enable the early detection of colorectal neoplasms. Furthermore, patients with certain risk factors need to undergo an intensified surveillance strategy; these risk factors include extensive colitis, family history of colorectal cancer, concurrent primary sclerosing cholangitis or post-inflammatory polyps (PIPs)[6-9].

Post-inflammatory polyps (PIPs) are usually formed from the alternating cycling of intestinal inflammation and mucous epithelial cell regeneration. According to published data, PIPs are not rare in IBD patients, with their prevalence ranging from 4% to 74%[10,11]. To date, there is controversy in the literature regarding the necessity of a strengthened surveillance strategy for IBD patients with PIPs. Some earlier case-control studies showed an increased risk of colorectal neoplasia in patients with PIPs [12,13]. For this reason, clinical guidelines suggest a strengthened surveillance strategy for IBD patients with previous or present PIPs in endoscopy. However, the

recommended endoscopic surveillance intervals for IBD patients with PIPs vary considerably from country to country. In addition, some recent multicenter cohort studies showed no significant correlation between PIPs and colorectal neoplasia in IBD patients, in contrast to prior views and clinical guidelines[14,15]. Unnecessary and frequent endoscopic surveillance not only decreases the quality of life of IBD patients but also increases the burdens of health care and resource stewardship. Therefore, it is crucial to explore the potential risk association between PIPs and colorectal neoplasia and to clarify the safe and reasonable endoscopic surveillance intervals for IBD patients with PIPs.

Because of the lack of large, randomized trials and meta-analyses specifically focused on the risk of PIPs and colorectal neoplasia, most of the current data are from small-scale, observational, nonrandomized studies. Therefore, researchers systematically identified and analyzed data from observed trials and evaluated the association between PIPs and colorectal neoplasia, advanced colorectal neoplasia, and colorectal cancer in IBD patients separately. This study aimed to determine whether IBD patients with PIPs bear an increased risk of various grades of colorectal neoplasia.

MATERIALS AND METHODS

This meta-analysis was conducted and presented according to the PRISMA and MOOSE guidelines. The methods were established prior to the conduct of the review. The protocol of this study was registered in PROSPERO (CRD42020172539).

Search strategy

The following databases were searched systematically from inception up to July 31, 2021: MEDLINE (PubMed), MEDLINE (Ovid), EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan-Fang Data, China Science and Technology Journal Database (VIP) and Chinese BioMedical Literature Database (CBM). The search items included "post-inflammatory polyps", "colorectal neoplasms", "inflammatory bowel diseases" and their associated words. The search strategy is detailed in the Supplementary data. Additional records were identified through hand searches of reference lists in clinical guidelines and relevant articles.

Study eligibility criteria

PIPs were defined as nonneoplastic lesions originating from the mucosa after the alternating cycling of intestinal inflammation and mucous epithelial cell regeneration and were proposed to be related to excessive healing processes. PIPs are usually diagnosed by endoscopists and pathologists and have been described as inflammatory polyps, pseudopolyps or post-inflammatory polyps in the literature[10].

The inclusion criteria were as follows: (1) Participants with confirmed IBD (including ulcerative colitis, Crohn's disease and unclassified IBD); (2) Comparison of the colorectal neoplasia burden and prognosis between patients with PIPs and patients without PIPs; (3) Reported outcomes of interest (such as colorectal neoplasia, advanced colorectal neoplasia, colorectal cancer); and (4) Cohort study or case-control study published in English or Chinese. The exclusion criteria were as follows: (1) Participants with a known history of colorectal neoplasm before IBD diagnosis; (2) Participants with synchronous diagnoses of IBD and colorectal neoplasm; (3) Full-text versions were not available for assessing risk of bias; and (4) Reviews, case reports, or poster abstracts. Two researchers (Lv YH and Huang J) applied eligibility criteria and selected studies for inclusion in the systematic review independently. Disagreements between individual judgments were resolved by discussion and consultation with a third researcher (Jialing Shi) until a consensus was reached.

Risk of bias assessment

The methodological quality of each included study was assessed using the Risk of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) assessment tool[16]. Two researchers (Yehong Lv, Jun Huang) assessed the methodological quality of each included study independently. Researchers were blinded to each other's decisions. Disagreements between individual judgments were resolved by discussion and consultation with a third researcher (Jialing Shi) until a consensus was reached. The final score was listed in a homemade Excel form.

Outcomes of interest

The outcomes of interest were the related variables of IBD-associated colorectal neoplasia, including dysplastic number, pathologic grading, cytologic type, and time from diagnosis to dysplastic change. However, many published studies reported only 1-2 relevant indices, and most of them focused on tumor incidence. This aspect made it difficult to synthesize and analyze many other useful outcome variables for colorectal neoplasia. Because the incidence of colorectal neoplasia (including the number of cases and its effect size) well reflected the potential associations between risk factors and tumorigenesis, the researchers ultimately chose the incidence of various grades of colorectal neoplasia (including colorectal neoplasia, advanced colorectal neoplasia and colorectal cancer) as the outcome of interest in this review. Neoplasia in this review was defined as not only the malignant transformation of PIPs but also the malignant transformation of colorectal mucosa. All cases of neoplasia were diagnosed by pathological examination. Colorectal neoplasia was defined as low-grade dysplasia, high-grade dysplasia and colorectal cancer. Advanced colorectal neoplasia was defined as high-grade dysplasia and colorectal cancer. All relevant dysplasia data were extracted from final pathology reports or electronic medical records. Relevant clinical data for cases were extracted from electronic medical records.

Data extraction

The following data were collected: study characteristics (first author, publication year, study design, follow-up time, study conclusions), participant characteristics (numbers of PIPs and control group, IBD phenotypes, country of origin, primary sclerosing cholangitis (PSC), family history of colon cancer, extensive colitis), andoutcome assessment (occurrence of various grades of colorectal neoplasia, including the numbers of colorectal neoplasia and its specific effective size). If the data were not reported in texts or tables, researchers contacted the corresponding author of the eligible study for additional information when necessary. Two researchers (Yehong Lv, Jun Huang) performed data extraction independently. Disagreements between individual judgments were resolved by discussion and consultation with a third researcher (Xue Huang until consensus was reached). The extracted data were listed in a homemade Excel form.

Data synthesis and analysis

Data synthesis was performed using STATA 15.0. The random-effects model was used for all data synthesis and statistical analysis. The pooled risk ratio (RR) and 95% confidence interval (95%CI:) were calculated to evaluate the potential risk between PIPs and colorectal neoplasia. When adjusted ratios were available, pooled adjusted ratios, such as the pooled adjusted hazard ratio (aHR), the pooled adjusted relative risk (aRR), or the pooled adjusted odds ratio (aOR), and their 95%CI:s were also calculated.

Researchers used the I^2 statistic to quantify statistical heterogeneity. An I^2 less than 25% was considered low-level heterogeneity, 25% to 50% was considered moderate-level heterogeneity, and more than 50% was considered high-level heterogeneity. Because the number of included studies was less than ten, funnel plots for evaluating the potential publication bias were not constructed. Instead, Begg's test and Egger's test were used to calculate the publication bias.

