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# BMJ Open

## Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

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**TITLE**

Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

**AUTHORSHIP**

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Word count: 1947

## ABSTRACT

### Introduction

Non-polypoid low-grade dysplasia in inflammatory bowel disease is associated with medium increased risk of colorectal cancer, while treatment recommendations remain controversial. We aim to evaluate the effectiveness and safety of endoscopic treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

### Methods and analysis

Medline, Embase, Cochrane Library, and clinical trials registry from database inception to the search date will be used to retrieve the eligible studies. Studies that report the curative resection rate or any of other secondary outcomes of endoscopic treatment in patients with non-polypoid dysplasia in patients with non-polypoid dysplasia in inflammatory bowel disease will be included in the analysis. Quantitative synthesis will be conducted if the eligible studies are homogeneous judging from clinical and methodological perspective.

### Ethics and dissemination

A formal ethical approval is waived since there is no individual data involved in the analysis and all the combined results will be retrieved from study-level data. The results will be disseminated through peer-reviewed journals or conference abstracts.

### Registration number

CRD42019120413.

### Key words

Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review, protocol.

## INTRODUCTION

### Description of the condition

Inflammatory Bowel Disease (IBD) is a chronic relapsing disease including Ulcerative Colitis (UC) and Crohn's Disease (CD). The annual incidence of IBD is 37.0-39.4/100,000 person-years in western countries and 11.3/10000 person-years in Asian area.<sup>1</sup> Patients with long-term IBD have an increased risk of colorectal cancer (CRC), and most cases of CRC are believed to arise from dysplasia.<sup>2</sup> The cumulative incidence of neoplasia (sporadic adenoma, dysplasia, and CRC) in long-standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.<sup>3</sup> The hazard ratio of developing CRC in IBD patients with dysplasia compared to IBD patients without dysplasia was 7.8 for low grade dysplasia (LGD) and 33.1 for high grade dysplasia (HGD).<sup>3</sup> Therefore, timely surveillance and early treatment of precancerous lesions (dysplasia) are essential to prevent CRC in IBD.

According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-visible. And visible lesions are further divided into polypoid dysplasia (PD, protruding from the mucosa into the lumen  $\geq$  2.5 mm) and non-polypoid dysplasia (NPD,  $<$  2.5 mm or no protrusion above the mucosa) dysplasia.<sup>4</sup> There is a strong association between high-grade dysplasia (HGD) and synchronous<sup>5</sup> or metachronous<sup>3</sup> CRC, justifying colectomy as a reasonable treatment for patients with IBD-HGD. With regards to low-grade dysplasia (LGD), polypoid LGD (PLGD) is believed to be an indication for endoscopic resection, due to technical feasibility and much lower risk of recurrence. Treatment recommendations for non-polypoid LGD (NPLGD), however, remain controversial,<sup>6</sup> since NPLGD has medium risk (e.g., between PLGD<sup>8</sup> and HGD<sup>3</sup>) to develop CRC<sup>7</sup> but requires much higher endoscopic skill to resect it.

### Description of the intervention

Endoscopic resection techniques for NPLGD consist of endoscopic mucosal resection

(EMR) and endoscopic submucosal dissection (ESD). The safety of endoscopic resection for PLGD has been well confirmed by meta-analysis with post-operation CRC risk of as low as 5/1000 person-years.<sup>8</sup> Data about cancer risk after resection of NPD in IBD are scarce. The submucosal fibrosis and obscure margin of NPD in IBD are responsible for technical difficulties in endoscopic resection.<sup>9</sup> With the development of endoscopic techniques, several studies started to fill the gap in the literature on endoscopic resection in the management of NPD.<sup>10</sup>

### **Why it is important to do this review**

The small sample sizes and heterogeneity of these studies compromised reliability of their conclusions. Therefore, it is important to perform a systematic review collecting and evaluating available evidence and to establish a body of evidence for IBD patients with NPD undergoing endoscopic resection.

### **Objectives**

This systematic review and meta-analysis aims to evaluate effectiveness (curative resection rate, etc.) and safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

### **METHODS AND ANALYSIS**

The protocol was registered on the PROSPERO website (CRD42019120413) and reported in compliance with PRISMA-P statement.<sup>11</sup> Any further amendments in the protocol and conducting of this systematic review will be recorded and submitted to the PROSPERO website and reported in the future publications.

### **Inclusion criteria for study selection**

#### Types of studies

Eligible studies may include retrospective or prospective cohort studies (single-arm or multiple exposure groups), consecutive case series, cross-sectional studies, or randomized controlled trials that reporting at least one of the primary outcomes

(curative resection rate) and secondary outcomes (en-bloc resection rate, incidence of carcinogenesis, local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and perforation during the procedure, rate of submucosal fibrosis, and overall survival).

#### Types of participants

Patients diagnosed with inflammatory bowel disease and non-polypoid dysplasia confirmed by clinical, endoscopic and histological evaluation. Due to the update of terminology, the term non-polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally spreading tumors.<sup>4</sup>

#### Types of interventions

The endoscopic resection includes EMR and ESD for non-polypoid dysplasia in IBD.

#### Types of outcome measures

The primary outcome in our systematic review is curative resection rate of non-polypoid dysplasia.<sup>12</sup> The secondary outcomes in this systematic review include en-bloc resection rate, complete resection rate, incidence of carcinogenesis, local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and perforation during the procedure, rate of submucosal fibrosis, and overall survival.

#### **Search methods for identification of studies**

Potentially relevant studies will be searched using Medline, Embase, the Cochrane Controlled Register of Trials (CENTRAL), and clinicaltrials.gov registry from database inception up to 1 February 2019. Free text and MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will be used in the literature search. No filter for study design will be used. Hand search of the bibliographies of relevant review and systematic review articles will be also conducted. There is no language limitation in the literature search. Detailed literature search strategy is shown in Supplemental Table S1.