In the sensitivity analysis, the following two methods were performed to verify the robustness of the results: (1) The use of the fixed-effects model; and (2) The exclusion of outliers or studies with significant clinical heterogeneity.

For further analysis, subgroup analysis was performed according to study design (cohort *vs* case-control study) and methodological quality (serious/critical *vs* low/moderate/unclear risk of bias) for screening the heterogeneous origin. Because geography plays a role in IBD-associated colorectal cancer, the recommended endoscopic surveillance intervals vary considerably in different countries and societies. The geographic heterogeneity between PIPs and colorectal neoplasia was investigated in further analysis. The potential risk between PIPs and colorectal neoplasia in different IBD phenotypes (ulcerative colitis, Crohn's disease, unclassified IBD) was also investigated in further analysis. A P value less than 0.05 was considered significant.

Statistical analysis

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of evidence supporting the outcomes of interest[17]. The final quality of evidence was classified as high, moderate,

low or very low. The quality of evidence was assessed using GRADE profiler 3.6.

RESULTS

Study selection

A literature search was conducted up to July 31, 2021, with 779 records identified through database searching and 13 additional records identified through other sources. After removing duplicates, 207 articles were eligible for screening. Researchers excluded 160 articles after screening the titles and abstracts, and 47 articles remained. In the full-text articles assessed, 38 articles were excluded for the following reasons: review (n = 10), case report (n = 14), conference abstracts (n = 7), and paper written in Korean (n = 1). All participants were IBD patients with colorectal cancer (n = 1). All participants were ulcerative colitis patients with low-grade dysplasia (n = 1), interventions focused on endoscopy techniques (n = 3), and there were no reports of the outcomes of interest (n = 1). Ultimately, 9 studies met the inclusion criteria and were all included in the qualitative and quantitative synthesis[12-15,18-22] (Figure 1).

Included study characteristics

Four cohort studies and five case-control studies were included in this study. The sample sizes of participants ranged from 204 to 1582. PIPs were present in 1944/5424 (35.8%) IBD patients (median prevalence, 29.7%). The median follow-up durations ranged from 3.0 to 22.9 years (median follow-up, 13.0 years). In different IBD phenotypes, five studies exclusively focused on ulcerative colitis (UC), and four remaining studies focused on mixed IBD phenotypes. In different cohort geographies, the included studies were conducted in the Netherlands (n = 4), the United States of America (n = 3), the United Kingdom (n = 2), Belgium (n = 1) and China (n = 1). The summarized characteristics from the included studies are presented in Table 1.

Risk of bias assessment

Methodological quality was assessed using the ROBINS-I. The overall bias in each included study ranged from moderate to serious. Overall, five studies had a moderate risk of bias, three studies had a serious risk of bias, and one study had an unknown risk of bias. Because of the lack of information on missing data, the study by M D Rutter had unknown risks of missing data and overall bias. The outcomes of interest in our research were not the main outcomes in some studies, which may have led to the lack of detailed data and processing methods. For this reason, studies commonly have a moderate or serious risk in the sections of "bias due to confounding", "bias in the selection of participants for the study", and "bias in classification of interventions". The risk of bias assessment from each included study is presented in Table 2.

Association of PIPs with colorectal neoplasia

All nine included studies evaluated the association between PIPs and colorectal neoplasia and involved 5424 IBD patients (1944 with PIPs *vs* 3480 without PIPs). A total of 553 (28.4%) IBD patients with PIPs were diagnosed with colorectal neoplasia, compared with 546 (15.7%) IBD patients without PIPs. Using a random-effects model, IBD patients with PIPs were significantly associated with a higher risk of colorectal neoplasia than IBD patients without PIPs (RR = 1.74, 95%CI: 1.35-2.24, P < 0.001, I^2 = 81.4%) (Figure 2A). Four studies reported the adjusted aHR ratio, three studies reported the adjusted aOR ratio, and one study reported the adjusted aRR ratio. When pooling the aHR and aOR, significant differences between these two groups were still observed (pooled aHR = 1.31, 95%CI: 1.01-1.70, P = 0.04, I^2 = 26.2%; pooled aOR = 2.62, 95%CI: 1.77-3.88, P < 0.001, I^2 = 0%) (Figure 2B, 2C). Publication bias was not observed in Begg's test or Egger's test.

In the sensitivity analysis, IBD patients with PIPs were still significantly associated with a higher risk of colorectal neoplasia than IBD patients without PIPs when researchers used the fixed-effects model (RR = 1.67, 95%CI: 1.50-1.85, P < 0.001, I^2 = 81.4%). The results did not change after excluding outliers or studies with significant clinical heterogeneity.

In the subgroup analysis, different study designs and methodological qualities did not change the results or heterogeneity of each group. In different IBD phenotypes, five studies exclusively focused on UC and involved 2280 patients (921 with PIPs *vs* 1359 without PIPs). PIPs were also significantly associated with a higher risk of colorectal neoplasia in UC patients (RR = 1.76, 95%CI: 1.18-2.63, P = 0.006, I^2 = 81.6%).

Table 1 The summarized characteristics of the included studies

Included studies	Study design	IBD phenotypes	Country	Median disease duration(yr)	PSC (*n*, %)	Family history of CRC (*n*, %)	Extensive colitis (*n*, %)	Median follow-up time (yr)	The risk of various grades of colorectal neoplasia (PIPs *vs* nonPIPs)	Conclusion
Jong MEd 2019[21]	Cohort Study	UC, CD, UNCLASSIFIED IBD	Netherlands	≥ 8.0	27 (5.2%)	74 (14.3%)	345 (66.5%)	21.6 years in PIPs, 22.9 yr in nonPIPs	CRN 36/154 *vs* 65/365 (aHR = 1.08, 95%CI: 0.66-1.75[a]); ACRN 9/154 *vs* 10/365 (aHR = 1.38, 95%CI: 0.52-3.68[b]); CRC 6/154 *vs* 7/365	PIPs did not increase the risk of CRN, ACRN or CRC
Mahmoud R 2019[15]	Cohort Study	UC, CD, UNCLASSIFIED IBD	NetherlandsAmerica	≥ 8.0	234 (14.8%)	93 (5.9%)	1275 (80.6%)	5.4 years in PIPs, 4.5 years in nonPIPs	CRN 64/462 *vs* 124/1120 (aHR = 1.25, 95%CI: 0.88-1.77[c]); ACRN 17/462 *vs* 24/1120 (aHR = 1.17, 95%CI: 0.59-2.31[d])	PIPs did not increase the risk of CRN or ACRN
Xu W 2020 [22]	Cohort Study	UC	China	6.0	10 (4.1%)	NR	116 (47.2%)	13.0	ACRN 11/57 *vs* 8/189 (aOR = 5.46, 95%CI: 1.69-17.638[e])	PIPs increased the risk of ACRN
Choi C-HR 2017[14]	Cohort Study	UC	United Kingdom	≥ 8.0	42 (4.3%)	48 (4.9%)	987 (100%)	13.0	CRN 66/447 *vs* 31/540 (aHR = 1.20, 95%CI: 0.80-1.80[f])	PIPs did not increase the risk of CRC
Jegadeesan R 2016[20]	Case-Control Study	UC	American	12.5	47 (10.1%)	65 (13.1%)	457 (97.9%)	3.0	CRN 32/138 *vs* 79/329	PIPs did not increase the risk of CRN
Lutgens M 2015[19]	Case-Control Study	UC, CD, UNCLASSIFIED IBD	Netherlands Belgium	NR	30 (5.7%)	33 (6.2%)	349 (65.7%)	NR	CRC 126/260 *vs* 62/270 (aHR = 2.30, 95%CI: 1.20-4.10[g])	PIPs increased the risk of CRC
Baars JE 2011[13]	Case-Control Study	UC, CD, UNCLASSIFIED IBD	Netherlands	9.0	22 (4.3%)	34 (6.6%)	156 (30.4%)	15.5	CRC 71/147 *vs* 68/366 (aRR = 1.92, 95%CI: 1.28-2.88[h])	PIPs increased the risk of CRC
Velayos FS 2006[12]	Case-Control Study	UC	American	17.0	50 (13.3%)	24 (6.4%)	318 (84.6%)	NR	CRC 105/184 *vs* 83/192 (aOR = 2.50, 95%CI: 1.40-4.60[i])	PIPs increased the risk of CRC
Rutter MD 2004[18]	Case-Control Study	UC	United Kingdom	22.0	NR	NR	204 (100%)	NR	CRN 42/95 *vs* 26/109 (aOR = 2.29, 95%CI: 1.28-4.11[j])	PIPs increased the risk of CRN

[a]Adjusted factors: IBD type, sex, concomitant PSC, age at IBD diagnosis, maximum disease extent, medication use, family history of CRC, and the mean inflammation score.

[b]Adjusted factors: concomitant PSC, and the mean inflammation score.

[c]Study did not report.
[d]Thirty-eight patients (including 1 ACRN) were excluded due to missing values.
[e]Adjusted factors: colorectal stricture, the presence of PIPs, age at IBD diagnosis, disease duration, and concomitant PSC.
[f]Adjusted factors: patient's age, average number of biopsies, surveillance interval, and colonoscopy type (i.e., white-light or chromoendoscopy).
[g]Adjusted factors: IBD type, concomitant PSC, microscopic disease extent, and the presence of PIPs.
[h]Adjusted factors: age at IBD diagnosis, sex, duration of PSC, disease duration, disease extent at onset, and the presence of PIPs.
[i]Adjusted factors: age at IBD diagnosis, and disease duration.
[j]Adjusted factors: backwash ileitis, shortened colon, tubular colon, scarring, segment of severe inflammation, normal colonic appearance, the presence of PIPs, and colonic stricture. IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis; CRC: Colorectal cancer; PIPs: Post-inflammatory polyps; UC: Ulcerative colitis; CD: Crohn's disease; UNCLASSIFIED IBD: Unclassified inflammatory bowel disease; CRN: Colorectal neoplasia; ACRN: Advanced colorectal neoplasia; NR: Not reported.

Table 2 The methodological quality of each included study was assessed by using the Risk of Bias in Nonrandomized Studies - of Interventions (ROBINS-I) assessment tool

Included study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Jong *et al* [21], 2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Mahmoud *et al*[15], 2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Xu *et al*[22], 2020	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Choi *et al* [14], 2017	Serious	Moderate	Moderate	Low	Low	Low	Moderate	Serious
Jegadeesan *et al*[20], 2016	Serious	Moderate	Moderate	Low	Low	Low	Moderate	Serious
Lutgens *et al* [19], 2015	Serious	Moderate	Moderate	Low	Low	Low	Low	Serious
Baars *et al* [13], 2011	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Velayos *et al* [12], 2006	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Rutter *et al* [18], 2004	Moderate	Moderate	Moderate	Low	No information	Low	Moderate	No information

Because of the lack of CD and UNCLASSIFIED IBD data, the effects of PIPs on colorectal neoplasia in CD and UNCLASSIFIED IBD patients are not available. In different cohort geographies, patients with PIPs had an increased risk of colorectal neoplasia in Europe (RR = 2.05, 95%CI: 1.62-2.59, $P < 0.001$, $I^2 = 60.7\%$) and Asia (RR = 4.56, 95%CI: 1.93-10.79, $P < 0.001$, I^2 not available). No association was observed in the US (RR = 1.17, 95%CI: 0.86-1.59, $P = 0.314$, $I^2 = 56.1\%$) (Table 3).

Association of PIPs with advanced colorectal neoplasia

Three cohort studies and three case-control studies evaluated the association between PIPs and advanced colorectal neoplasia and involved 3766 IBD patients (1264 with PIPs *vs* 2502 without PIPs). A total of 339 (26.8%) IBD patients with PIPs were diagnosed with advanced colorectal neoplasia, compared with 255 (10.2%) IBD patients without PIPs. Using a random-effects model, IBD patients with PIPs were significantly associated with a higher risk of advanced colorectal neoplasia than IBD patients without PIPs (RR = 2.07, 95%CI: 1.49-2.87, $P < 0.001$, $I^2 = 77.4\%$) (Figure 3A).

Three studies reported the adjusted aHR ratio, two studies reported the adjusted aOR ratio, and one study reported the adjusted aRR ratio. When pooling the aHR, significant differences between these two groups were still observed (pooled aHR = 1.63, 95%CI: 1.05-2.53, $P = 0.03$, $I^2 = 10.1\%$) (Figure 3B). Publication bias was not

Table 3 The results of subgroup analysis in colorectal neoplasia and advanced colorectal neoplasia

Subgroup	Study	Pooled RR (95%CI)	*P* value	I^2 value%
Colorectal neoplasia				
Study design				
Cohort study	4	1.88 (1.18-3.00)	0.008	80.0
Case-control study	5	1.68 (1.20-2.35)	0.002	85.6
Methodological quality				
Serious/Critical risk of bias	3	1.74 (1.00-3.01)	0.049	87.5
Low/Moderate/Unclear risk of bias	6	1.74 (1.28-2.36)	0.000	80.7
IBD phenotypes				
UC	5	1.76 (1.18-2.63)	0.006	81.6
CD	NA	NA	NA	NA
UNCLASSIFIED IBD	NA	NA	NA	NA
Geographic regions				
Europe	5	2.05 (1.62-2.59)	0.000	60.7
America	2	1.17 (0.86,1.59)	0.314	56.1
Asia	1	4.56 (1.93,10.79)	0.000	NA
Advanced colorectal neoplasia (ACRN)				
Study design				
Cohort study	3	2.42 (1.36-4.32)	0.003	40.1
Case-control study	3	1.92 (1.27-2.90)	0.002	88.6
Methodological quality				
Serious/Critical risk of bias	1	2.11 (1.64-2.71)	0.000	NA
Low/Moderate/Unclear risk of bias	5	2.1 (1.35-3.27)	0.001	80.6

RR: Risk ratio; CRN: Colorectal neoplasia; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; UNCLASSIFIED IBD: Unclassified inflammatory bowel disease; ACRN: Advanced colorectal neoplasia; NA: Not available.

observed in Begg's test or Egger's test.