#### **Data collection and analysis**

## Selection of studies

Records retrieved from literature search will be imported into Endnote and duplicated citations will be removed. Two investigators (CW and ZY) will independently assess the eligibility of the citations using the title and abstract and full texts of potentially eligible studies will be used to judge the final eligibility. Disagreement during the literature screening and inclusion will be resolved by discussion with a methodologist (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

## Data extraction and management

Data will be extracted into an Excel extraction form by one investigator (CW) and double-checked by one methodologist (ZYL). The following information will be extracted from each eligible study: 1) basic information of the study (author, publication year, design); 2) patients' characteristics (age, sex, duration of disease, lesion size, lesion location, submucosal fibrosis and different types of IBD (UC and CD)); 3) detailed information of the endoscopic therapy (EMR, ESD, etc.); 4) outcome data (total number of patients receiving the endoscopic resection for non-polypoid dysplasia, number of patients with en-bloc/complete/curative resection, postoperative bleeding and perforation, submucosal fibrosis, carcinogenesis, local recurrence, and metachronous recurrence, and overall survival in long-term follow-up). We will make the largest use of all the available materials of the relevant studies, including but not limited to the publication for the main results and study design, unpublished report, information from study registry, and online appendices. If the key information was not reported in the above sources, we will try to contact the investigators to get the relevant data through email.

## Risk of bias assessment

This planned systematic review aims to collect evidence from randomized clinical trials and observational studies. The current available tools for the risk of bias assessment need to be modified to assess the risk of bias of eligible studies, since we anticipate that



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4 the data of resection rate will be mostly reported in single-arm cohort studies, lacking  
5 comparison between different intervention groups that could be addressed by  
6 commonly used tools such as the Newcastle-Ottawa Scale (NOS). Thus we will use a  
7 modified tool to assess the risk of bias of eligible studies based on the Agency for  
8 Healthcare Research and Quality (AHRQ) tool.<sup>13</sup> Selection bias, performance bias,  
9 attrition bias, detection bias, and reporting bias will be evaluated by one investigator (CW)  
10 and double checked by one methodologist (ZYL). Any disagreement will be resolved  
11 by discussion with a senior investigator (WD). Detailed criteria to assess the risk of bias  
12 are shown in Supplemental Table S2. Results from risk of bias assessment will be  
13 tabulated shown.  
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### 23 Statistical analysis

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26 We will firstly describe the basic characteristics and risk of bias of eligible studies. If  
27 studies with different designs were eligible, they will be reported and synthesized  
28 separately. The eligible studies will be assessed in terms of heterogeneity by evaluating  
29 the clinical and methodological differences qualitatively, and if there was significant  
30 heterogeneity, quantitative synthesis will be abandoned. Considering the potential  
31 heterogeneity among eligible studies, random-effects model will be used to combine  
32 the effect. The curative resection rate and other secondary outcomes with 95% CI will  
33 be pooled as proportion with logit transformation. Clopper-Pearson interval method  
34 will be used to estimate the CI in each individual study. The between-study variance  
35 will be estimated using the restricted maximum-likelihood estimator. We will measure  
36 heterogeneity between studies using  $I^2$  statistics and we will not use predefined criteria  
37 of  $I^2$  statistics for significant heterogeneity. There is no planned assessment for  
38 reporting bias in this systematic review since the hypothesis behind the commonly  
39 applied methods for detecting reporting bias may not be satisfied in the meta-analysis  
40 for single-armed rate or proportions.  
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56 Subgroup analysis will be conducted with regards to lesion size, lesion location,  
57 duration of the disease, submucosal fibrosis and different types of IBD (UC and CD).  
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4 Post-hoc subgroup analysis will be conducted if there is evidence that some important  
5 sources contribute to the statistical heterogeneity. The potential sources of  
6 heterogeneity will be further assessed using multiple random-effects meta-regression  
7 to explore the independent contribution of each variable to the main outcome. Results  
8 from post-hoc subgroup analysis will be interpreted as hypothesis-generating rather  
9 than definite evidence for subgroup difference.  
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16 Sensitivity analysis using different transformation methods (log transformation,  
17 Freeman-Tukey Double arcsine transformation, Arcsine transformation, or raw  
18 proportion without transformation) will be conducted to check if the main findings are  
19 robust. All the statistical analysis will be completed in R (version 3.5.2) with two-sided  
20  $\alpha$  of 0.05.  
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#### 26 Grading the quality of evidence

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29 The quality of evidence for all the outcomes will be assessed using the Grading of  
30 Recommendations Assessment, Development and Evaluation (GRADE) working  
31 group methodology.<sup>14</sup> Detailed evaluation methods will follow the recommendations  
32 from GRADE working group.  
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#### 36 Role of funding source, ethics, conflict of interest, and dissemination

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39 This systematic review and meta-analysis is funded by Peking Union Medical College  
40 (100232017). The sponsor has no role in study design, data collection, data analysis,  
41 and results interpretation. A formal ethical approval is waived since there is no  
42 individual data involved in the analysis and all the combined results will be retrieved  
43 from study-level data. This is a research protocol for a systematic review and the data  
44 are not collected yet, hence, there is no data published in a data repository. All the  
45 authors declared that there was no conflict of interest. The results will be disseminated  
46 through peer-reviewed publications or conference abstracts.  
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## 55 **DISCUSSION**

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58 Taking into account the lack of evidence in natural history for non-polypoid dysplastic  
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4 lesions after endoscopic resection,<sup>4</sup> this planned systematic review and meta-analysis  
5 will provide useful information leading to reasonable therapeutic strategies for  
6 management of non-polypoid dysplasia in IBD. This systematic review may have some  
7 potential limitations. The best evidence evaluating the effect of endoscopic resection  
8 should come from randomized controlled trials comparing the endoscopic resection  
9 versus other therapies in patients with non-polypoid dysplasia in inflammatory bowel  
10 disease. However, based on our pilot literature search, few studies, if any, have  
11 addressed this problem in a randomized design. The data synthesis from a single-arm  
12 cohort studies or other relevant data sources may be highly sensitive to the selection of  
13 population, hence, there may be significant heterogeneity between studies.  
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### 23 **CONTRIBUTION**

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26 WD is the guarantor of this systematic review and launched this research. CW and ZY  
27 completed the pilot literature search and will conducted the formal literature search and  
28 screening. ZYL designed the data extraction form, the tool for risk of bias assessment,  
29 and data synthesis plan. CW and ZY will extract the data. ZYL will conduct the  
30 quantitative synthesis. WD, CW, ZY, and ZYL will interpret the results. All the authors  
31 contributed to the drafting of the manuscript and approved the publication.  
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### 39 **ACKNOWLEDGEMENTS**

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42 College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical  
43 College) and Dr. Shi, Wen (Department of Gastroenterology, Peking Union Medical  
44 College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical  
45 College) for providing critical comments for the overall design and manuscript.  
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## ARTICLE SUMMARY

### Strengths and limitations of this study

The systematic review will evaluate the current available evidence of the treatment effectiveness of endoscopic resection for non-polypoid in inflammatory bowel disease.

There is no restriction on population, study design, or publication characteristics (e.g. language).

The planned quantitative synthesis will overcome the limited statistical power in the previous original studies.

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## FIGURES AND TABLES

Table. Literature search strategy in Medline.

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

**ONLINE ONLY APPENDICES**

Supplemental Table. Criteria for risk of bias assessment of eligible studies.

<b>Domain</b>	<b>Item</b>	<b>Response</b>
Selection bias	Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.



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Domain	Item	Response
	<p>that might bias results?</p> <p>Did variation from the study protocol compromise the conclusions of the study?</p>	<p>Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the registration or study protocol; unclear, there is no available registration or protocol.</p>
Attrition bias	<p>Was the follow-up completed in all subjects?</p>	<p>Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.</p>
Detection bias	<p>Were the outcome assessors blinded to the intervention or exposure status of participants?</p>	<p>Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.</p>

Domain	Item	Response
	Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	Were the potential	Low risk, all the predefined outcomes in registration or study protocol were reported in the

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Domain	Item	Response
	<p>outcomes pre-specified by the researchers? Are all pre-specified outcomes reported?</p>	<p>study; high risk, the investigators selectively reported some predefined outcomes, or there are changes in the outcomes of interest; unclear, there is no available registration or study protocol.</p>

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# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

1		#2	If registered, provide the name of the registry (such as	Page 2.
2			PROSPERO) and registration number	
3				
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5				
6	Contact	#3a	Provide name, institutional affiliation, e-mail address of	Page 1.
7			all protocol authors; provide physical mailing address of	
8			corresponding author	
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14	Contribution	#3b	Describe contributions of protocol authors and identify	Page 7.
15			the guarantor of the review	
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20		#4	If the protocol represents an amendment of a previously	Page 2.
21			completed or published protocol, identify as such and	
22			list changes; otherwise, state plan for documenting	
23			important protocol amendments	
24				
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29	Sources	#5a	Indicate sources of financial or other support for the	Page 6.
30			review	
31				
32				
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35	Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 6.
36				
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38	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and / or	Page 6.
39			institution(s), if any, in developing the protocol	
40	or funder			
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43	Rationale	#6	Describe the rationale for the review in the context of	Page 1 to 2.
44			what is already known	
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49	Objectives	#7	Provide an explicit statement of the question(s) the	Page 2.
50			review will address with reference to participants,	
51			interventions, comparators, and outcomes (PICO)	
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56	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.
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design, setting, time frame) and report characteristics  
(such as years considered, language, publication status)  
to be used as criteria for eligibility for the review

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8	Information	#9	Describe all intended information sources (such as	Page 3.
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10	sources		electronic databases, contact with study authors, trial	
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18	Search strategy	#10	Present draft of search strategy to be used for at least	Page 3 and 9.
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20			one electronic database, including planned limits, such	
21				
22			that it could be repeated	
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24				
25	Study records -	#11a	Describe the mechanism(s) that will be used to manage	Page 4.
26				
27	data		records and data throughout the review	
28				
29				
30	management			
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33	Study records -	#11b	State the process that will be used for selecting studies	Page 4.
34				
35	selection process		(such as two independent reviewers) through each	
36				
37			phase of the review (that is, screening, eligibility and	
38				
39			inclusion in meta-analysis)	
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42				
43	Study records -	#11c	Describe planned method of extracting data from reports	Page 4.
44				
45	data collection		(such as piloting forms, done independently, in	
46				
47	process		duplicate), any processes for obtaining and confirming	
48				
49			data from investigators	
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53	Data items	#12	List and define all variables for which data will be sought	Page 4.
54				
55			(such as PICO items, funding sources), any pre-planned	
56				
57			data assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be	Page 3.
2			sought, including prioritization of main and additional	
3	prioritization		outcomes, with rationale	
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9	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias	Page 4 and 5.
10	individual studies		of individual studies, including whether this will be done	
11			at the outcome or study level, or both; state how this	
12			information will be used in data synthesis	
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19	Data synthesis	#15a	Describe criteria under which study data will be	Page 5.
20			quantitatively synthesised	
21				
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24		#15b	If data are appropriate for quantitative synthesis,	Page 5.
25			describe planned summary measures, methods of	
26			handling data and methods of combining data from	
27			studies, including any planned exploration of	
28			consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
29				
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35				
36		#15c	Describe any proposed additional analyses (such as	Page 5 and 6.
37			sensitivity or subgroup analyses, meta-regression)	
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41				
42		#15d	If quantitative synthesis is not appropriate, describe the	Page 5.
43			type of summary planned	
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47	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such	Page 5.
48			as publication bias across studies, selective reporting	
49			within studies)	
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55	Confidence in	#17	Describe how the strength of the body of evidence will	Page 6.
56	cumulative		be assessed (such as GRADE)	
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1 evidence

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3 The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License  
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6 CC-BY 4.0. This checklist was completed on 17. January 2019 using <https://www.goodreports.org/>, a  
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8 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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For peer review only



# BMJ Open

## Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

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Secondary Subject Heading:	Evidence based practice
Keywords:	Non-polypoid dysplasia, Inflammatory bowel diseases, Endoscopy < GASTROENTEROLOGY, Systematic review, Protocol

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Manuscripts

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4 1 **TITLE**

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6 2 Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a  
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8 3 systematic review protocol  
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13 5 **AUTHORSHIP**

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## 1 **ABSTRACT**

### 2 **Introduction**

3 Non-polypoid low-grade dysplasia (LGD) in inflammatory bowel disease is associated  
4 with medium increased risk of colorectal cancer, while treatment recommendations  
5 remain controversial. We aim to evaluate the effectiveness and safety of endoscopic  
6 treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

### 7 **Methods and analysis**

8 Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials  
9 registry from database inception to the search date will be used to retrieve the eligible  
10 studies. Studies that report the curative resection rate or any of other secondary  
11 outcomes of endoscopic treatment in patients with non-polypoid dysplasia in patients  
12 with non-polypoid dysplasia in inflammatory bowel disease will be included in the  
13 analysis. Quantitative synthesis will be conducted if the eligible studies are  
14 homogeneous judging from clinical and methodological perspective.