In the sensitivity analysis, IBD patients with PIPs were still significantly associated with a higher risk of advanced colorectal neoplasia than IBD patients without PIPs when researchers used the fixed-effects model (RR = 1.91, 95%CI: 1.67-2.18, $P < 0.001$, $I^2 = 77.4\%$). The results did not change when researchers excluded outliers or studies with significant clinical heterogeneity. In the subgroup analysis, different study designs and methodological qualities did not change the results or heterogeneity of each group (Table 3).

Association of PIPs with colorectal cancer

One cohort study and three case-control studies evaluated the association between PIPs and colorectal cancer and involved 1938 IBD patients (745 with PIPs *vs* 1193 without PIPs). A total of 308 (41.3%) IBD patients with PIPs were diagnosed with colorectal cancer, compared with 220 (18.4%) IBD patients without PIPs. Using a random-effects model, IBD patients with PIPs were significantly associated with a higher risk of developing colorectal cancer than IBD patients without PIPs (RR = 1.93, 95%CI: 1.32-2.82, $P = 0.001$, $I^2 = 83.0\%$) (Figure 4). Publication bias was not observed in Begg's test or Egger's test. Because the adjusted ratios were not available, the pooled adjusted ratio was not calculated. Because few studies were included in this section, sensitivity analysis and subgroup analysis were not performed.

Quality of evidence

The GRADE approach was used to assess the overall quality of evidence. There is low-quality evidence to support that IBD patients with PIPs bear an increased risk of

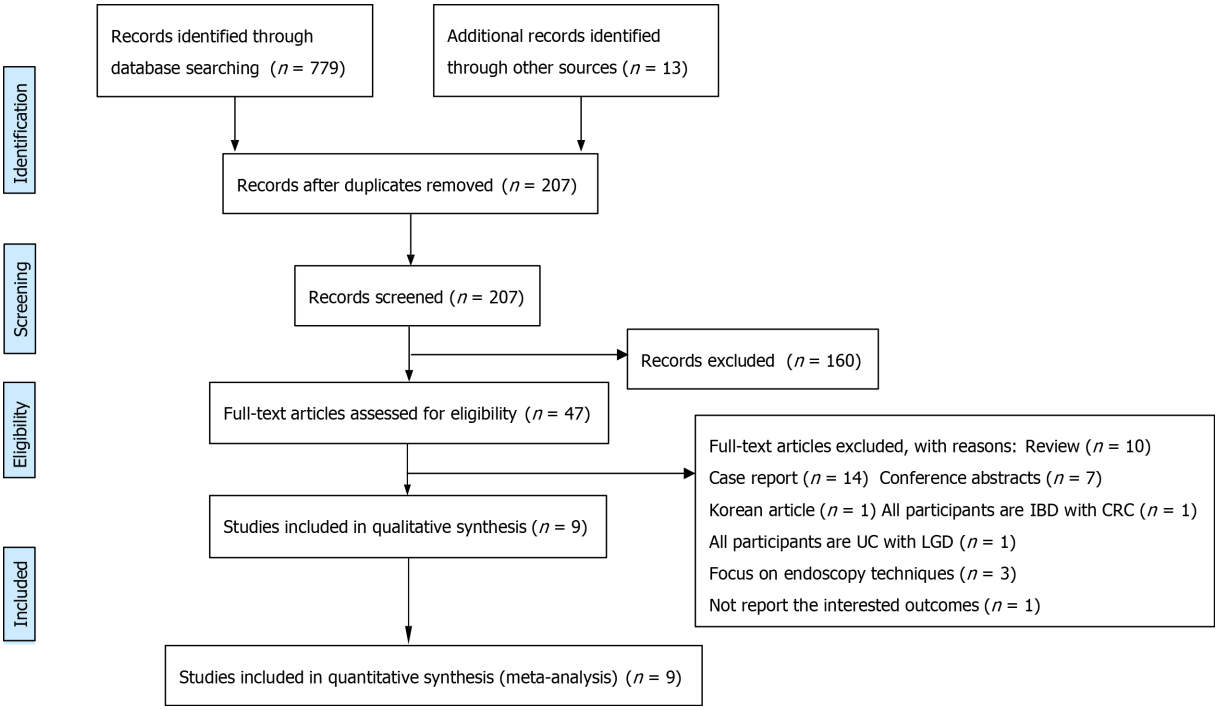

Figure 1 Flow diagram of search strategy and study selection.

colorectal neoplasia and colorectal cancer. There is moderate-quality evidence to support that IBD patients with PIPs bear an increased risk of advanced colorectal neoplasia. A summary of the assessment is presented in Table 4.

DISCUSSION

This study aimed to explore the potential association between PIPs and colorectal neoplasia in IBD patients. The results indicated that IBD patients with PIPs bear an increased risk of colorectal neoplasia, advanced colorectal neoplasia, and colorectal cancer.

In contrast to sporadic colorectal cancer, IBD-related colorectal cancer follows a sequence of "inflammation-dysplasia-carcinoma". In IBD patients, recurrent mucosal inflammation is the primary risk factor for intestinal neoplasia. The alternating cycling of intestinal inflammation and mucous epithelial cell regeneration provides more opportunities for transcription errors and the subsequent development of neoplasia by activating procarcinogenic genes and inhibiting tumor suppressor genes. The development of colorectal neoplasia is frequently associated with mutations, methylation and dysregulation of genes. It induces microsatellite instability, telomere shortening, and chromosomal instability and further induces tumor progression[23-26]. The related genes and molecules involve the *adenomatous polyposis coli (APC) gene*, *k-ras*, *deleted in colorectal cancer (DCC)* genes, *deleted in pancreatic cancer-4 (DPC4)* genes, and *tumor protein* 53 (p53), among others[27-31]. Meanwhile, the inflammatory microenvironment of IBD, which consists of a variety of immune cells, epithelial cells, stromal cells, cytokines and chemokines, has many similarities to the microenvironment of cancer[32]. The innate and adaptive immune systems are involved in tumor development by the release of reactive oxygen species, nitrogen species and cytokines [25]. The use of immunosuppression may also allow neoplasia to progress at a faster rate. Moreover, intestinal dysbacteriosis also appears to play a role in IBD-related colorectal neoplasia, such as *Escherichia coli, Bacteroides fragilis, Enterococcus faecalis and Fusobacterium nucleatum*[24,33,34].