### 15 **Ethics and dissemination**

16 A formal ethical approval is waived since there is no individual data involved in the  
17 analysis and all the combined results will be retrieved from study-level data. The results  
18 will be disseminated through peer-reviewed journals or conference abstracts.

### 19 **Registration number**

20 CRD42019120413.

### 21 **Key words**

22 Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review,  
23 protocol.

24

## 1 **Strengths and limitations of this study**

- 2 ➤ The planned quantitative synthesis addressing the endoscopic resection for non-  
3 polypoid in inflammatory bowel disease will overcome the limited statistical power  
4 in the previous original studies.
- 5 ➤ There is no restriction on population, study design, or publication characteristics  
6 providing an overall evidence map for the patients' care and clinical practice.
- 7 ➤ Limited evidence from randomised controlled trials may weaken the confidence of  
8 the treatment effectiveness.

## 1 INTRODUCTION

2 Inflammatory Bowel Disease (IBD) is a chronic relapsing disease including Ulcerative  
3 Colitis (UC) and Crohn's Disease (CD). The annual incidence of IBD is 37.0-  
4 39.4/100,000 person-years in western countries and 11.3/10000 person-years in Asian  
5 area.[1] Patients with long-term IBD have an increased risk of colorectal cancer (CRC),  
6 and most cases of CRC are believed to arise from dysplasia.[2] The cumulative  
7 incidence of neoplasia (sporadic adenoma, UC associated dysplasia, and CRC) in long-  
8 standing UC patients was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and  
9 38.9% at 40 years, with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[3] The  
10 hazard ratio of developing CRC in IBD patients with dysplasia compared to IBD  
11 patients without dysplasia was 7.8 for low grade dysplasia (LGD) and 33.1 for high  
12 grade dysplasia (HGD).[3] Therefore, timely surveillance and early treatment of  
13 precancerous lesions (dysplasia) are essential to prevent CRC in IBD.

14 According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-  
15 visible. And visible lesions are further divided into polypoid dysplasia (protruding from  
16 the mucosa into the lumen  $\geq$  2.5 mm) and non-polypoid dysplasia ( $<$  2.5 mm or no  
17 protrusion above the mucosa) dysplasia.[4] There is a strong association between HGD  
18 and synchronous[5] or metachronous[3] CRC, justifying colectomy as a reasonable  
19 treatment for patients with IBD-HGD. With regards to LGD, polypoid LGD is believed  
20 to be an indication for endoscopic resection, due to technical feasibility and much lower  
21 risk of recurrence. Treatment recommendations for non-polypoid LGD, however,  
22 remain controversial,[6] since non-polypoid LGD has medium risk (e.g., between  
23 polypoid LGD[7] and HGD[3]) to develop CRC[8] but requires much higher  
24 endoscopic skill to resect it.

25 Endoscopic resection techniques for non-polypoid LGD consist of endoscopic mucosal  
26 resection (EMR) and endoscopic submucosal dissection (ESD). The safety of  
27 endoscopic resection for polypoid LGD has been well confirmed by meta-analysis with

1 post-operation CRC risk of as low as 5/1000 person-years.[7] Data about cancer risk  
2 after resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis  
3 and obscure margin of non-polypoid dysplasia in IBD are responsible for technical  
4 difficulties in endoscopic resection.[9] With the development of endoscopic techniques,  
5 several studies started to fill the gap in the literature on endoscopic resection in the  
6 management of non-polypoid dysplasia.[10]

7 The small sample sizes and heterogeneity of these studies compromised reliability of  
8 their conclusions. Therefore, it is important to perform a systematic review collecting  
9 and evaluating available evidence and to establish a body of evidence for IBD patients  
10 with non-polypoid dysplasia undergoing endoscopic resection.

## 11 **Objectives**

12 This research protocol aims to report the methodology of a planned systematic review  
13 and meta-analysis that will evaluate the effectiveness (curative resection rate, etc.) and  
14 safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-  
15 polypoid dysplasia in patients with inflammatory bowel disease.

## 16 **METHODS AND ANALYSIS**

17 The protocol was registered on the PROSPERO website (CRD42019120413) and  
18 reported in compliance with PRISMA-P statement.[11] Any further amendments in the  
19 protocol and conducting of this systematic review will be recorded and submitted to the  
20 PROSPERO website and reported in the future publications.

### 21 **Inclusion criteria for study selection**

#### 22 Types of studies

23 Eligible studies may include retrospective or prospective cohort studies (single-arm or  
24 multiple exposure groups), consecutive case series, cross-sectional studies, or  
25 randomized controlled trials that reported at least one of the primary outcomes (curative

1 resection rate) and secondary outcomes (en-bloc resection rate, CRC incidence rate,  
2 local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and  
3 perforation during the procedure, rate of submucosal fibrosis, and overall survival).

#### 4 Types of participants

5 Patients diagnosed with inflammatory bowel disease and non-polypoid dysplasia  
6 confirmed by clinical, endoscopic and histological evaluation. Here, dysplasia refers to  
7 an unequivocal neoplastic alteration of the colonic epithelium with the potential to  
8 become invasive, which is characterized by specific nuclear, cellular and architectural  
9 changes to the epithelium.[12] Due to the update of terminology,[4] the term non-  
10 polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally  
11 spreading tumors (lesions reach a large (>10 mm) lateral diameter without increasing  
12 their height or protrusion above the mucosa).[4,13] Besides, as the term DALM is  
13 confusing and also used to describe all irregular, diffuse masses or plaque lesions in  
14 actively or previously inflamed areas of the colon, to avoid missing eligible studies, we  
15 will carefully check the definition of DALM and will only include those that fulfill the  
16 criteria of non-polypoid dysplasia.

#### 17 Types of interventions

18 The endoscopic resection includes EMR and ESD for non-polypoid dysplasia in IBD.

#### 19 Types of outcome measures

20 The primary outcome in our systematic review is curative resection rate of non-  
21 polypoid dysplasia.[14] The secondary outcomes in this systematic review include en-  
22 bloc resection rate, complete resection rate, CRC incidence rate, local recurrence rate,  
23 metachronous recurrence rate, rate of postoperative bleeding and perforation during the  
24 procedure, rate of submucosal fibrosis, and overall survival.

#### 25 **Search methods for identification of studies**

1 Potentially relevant studies will be searched using Medline, Embase, the Cochrane  
2 Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and  
3 clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and  
4 MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will  
5 be used in the literature search. No filter for study design will be used. Hand search of  
6 the bibliographies of relevant review and systematic review articles will be also  
7 conducted. There is no language limitation in the literature search. Detailed literature  
8 search strategy is shown in Supplemental Table S1.