These changes were detectable not only in dysplastic mucosa but also in morphologically normal intestinal mucosa. Their accumulation will lead to extensive genomic and epigenomic alterations and then create a favorable microenvironment for tumor progression. This phenomenon is called field cancerization[35-37]. In theory, the earlier the field cancerization can be detected, the earlier the interventions will be to slow or stop tumor progression. Unfortunately, the above changes are invisible under

Table 4 Assessing the overall quality of evidence supporting each outcome using Grading of Recommendations, Assessment, Development and Evaluation

Outcomes	Illustrative comparative risks[a] (95%CI)		Relative effect (95%CI)	No of Participants (studies)	Quality of the evidence(GRADE)
	Assumed risk	Corresponding risk			
	NonPIPs	PIPs			
Association of PIPs with colorectal neoplasia; Follow-up: 3.0-22.9 yr	Study population[b]				
	157 per 1000	273 per 1000(212 to 351)	RR 1.74 (1.35 to 2.24)	5424 (9 studies)	Low
Association of PIPs with advanced colorectal neoplasia; Follow-up: 3.0-22.9 yr	Study population[b]				
	102 per 1000	211 per 1000(151 to 293)	RR 2.07 (1.48 to 2.87)	3766 (6 studies)	Moderate due to large effect
Association of PIPs with colorectal cancer; Follow-up: 3.0-22.9 yr	Study population[b]				
	184 per 1000	356 per 1000(243 to 520)	RR 1.93 (1.32 to 2.82)	1938 (4 studies)	Low

[a]The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI).
[b]Label: Moderate. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate. CI: Confidence interval; RR: Risk ratio.

endoscopy. Accurately predicting the risk of colorectal neoplasia in IBD patients in the early stage is still challenging. Therefore, looking for visible warning markers of colorectal neoplasia in IBD patients is the focus of current research.

PIPs are formed as a consequence of repeated cycles of active inflammation and regeneration of the intestinal epithelium. Under endoscopy, PIPs look like polyps or loose mucosal tags[10,38]. Although malignant transformation from PIPs is rare, IBD patients with PIPs are at an increased risk of various grades of colorectal neoplasia. Previous studies have shown that PIPs positively correlate with the severity of inflammation and are considered surrogate markers of significant cumulative inflammatory burden[26,39,40]. Given this finding, researchers have proposed that PIPs are visible markers of severe inflammation under endoscopy and an early warning of an increased risk of colorectal neoplasia in IBD patients.

In different IBD phenotypes, the colorectal neoplasia burden of UC patients with PIPs is also increased, which is consistent with the burden of IBD patients. Thus, compared with UC patients without PIPs, a strengthened surveillance strategy is preferable for UC patients with PIPs. Meanwhile, because of the lack of data on Crohn's colitis patients, there is still doubt whether surveillance intervals should be independent of IBD phenotypes. Additional well-designed trials are needed for further research.

Geographic heterogeneity exists in the incidence of IBD and IBD-associated colorectal cancer[41-43]. Currently, there is controversy regarding reasonable endoscopic surveillance intervals for patients with PIPs. The recommended intervals vary considerably from country to country. Therefore, what actual role does geography play in PIPs and colorectal neoplasia? In this study, compared with patients without PIPs, patients with PIPs had an increased risk of colorectal neoplasia in Europe and Asia. Conversely, no association between PIPs and colorectal neoplasia has been observed in the United States. The reason for this geographic heterogeneity is multifactorial and includes genetics, diet, IBD phenotype, inflammation burden, treatment options, and differences in endoscopic surveillance. However, it is important to note that this result should be interpreted and applied cautiously because

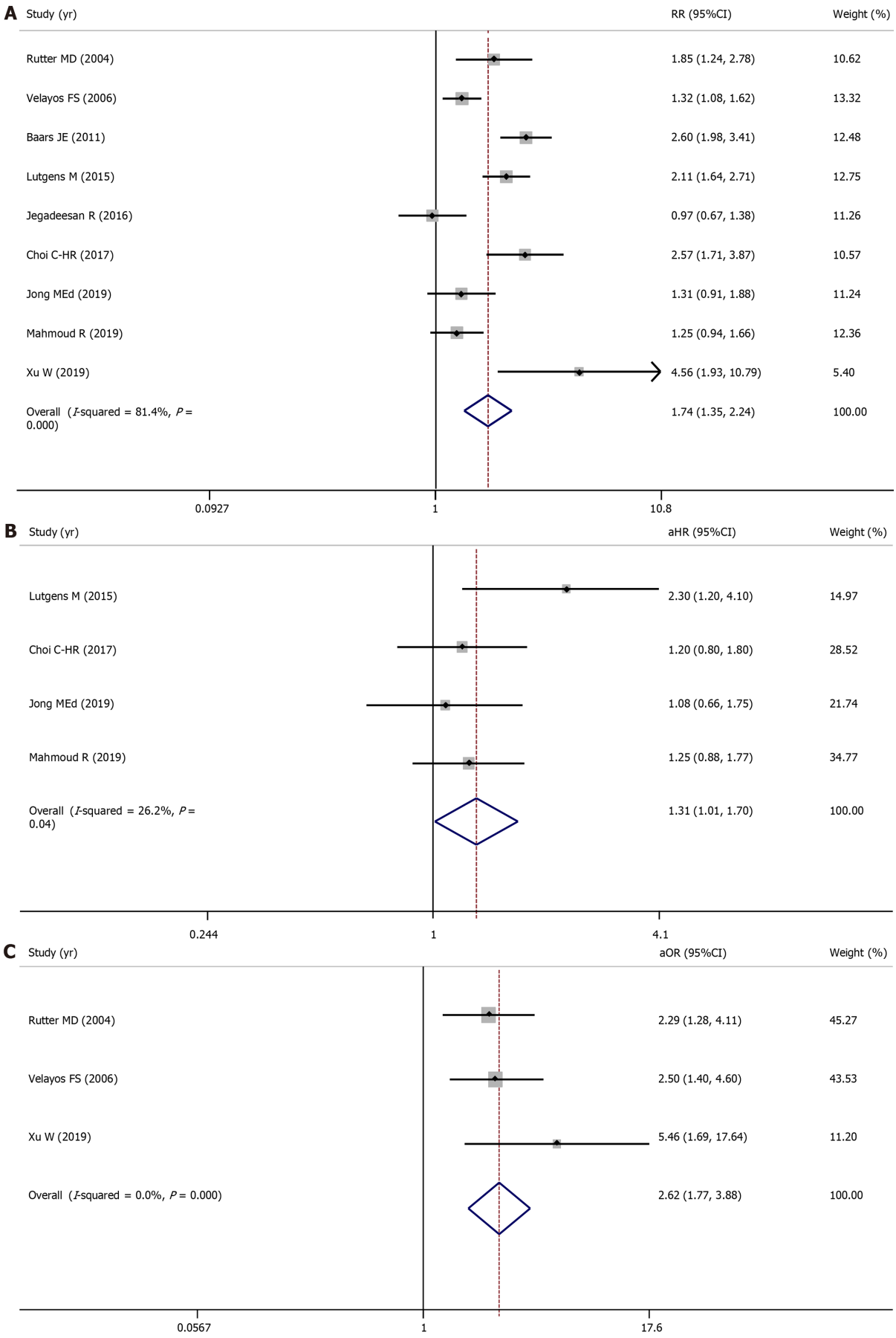

Figure 2 Forest plot showing the association of post-inflammatory polyps with colorectal neoplasia in inflammatory bowel disease patients. A: Forest plot of pooling unadjusted risk ratio; B: Forest plot of pooling adjusted hazard ratio; C: Forest plot of pooling adjusted odds ratio.

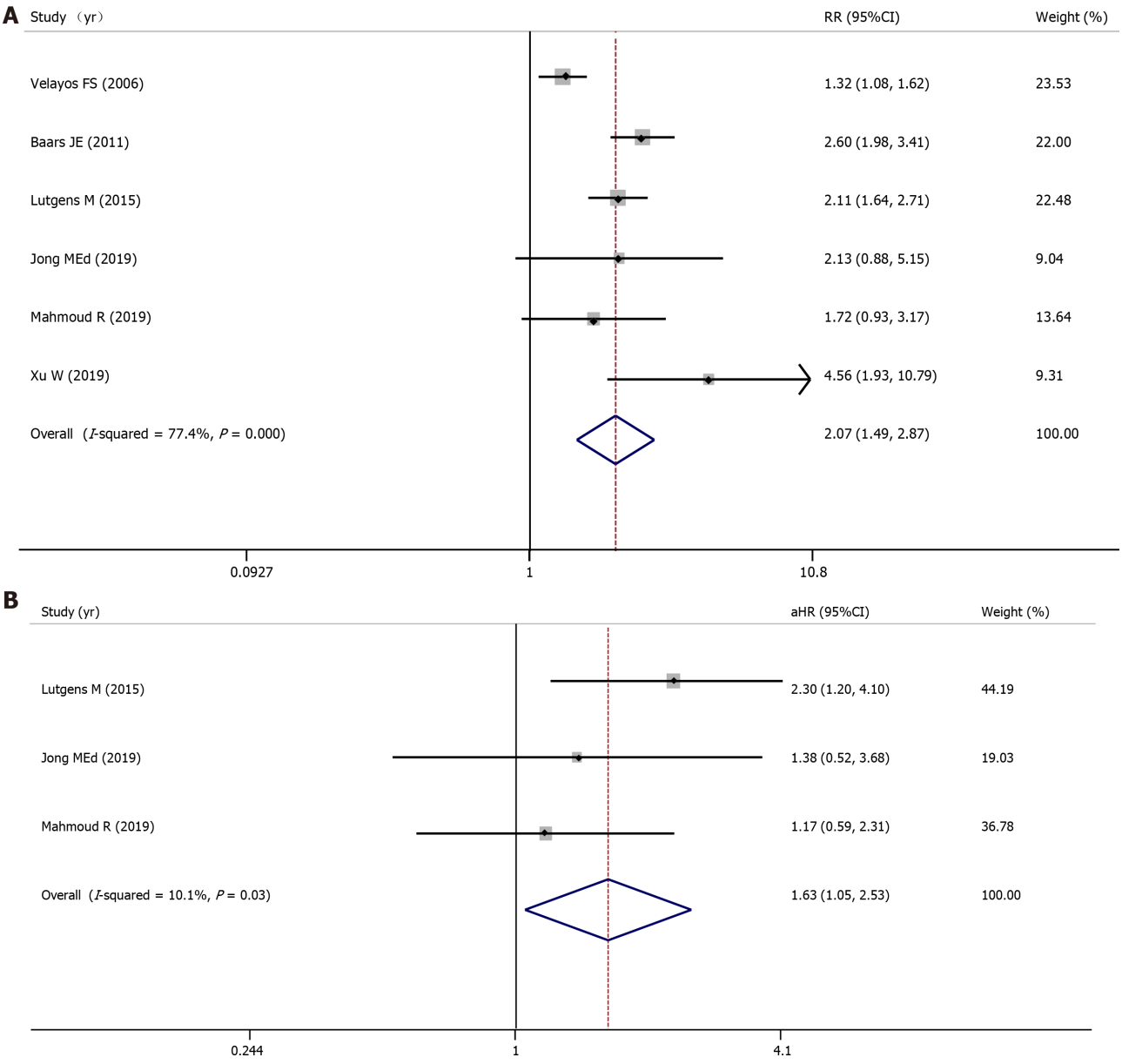

Figure 3 Forest plot showing the association of post-inflammatory polyps with advanced colorectal neoplasia in inflammatory bowel disease patients. A: Forest plot of pooling unadjusted risk ratio; B: Forest plot of pooling adjusted hazard ratio.

of the small numbers of included studies on certain national cohorts. More well-designed trials are needed to verify this variation in future research. In contrast to these results, the *American Society of Gastrointestinal Endoscopy (ASGE)* recommends annual endoscopic surveillance for IBD patients with PIPs, which is more frequent than the every 2-3 years that is recommended by the *European Crohn's and Colitis Organization (ECCO)*, the *British Society of Gastroenterology (BSG)*, the *Association of Coloproctology for Great Britain and Ireland (ACPGBI) and the National Institute for Clinical Excellence (NICE)*[6,8,44,45].

When an endoscopist identifies an IBD patient with concurrent PIPs, what should they do? Because IBD patients with PIPs bear an increased risk of colorectal neoplasia, it is necessary for them to enroll in a rigorous treatment program that includes strengthened endoscopic surveillance strategies to achieve complete histological mucosal healing and identify colorectal neoplasia in an early stage. The purpose of endoscopic surveillance is to detect early dysplastic changes to allow for appropriate management so that there are improvements in quality of life and survival rates. To reduce the rate of missing dysplasia, surveillance should be performed by an experienced gastroenterologist in IBD when the disease is in remission. Adequate bowel preparation, meticulous inspection with slow withdrawal, and the application of advanced endoscopic equipment are key for high-quality surveillance. Detailed recommendations of various societies for IBD patients with PIPs are summarized in