## 9 **Data collection and analysis**

### 10 Selection of studies

11 Records retrieved from literature search will be imported into Endnote and duplicated  
12 citations will be removed. Two investigators (CW and ZY) will independently assess  
13 the eligibility of the citations using the title and abstract and full texts of potentially  
14 eligible studies will be used to judge the final eligibility. Disagreement during the  
15 literature screening and inclusion will be resolved by discussion with a methodologist  
16 (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

### 17 Data extraction and management

18 Data will be extracted into an Excel extraction form by one investigator (CW) and  
19 double-checked by one methodologist (ZYL). The following information will be  
20 extracted from each eligible study: 1) basic information of the study (author, publication  
21 year, design); 2) patients' characteristics (age, sex, duration of disease, inflammatory  
22 endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis and  
23 different types of IBD (UC and CD), primitive sclerosing cholangitis (PSC)); 3)  
24 detailed information of the endoscopic equipments for surveillance and techniques for  
25 therapy (WLE, CE, NBI, EMR, ESD, etc.); 4) outcome data (total number of patients  
26 receiving the endoscopic resection for non-polypoid dysplasia, number of patients with



1 en-bloc/complete/curative resection (complete resection with submucosal invasion <  
2 1000 mm, absent lymphovascular involvement, good cell differentiation),  
3 postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local  
4 recurrence, and metachronous recurrence, and overall survival in long-term follow-up).  
5 We will make the largest use of all the available materials of the relevant studies,  
6 including but not limited to the publication for the main results and study design,  
7 unpublished report, information from study registry, and online appendices. If the key  
8 information was not reported in the above sources, we will try to contact the  
9 investigators to get the relevant data through email. All the extracted data will be  
10 transformed into the International System of Units.

#### 11 Risk of bias assessment

12 This planned systematic review aims to collect evidence from randomized clinical trials  
13 and observational studies. The current available tools for the risk of bias assessment  
14 need to be modified to assess the risk of bias of eligible studies, since we anticipate that  
15 the data of resection rate will be mostly reported in single-arm cohort studies, lacking  
16 comparison between different intervention groups that could be addressed by  
17 commonly used tools such as the Cochrane Collaboration's tool for assessing risk of  
18 bias in randomised controlled trials and the Newcastle-Ottawa Scale (NOS). If there  
19 were any evidence from traditional randomised studies or cohort studies, we will use  
20 the Cochrane Collaboration's tool and the NOS to evaluate the risk of bias. Otherwise,  
21 we will use a modified tool to assess the risk of bias of eligible studies based on the  
22 Agency for Healthcare Research and Quality (AHRQ) tool.[15] Selection bias,  
23 performance bias, attrition bias, detection bias, and reporting bias will be evaluated by one  
24 investigator (CW) and double checked by one methodologist (ZYL). Any disagreement  
25 will be resolved by discussion with a senior investigator (WD). Detailed criteria to  
26 assess the risk of bias are shown in Supplemental Table S2. Results from risk of bias  
27 assessment will be tabulated shown.

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4 1 Statistical analysis  
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6 2 We will firstly describe the basic characteristics and risk of bias of eligible studies. If  
7  
8 3 studies with different designs were eligible, they will be reported and synthesized  
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10 4 separately. The eligible studies will be assessed in terms of heterogeneity by evaluating  
11  
12 5 the clinical and methodological differences qualitatively, and if there was significant  
13  
14 6 heterogeneity, quantitative synthesis will be abandoned. Considering the potential  
15  
16 7 clinical and methodological heterogeneity among eligible studies, random-effects  
17  
18 8 model will be used to combine the effect. The curative resection rate and other  
19  
20 9 secondary outcomes with 95% CI will be pooled as proportion with logit  
21  
22 10 transformation.[16] Clopper-Pearson interval method will be used to estimate the CI in  
23  
24 11 each individual study.[17] The between-study variance will be estimated using the  
25  
26 12 restricted maximum-likelihood estimator.[18] We will measure heterogeneity between  
27  
28 13 studies using  $I^2$  statistics and we will not use predefined criteria of  $I^2$  statistics for  
29  
30 14 significant heterogeneity.[19,20] There is no planned assessment for reporting bias in  
31  
32 15 this systematic review since the hypothesis behind the commonly applied methods for  
33  
34 16 detecting reporting bias may not be satisfied in the meta-analysis for single-armed rate  
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36 17 or proportions.[21]

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39 18 Subgroup analysis will be conducted with regards to lesion size, lesion location,  
40  
41 19 duration of the disease, submucosal fibrosis and different types of IBD (UC and CD).  
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43 20 Post-hoc subgroup analysis will be conducted if there is evidence that some important  
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45 21 sources contribute to the statistical heterogeneity. The potential sources of  
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47 22 heterogeneity will be further assessed using multiple random-effects meta-regression  
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49 23 to explore the independent contribution of each variable to the main outcome. Results  
50  
51 24 from post-hoc subgroup analysis will be interpreted as hypothesis-generating rather  
52  
53 25 than definite evidence for subgroup difference.

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56 26 Sensitivity analysis using different transformation methods (log transformation,  
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58 27 Freeman-Tukey Double arcsine transformation, Arcsine transformation, or raw  
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1 proportion without transformation) will be conducted to check if the main findings are  
2 robust. All the statistical analysis will be completed in R (R Foundation for Statistical  
3 Computing, Vienna, Austria, version 3.5.2) with two-sided  $\alpha$  of 0.05.

#### 4 Grading the quality of evidence

5 The quality of evidence for all the outcomes will be assessed using the Grading of  
6 Recommendations Assessment, Development and Evaluation (GRADE) working  
7 group methodology.[22] Detailed evaluation methods will follow the recommendations  
8 from GRADE working group.

#### 9 Role of funding source, ethics, conflict of interest, and dissemination

10 This systematic review and meta-analysis is funded by Peking Union Medical College  
11 (100232017). The sponsor has no role in study design, data collection, data analysis,  
12 and results interpretation. A formal ethical approval is waived since there is no  
13 individual data involved in the analysis and all the combined results will be retrieved  
14 from study-level data. This is a research protocol for a systematic review and the data  
15 are not collected yet, hence, there is no data published in a data repository. The results  
16 will be disseminated through peer-reviewed publications or conference abstracts.