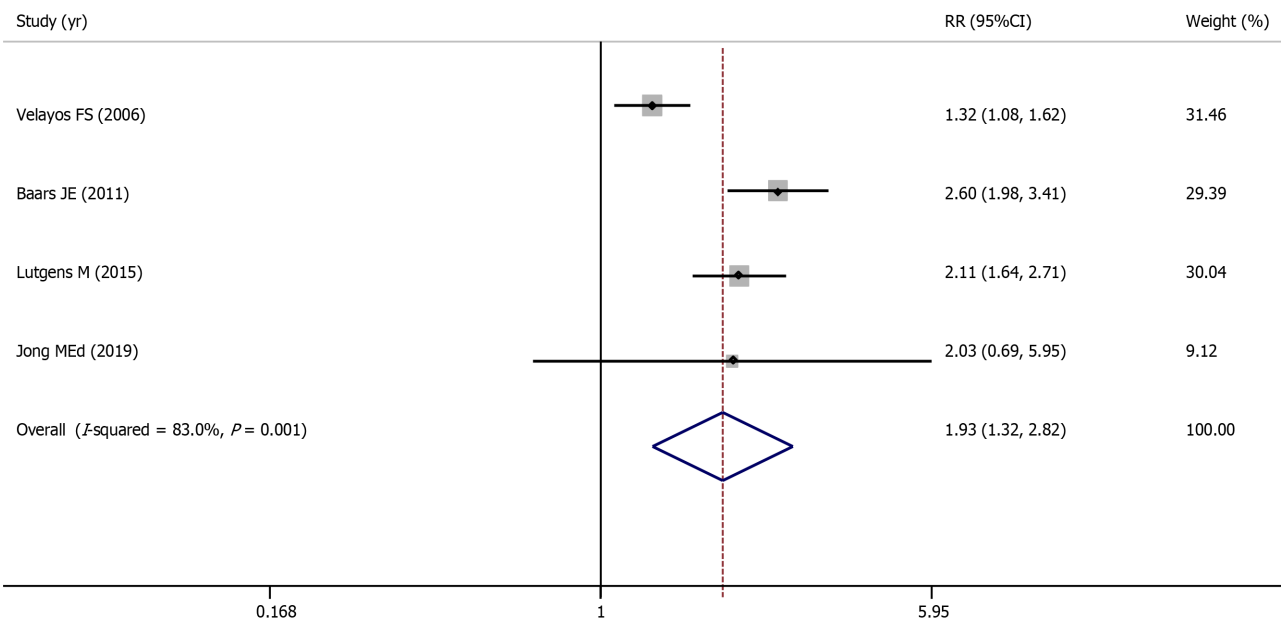

Figure 4 Forest plot showing the association of post-inflammatory polyps with colorectal cancer in inflammatory bowel disease patients by pooling the unadjusted risk ratios.

Table 5.

When considering endoscopic surveillance intervals, societies recommend different intervals that range from one to three years. European societies suggest that PIPs are an intermediate risk factor for developing colorectal cancer in IBD patients and that IBD patients with PIPs should undergo endoscopic surveillance every 2-3 years[6,44,45]. Nevertheless, US and Australian societies suggest shortening the surveillance interval to every year because they believe that IBD patients with PIPs are at high risk of colorectal cancer[8,46]. In China and Japan, current guidelines and specifications do not mention a definite interval for patients with PIPs. Correspondingly, these Asian societies advocate initiating endoscopic surveillance from 8-10 years after disease onset and recommend annual or biennial endoscopic surveillance for patients with left-sided colitis or extensive colitis[47-49]. To summarize, the optimal interval of endoscopic surveillance for IBD patients with PIPs has not been established, and additional well-designed trials are needed for further research.

How can colonoscopy screening be performed for IBD-associated colorectal cancer? During recent decades, new technology has improved in terms of endoscopic devices, including white light endoscopy (WLE), chromoendoscopy, magnifying endoscopy, endomicroscopy, narrow band imaging (NBI), and endoscopic molecular imaging. Among them, the majority of clinical guidelines recommend methylene blue or indigo carmine chromoendoscopy with targeted biopsies for surveillance colonoscopy. Under chromoendoscopy, the visualization of the colonic epithelium is improved by highlighting the areas of mucosal irregularities and delineating the borders of suspected lesions. Studies have shown that 61%-84% of neoplastic lesions could be visualized by recent endoscopy[50-53]. In this context, targeted biopsies have the advantage of fewer samples. Therefore, although chromoendoscopy takes a longer time and may be more cumbersome, chromoendoscopy with targeted biopsies has a higher dysplasia detection rate and is more cost-effective than conventional colonoscopy[54-58]. However, random biopsies are beneficial for monitoring disease progression, evaluating histologic stage and assessing treatment efficacy. In special circumstances, such as a known history of dysplasia, concomitant PSC or a foreshortened colon, random biopsies are still recommended regardless of the screening method. With advances in optical imaging techniques, it is unclear whether chromoendoscopy should still be used when surveillance is performed with high-definition colonoscopy or new endoscopic imaging. Additional well-designed trials are needed for further research.

The increased risk of colorectal neoplasia in IBD patients with PIPs probably reflects the increased risk of previous severe inflammation rather than the PIPs themselves having malignant potential. In a multicenter cohort study, researchers found that most patients with PIPs undergo colectomy due to uncontrolled inflammation but not colorectal neoplasia[15]. Therefore, it is not necessary to remove PIPs conventionally

Table 5 Societal recommendations for colorectal cancer surveillance in inflammatory bowel disease patients with post-inflammatory polyps

Society	Surveillance intervals	Surveillance techniques
AGA 2010	More frequent surveillance (No specific interval recommended)	Chromoendoscopy with targeted biopsies OR Standard or high-definition colonoscopy along with random biopsies
ASGE 2015	Every year	Chromoendoscopy with targeted biopsies OR Random biopsies (2-4 biopsies every from 10 cm) and targeted biopsies if chromoendoscopy is not available or the yield of chromoendoscopy is reduced
Cancer Council Australian 2019	Every year	Chromoendoscopy with targeted biopsies
BSG/ACPGBI 2010	Every 3 yr	Chromoendoscopy with targeted biopsies OR Random biopsies (2-4 biopsies every from 10 cm) and targeted biopsies if chromoendoscopy is not available
NICE 2011	Every 3 yr	Chromoendoscopy with targeted biopsies
ECCO 2013/2017	Every 2-3 yr	Chromoendoscopy with targeted biopsies OR White light endoscopy with random biopsies (4 biopsies every from 10 cm) and targeted biopsies
JSGE 2018/2020	Not mention the definite interval (Every 1-2 yr for patients with left-sided colitis or extensive colitis)	Chromoendoscopy with targeted biopsies OR Available endoscopic technology with targeted biopsies to increase the neoplasia detection rate
Chinese Society of Gastroenterology 2018/2020	Not mention the definite interval (Every 1-2 yr for patients with left-sided colitis or extensive colitis)	Chromoendoscopy/magnifying endoscopy with targeted biopsies

IBD: Inflammatory bowel disease; PIPs: Post-inflammatory polyps; AGA: American Gastroenterology Association; ASGE: American Society of Gastrointestinal Endoscopy; BSG: The British Society of Gastroenterology; ACPGBI: The Association of Coloproctology for Great Britain and Ireland; NICE: National Institute for Clinical Excellence; ECCO: The European Crohn's and Colitis Organization; JSGE: The Japanese Society of Gastroenterology.

unless there is diagnostic uncertainty or concerning malignant features or clinical symptoms, such as bleeding or intussusception. Features of underlying malignancy include uneven redness, nodularity, villous texture, slight elevation or depression, friability, obscured vascular pattern, ulcerated or velvety surface, disruption of innominate lines, and inability to lift with submucosal injection[57,59,60]. In patients with multiple PIPs or uncontrolled inflammation, a terrible intestinal mucosal environment makes it difficult for endoscopists to identify abnormal lesions, and prophylactic colectomy should be considered[18]. To summarize, the management of IBD patients with PIPs, including prophylactic colectomy and enhanced endoscopic surveillance, requires careful consideration of the individual patient, their disease, and endoscopic and histologic factors and involves a multidisciplinary team discussion that should include gastroenterologists, surgeons and pathologists.

In this study, the overall quality of evidence was assessed as moderate to low. There are several obstacles to designing and performing randomized controlled trials for endoscopic surveillance of IBD patients, such as ethical issues and the relatively low incidence of colorectal neoplasia. Thus, robust and available evidence usually comes from well-designed multicenter observational trials. Having recognized these limitations, we systematically searched several databases, undertook a meta-analysis of the latest and most favorable evidence, and used multiple methods to verify the robustness of the potential risk between PIPs and colorectal neoplasia. In the three outcomes of interest, the results did not change when researchers excluded outliers or studies with significant clinical heterogeneity. This result indicated that based on the current studies, the results of this meta-analysis are robust and that individual studies have less influence.

A meta-analysis that focused on the prognostic factors for ACRN in IBD patients was published in 2021[61]. Similar to our study, the researchers found that patients with PIPs were at higher risk for ACRN based on three cohort studies and two case-control studies (OR = 3.29, 95%CI: 2.41-4.48, $P < 0.001$, $I^2 = 0\%$). However, this association was not confirmed in the pooled HR analysis (univariable HR = 1.67, 95%CI: 0.99-2.82, $P = 0.05$, $I^2 = 0\%$; multivariable HR = 1.73, 95%CI: 0.88-3.40, $P = 0.11$, $I^2 = 56\%$). A probable reason for this result was that the number of available studies and patients included was too small for an accurate performance assessment. In contrast, we extended the search cutoff time to July 31, 2021 to include additional literature and participants. Finally, three cohort studies and three case-control studies involving 3766 IBD patients (1264 with PIPs *vs* 2502 without PIPs) were included. The results showed

that patients with PIPs were at higher risk for ACRN, which was confirmed in both pooled RR analysis and pooled HR analysis.

This study is the first meta-analysis to separately assess the relationship between PIP and CRN, ACRN and CRC. This study has several strengths. First, this study evaluated the association between PIPs and colorectal neoplasia, advanced colorectal neoplasia, and colorectal cancer separately. Disparity in the risk stratification of different grades of colorectal neoplasia can provide bases for surveillance strategy, treatment options and prognosis judgment. Second, this study used a new tool (ROBINS-I) to assess the methodological quality of each included study. Third, this study used multiple methods to identify the robustness of the results.

This study also has some limitations. First, the heterogeneity of outcomes is high. Therefore, researchers used multiple methods to identify the robustness of the results and conducted subgroup analyses to search for the source of heterogeneity. Second, a family history of colon cancer and concurrent primary sclerosing cholangitis have been reported as risk factors for colorectal neoplasia in several studies. However, because of missing data in the target population, no high-quality evidence could be obtained.

CONCLUSION

IBD patients with PIPs may have an increased incidence of various grades of colorectal neoplasia. Due to the lower rate of malignant transformation, PIPs do not need to be removed conventionally. However, due to the increased risk of colorectal neoplasia, IBD patients with PIPs should undergo strengthened surveillance to detect early dysplastic changes to allow for appropriate management to improve quality of life and survival rates. Meanwhile, there are still many gaps in this field of research, such as information on safe and reasonable endoscopic surveillance intervals for patients with PIPs and the pathogenic process of PIPs in colorectal neoplasia. Therefore, additional well-designed multicenter trials are needed.

ARTICLE HIGHLIGHTS

Research background

Longstanding intestinal inflammation increases the risk of colorectal neoplasia in patients with inflammatory bowel disease (IBD). Accurately predicting the risk of colorectal neoplasia in IBD patients in the early stage is still challenging. Post-inflammatory polyps (PIPs) are visible markers of severe inflammation under endoscopy. To date, there is controversy in the literature regarding the necessity of a strengthened surveillance strategy for IBD patients with PIPs.

Research motivation

Unnecessary and frequent endoscopic surveillance not only decreases the quality of life of IBD patients but also increases the burdens of health care and resource stewardship. Therefore, it is crucial to explore the potential risk association between PIPs and colorectal neoplasia. A better insight into this topic would help physicians to clarify the safe and reasonable endoscopic surveillance intervals for IBD patients with PIPs.

Research objectives

To determine whether IBD patients with PIPs bear an increased risk of various grades of colorectal neoplasia.

Research methods

Researchers systematically searched eight databases up to July 31, 2021. Cohort and case-control studies that compared the risk of colorectal neoplasia between IBD patients with or without PIPs and published in English or Chinese were included. Methodological quality was assessed using the Risk of Bias in Nonrandomized Studies-of Interventions (ROBINS-I) assessment tool. The outcomes of interest were the rates of various grades of colorectal neoplasia. The pooled risk ratio (RR) and 95% confidence interval (95%CI:) were calculated using the random-effects model. Begg's test and Egger's test were used to calculate the publication bias. Sensitivity and subgroup analyses were performed to verify the robustness of the results. The Grading

of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to assess the overall quality of evidence supporting the outcomes of interest.

Research results

Of 792 records, four cohort studies and five case-control studies involving 5424 IBD patients (1944 with PIPs *vs* 3480 without PIPs) were included in this study. The overall bias in each included study ranged from moderate to serious. After meta-analyses, IBD patients with PIPs were significantly associated with a higher risk of colorectal neoplasia than IBD patients without PIPs (RR = 1.74, 95%CI: 1.35-2.24, $P < 0.001$, I^2 = 81.4%). Meanwhile, patients with PIPs also had a higher risk of advanced colorectal neoplasia (RR = 2.07, 95%CI: 1.49-2.87, $P < 0.001$, I^2 = 77.4%) and colorectal cancer (RR = 1.93, 95%CI: 1.32-2.82, $P = 0.001$, I^2 = 83.0%). Publication bias was not observed. And Sensitivity and subgroup analyses showed that the results are robust. The overall quality of evidence was assessed as moderate to low.

Research conclusions

IBD patients with PIPs may have an increased incidence of various grades of colorectal neoplasia. Due to the lower rate of malignant transformation, PIPs do not need to be removed conventionally. However, due to the increased risk of colorectal neoplasia, IBD patients with PIPs should undergo strengthened surveillance to detect early dysplastic changes to allow for appropriate management to improve quality of life and survival rates.

Research perspectives

There are still many gaps in this field of research, such as information on safe and reasonable endoscopic surveillance intervals for patients with PIPs and the pathogenic process of PIPs in colorectal neoplasia. Therefore, additional well-designed multicenter trials are needed.

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