#### 17 **Competing Interest statement**

18 All the authors declared that there was no conflict of interest.

#### 19 **Patient and Public Involvement**

20 Patients and or public are not involved.

#### 21 **DISCUSSION**

22 There exist technical difficulties for endoscopic resection of non-polypoid dysplasia  
23 due to indefinite margin and submucosal fibrosis. Our meta-analysis will evaluate the  
24 overall en-bloc/complete/curative resection rate and implement subgroup analysis  
25 according to potential influence factors such as lesion size, inflammatory activity to

1 select patients who may benefit more from endoscopic therapy. In another aspect,  
2 taking into account the lack of evidence in natural history for non-polypoid dysplasia  
3 after endoscopic resection especially for metachronous dysplasia and CRC incidence  
4 rate,[4] this planned systematic review and meta-analysis will provide useful  
5 information of long-term prognosis. We will also compare our results with the evidence  
6 from polypoid dysplasia which was cited by ECCO[6] and SENIC[4] guidelines which  
7 may help to make reasonable therapeutic strategies for management of non-polypoid  
8 dysplasia in IBD. Besides, endoscopic resection has advantage for less complication  
9 risk and confirms to patients' preference,[23] therefore, if endoscopic resection is  
10 reasonable for management of non-polypoid dysplasia, it could be recommended as  
11 primary management. However, this systematic review may have some potential  
12 limitations. The best evidence evaluating the effect of endoscopic resection should  
13 come from randomized controlled trials comparing the endoscopic resection versus  
14 other therapies in patients with non-polypoid dysplasia in inflammatory bowel disease.  
15 However, based on our pilot literature search, few studies, if any, have addressed this  
16 problem in a randomized design. The data synthesis from a single-arm cohort studies  
17 or other relevant data sources may be highly sensitive to the selection of population and  
18 the practice setting, hence, there may be significant heterogeneity between studies.  
19 Moreover, the potential limited follow-up may be insufficient to observe enough cases  
20 for some long-term outcome events such as CRC incidence rate, local recurrence rate,  
21 and overall survival. The underlying heterogeneity regarding to clinical and  
22 methodological considerations should be evaluated using subgroup analysis or meta-  
23 regression. Nevertheless, the number of eligible studies are expected to be small given  
24 the relatively late application of this technique in practice, limiting our ability of  
25 analyzing the impact factor of the treatment effectiveness.

## 26 **CONTRIBUTION**

27 WD is the guarantor of this systematic review and launched this research. CW and ZY

1 completed the pilot literature search and will conducted the formal literature search and  
2 screening. ZYL designed the data extraction form, the tool for risk of bias assessment,  
3 and data synthesis plan. CW and ZY will extract the data. ZYL will conduct the  
4 quantitative synthesis. WD, CW, ZY, and ZYL will interpret the results. All the authors  
5 contributed to the drafting of the manuscript and approved the publication.

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9 College) and Dr. Shi, Wen (Department of Gastroenterology, Peking Union Medical  
10 College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical  
11 College) for providing critical comments for the overall design and manuscript.

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**Supplementary Table 1. Literature search strategy in Medline.**

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

**Supplementary Table 2. Detailed criteria to assess the risk of bias.**

Domain	Item	Response
Selection bias	1. Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2. Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2. Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	the registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1. Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1. Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

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Domain	Item	Response
	<p>2. Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?</p>	<p>Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of valid and reliable participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.</p>
	<p>3. Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?</p>	<p>Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.</p>
Reporting bias	<p>1. Were the potential outcomes pre-specified by</p>	<p>Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are</p>

Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

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# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

1		#2	If registered, provide the name of the registry (such as	Page 2.
2			PROSPERO) and registration number	
3				
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6	Contact	#3a	Provide name, institutional affiliation, e-mail address of	Title page.
7			all protocol authors; provide physical mailing address of	
8			corresponding author	
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14	Contribution	#3b	Describe contributions of protocol authors and identify	Page 8.
15			the guarantor of the review	
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20		#4	If the protocol represents an amendment of a previously	Page 2.
21			completed or published protocol, identify as such and	
22			list changes; otherwise, state plan for documenting	
23			important protocol amendments	
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29	Sources	#5a	Indicate sources of financial or other support for the	Page i and 7.
30			review	
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35	Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
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38	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and / or	Page 7.
39			institution(s), if any, in developing the protocol	
40	or funder			
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43	Rationale	#6	Describe the rationale for the review in the context of	Page 1 to 2.
44			what is already known	
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48	Objectives	#7	Provide an explicit statement of the question(s) the	Page 2.
49			review will address with reference to participants,	
50			interventions, comparators, and outcomes (PICO)	
51				
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56	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.
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design, setting, time frame) and report characteristics  
(such as years considered, language, publication status)  
to be used as criteria for eligibility for the review

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8	Information	#9	Describe all intended information sources (such as	Page 3.
9				
10	sources		electronic databases, contact with study authors, trial	
11				
12			registers or other grey literature sources) with planned	
13				
14			dates of coverage	
15				
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18	Search strategy	#10	Present draft of search strategy to be used for at least	Page 4.
19				
20			one electronic database, including planned limits, such	
21				
22			that it could be repeated	
23				
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25				
26	Study records -	#11a	Describe the mechanism(s) that will be used to manage	Page 4.
27	data		records and data throughout the review	
28				
29				
30	management			
31				
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33	Study records -	#11b	State the process that will be used for selecting studies	Page 4.
34	selection process		(such as two independent reviewers) through each	
35				
36			phase of the review (that is, screening, eligibility and	
37				
38			inclusion in meta-analysis)	
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43	Study records -	#11c	Describe planned method of extracting data from reports	Page 4.
44	data collection		(such as piloting forms, done independently, in	
45				
46			duplicate), any processes for obtaining and confirming	
47	process		data from investigators	
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53	Data items	#12	List and define all variables for which data will be sought	Page 4.
54				
55			(such as PICO items, funding sources), any pre-planned	
56				
57			data assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be	Page 3.
2			sought, including prioritization of main and additional	
3	prioritization		outcomes, with rationale	
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9	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias	Page 5.
10			of individual studies, including whether this will be done	
11	individual studies		at the outcome or study level, or both; state how this	
12			information will be used in data synthesis	
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19	Data synthesis	#15a	Describe criteria under which study data will be	Page 6.
20			quantitatively synthesised	
21				
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24		#15b	If data are appropriate for quantitative synthesis,	Page 6.
25			describe planned summary measures, methods of	
26			handling data and methods of combining data from	
27			studies, including any planned exploration of	
28			consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
29				
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36		#15c	Describe any proposed additional analyses (such as	Page 6 and 7.
37			sensitivity or subgroup analyses, meta-regression)	
38				
39				
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41				
42		#15d	If quantitative synthesis is not appropriate, describe the	Page 6.
43			type of summary planned	
44				
45				
46				
47	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such	Page 6 and 7.
48			as publication bias across studies, selective reporting	
49			within studies)	
50				
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55	Confidence in	#17	Describe how the strength of the body of evidence will	Page 7.
56			be assessed (such as GRADE)	
57	cumulative			
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1 evidence

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6 CC-BY 4.0. This checklist was completed on 17. January 2019 using <https://www.goodreports.org/>, a  
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8 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

Journal:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Gastroenterology and hepatology
Secondary Subject Heading:	Evidence based practice
Keywords:	Non-polypoid dysplasia, Inflammatory bowel diseases, Endoscopy < GASTROENTEROLOGY, Systematic review, Protocol

SCHOLARONE™  
Manuscripts

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4 1 **TITLE**

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6 2 Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a  
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8 3 systematic review protocol  
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13 5 **AUTHORSHIP**

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## 1 **ABSTRACT**

### 2 **Introduction**

3 Non-polypoid low-grade dysplasia (LGD) in inflammatory bowel disease is associated  
4 with medium increased risk of colorectal cancer, while treatment recommendations  
5 remain controversial. We aim to evaluate the effectiveness and safety of endoscopic  
6 treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

### 7 **Methods and analysis**

8 Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials  
9 registry from database inception to the search date will be used to retrieve the eligible  
10 studies. Studies that report the curative resection rate or any of other secondary  
11 outcomes of endoscopic treatment in patients with non-polypoid dysplasia in patients  
12 with non-polypoid dysplasia in inflammatory bowel disease will be included in the  
13 analysis. Quantitative synthesis will be conducted if the eligible studies are  
14 homogeneous judging from clinical and methodological perspective.

### 15 **Ethics and dissemination**

16 A formal ethical approval is waived since there is no individual data involved in the  
17 analysis and all the combined results will be retrieved from study-level data. The results  
18 will be disseminated through peer-reviewed journals or conference abstracts.

### 19 **Registration number**

20 CRD42019120413.

### 21 **Key words**

22 Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review,  
23 protocol.

24

## 1 **Strengths and limitations of this study**

- 2 ➤ The planned quantitative synthesis addressing the endoscopic resection for non-  
3 polypoid in inflammatory bowel disease will overcome the limited statistical power  
4 in the previous original studies.
- 5 ➤ There is no restriction on population, study design, or publication characteristics  
6 providing an overall evidence map for the patients' care and clinical practice.
- 7 ➤ Limited evidence from randomised controlled trials may weaken the confidence of  
8 the treatment effectiveness.

## 12 INTRODUCTION

13 Inflammatory Bowel Disease (IBD) is a chronic relapsing disease including Ulcerative  
14 Colitis (UC) and Crohn's Disease (CD). The annual incidence of IBD is 37.0-  
15 39.4/100,000 person-years in western countries and 11.3/10000 person-years in Asian  
16 area.[1] Patients with long-term IBD have an increased risk of colorectal cancer (CRC),  
17 and most cases of CRC are believed to arise from dysplasia.[2] Here, dysplasia refers  
18 to an unequivocal neoplastic alteration of the colonic epithelium without evidence of  
19 tissue invasion, which is characterized by specific cytological and/or architectural  
20 changes to the epithelium, and CRC refers to lesions that show histological evidence of  
21 invasion through the muscularis mucosa into the submucosa.[3] Besides, the colitis  
22 associated dysplasia should be distinguished from sporadic neoplasm by  
23 comprehensive judgement based on the site, morphology and histological feature of the  
24 lesion according to the European consensus.[4] The cumulative incidence of neoplasia  
25 (sporadic adenoma, UC associated dysplasia, and CRC) in long-standing UC patients  
26 was 4.1% at 10 years, 14.1% at 20 years, 28% at 30 years, and 38.9% at 40 years, with  
27 CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[5] The hazard ratio of developing  
28 CRC in IBD patients with dysplasia compared to IBD patients without dysplasia was  
29 7.8 for low grade dysplasia (LGD) and 33.1 for high grade dysplasia (HGD).[5]  
30 Therefore, timely surveillance and early treatment of precancerous lesions (dysplasia)  
31 are essential to prevent CRC in IBD.

32 According to the SCENIC consensus, IBD-dysplasia is classified into visible and non-  
33 visible. And visible lesions are further divided into polypoid dysplasia ( protruding from  
34 the mucosa into the lumen  $\geq$  2.5 mm) and non-polypoid dysplasia ( $<$  2.5 mm or no  
35 protrusion above the mucosa) dysplasia.[6] There is a strong association between HGD  
36 and synchronous[7] or metachronous[5] CRC, justifying colectomy as a reasonable  
37 treatment for patients with IBD-HGD. With regards to LGD, polypoid LGD is believed  
38 to be an indication for endoscopic resection, due to technical feasibility and much lower

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4 39 risk of recurrence. Treatment recommendations for non-polypoid LGD, however,  
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6 40 remain controversial,[8] since non-polypoid LGD has medium risk (e.g., between  
7  
8 41 polypoid LGD[9] and HGD[5]) to develop CRC[10] but requires much higher  
9  
10 42 endoscopic skill to resect it.

11  
12 43 Endoscopic resection techniques for non-polypoid LGD consist of endoscopic mucosal  
13  
14 44 resection (EMR) and endoscopic submucosal dissection (ESD). The safety of  
15  
16 45 endoscopic resection for polypoid LGD has been well confirmed by meta-analysis with  
17  
18 46 post-operation CRC risk of as low as 5/1000 person-years.[9] Data about cancer risk  
19  
20 47 after resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis  
21  
22 48 and obscure margin of non-polypoid dysplasia in IBD are responsible for technical  
23  
24 49 difficulties in endoscopic resection.[11] With the development of endoscopic  
25  
26 50 techniques, several studies started to fill the gap in the literature on endoscopic resection  
27  
28 51 in the management of non-polypoid dysplasia.[12]

29  
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31 52 The small sample sizes and heterogeneity of these studies compromised reliability of  
32  
33 53 their conclusions. Therefore, it is important to perform a systematic review collecting  
34  
35 54 and evaluating available evidence and to establish a body of evidence for IBD patients  
36  
37 55 with non-polypoid dysplasia undergoing endoscopic resection.

## 38 39 40 56 **Objectives**

41  
42  
43 57 This research protocol aims to report the methodology of a planned systematic review  
44  
45 58 and meta-analysis that will evaluate the effectiveness (curative resection rate, etc.) and  
46  
47 59 safety (recurrence, bleeding, perforation, etc.) of endoscopic treatment for the non-  
48  
49 60 polypoid dysplasia in patients with inflammatory bowel disease.

## 50 51 52 61 **METHODS AND ANALYSIS**

53  
54  
55 62 The protocol was registered on the PROSPERO website (CRD42019120413) and  
56  
57 63 reported in compliance with PRISMA-P statement.[13] Any further amendments in the  
58  
59 64 protocol and conducting of this systematic review will be recorded and submitted to the  
60



1  
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4 65 PROSPERO website and reported in the future publications.  
5

6 66 **Inclusion criteria for study selection**  
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9 67 Types of studies  
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11 68 Eligible studies may include retrospective or prospective cohort studies (single-arm or  
12 multiple exposure groups), consecutive case series, cross-sectional studies, or  
13  
14 69 randomized controlled trials that reported at least one of the primary outcomes (curative  
15 resection rate) and secondary outcomes (en-bloc resection rate, CRC incidence rate,  
16  
17 70 local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and  
18 perforation during the procedure, rate of submucosal fibrosis, and overall survival).  
19  
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24 74 Types of participants  
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26  
27 75 Patients diagnosed with inflammatory bowel disease and non-polypoid dysplasia  
28 confirmed by clinical, endoscopic and histological evaluation. Here, dysplasia refers to  
29  
30 76 an unequivocal neoplastic alteration of the colonic epithelium without evidence of  
31 tissue invasion, which is characterized by specific cytological and/or architectural  
32  
33 77 changes to the epithelium[3]. Due to the update of terminology,[6] the term non-  
34 polypoid dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally  
35  
36 78 spreading tumors (lesions reach a large (>10 mm) lateral diameter without increasing  
37 their height or protrusion above the mucosa).[6,14] Besides, as the term DALM is  
38  
39 79 confusing and also used to describe all irregular, diffuse masses or plaque lesions in  
40 actively or previously inflamed areas of the colon, to avoid missing eligible studies, we  
41  
42 80 will carefully check the definition of DALM and will only include those that fulfill the  
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44 81 criteria of non-polypoid dysplasia.  
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52 87 Types of interventions  
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55 88 The endoscopic resection includes EMR and ESD for non-polypoid dysplasia in IBD.  
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58 89 Types of outcome measures  
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4 90 The primary outcome in our systematic review is curative resection rate of non-  
5  
6 91 polypoid dysplasia.[15] The secondary outcomes in this systematic review include en-  
7  
8 92 bloc resection rate, complete resection rate, CRC incidence rate, local recurrence rate,  
9  
10 93 metachronous recurrence rate, rate of postoperative bleeding and perforation during the  
11  
12 94 procedure, rate of submucosal fibrosis, and overall survival.

#### 14 95 **Search methods for identification of studies**

16  
17 96 Potentially relevant studies will be searched using Medline, Embase, the Cochrane  
18  
19 97 Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and  
20  
21 98 clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and  
22  
23 99 MeSH terms relevant with endoscopy, inflammatory bowel disease, and dysplasia will  
24  
25 100 be used in the literature search. No filter for study design will be used. Hand search of  
26  
27 101 the bibliographies of relevant review and systematic review articles will be also  
28  
29 102 conducted. There will be no language limitation in the literature search. Detailed  
30  
31 103 literature search strategy is shown in Supplemental Table S1.

#### 34 104 **Data collection and analysis**

##### 36 105 Selection of studies

37  
38  
39 106 Records retrieved from literature search will be imported into Endnote and duplicated  
40  
41 107 citations will be removed. Two investigators (CW and ZY) will independently assess  
42  
43 108 the eligibility of the citations using the title and abstract and full texts of potentially  
44  
45 109 eligible studies will be used to judge the final eligibility. Disagreement during the  
46  
47 110 literature screening and inclusion will be resolved by discussion with a methodologist  
48  
49 111 (ZYL). Reasons for excluding citations in each stage will be noted in Endnote library.

##### 52 112 Data extraction and management

53  
54  
55 113 Data will be extracted into an Excel extraction form by one investigator (CW) and  
56  
57 114 double-checked by one methodologist (ZYL). The following information will be  
58  
59 115 extracted from each eligible study: 1) basic information of the study (author, publication  
60

1  
2  
3  
4 116 year, design); 2) patients' characteristics (age, sex, duration of disease, inflammatory  
5  
6 117 endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis and  
7  
8 118 different types of IBD (UC and CD), primitive sclerosing cholangitis (PSC)); 3)  
9  
10 119 detailed information of the endoscopic equipments for surveillance and techniques for  
11  
12 120 therapy (WLE, CE, NBI, EMR, ESD, etc.); 4) outcome data (total number of patients  
13  
14 121 receiving the endoscopic resection for non-polypoid dysplasia, number of patients with  
15  
16 122 en-bloc/complete/curative resection (complete resection with submucosal invasion <  
17  
18 123 1000 mm, absent lymphovascular involvement, good cell differentiation),  
19  
20 124 postoperative bleeding and perforation, submucosal fibrosis, CRC incidence, local  
21  
22 125 recurrence, and metachronous recurrence, and overall survival in long-term follow-up).  
23  
24 126 We will make the largest use of all the available materials of the relevant studies,  
25  
26 127 including but not limited to the publication for the main results and study design,  
27  
28 128 unpublished report, information from study registry, and online appendices. If the key  
29  
30 129 information was not reported in the above sources, we will try to contact the  
31  
32 130 investigators to get the relevant data through email. All the extracted data will be  
33  
34 131 transformed into the International System of Units.

### 36 132 Risk of bias assessment

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38  
39 133 If there were any evidence from randomised studies or two-armed cohort studies, we  
40  
41 134 will use the Cochrane Collaboration's tool for assessing risk of bias in randomised  
42  
43 135 controlled trials and the Newcastle-Ottawa Scale (NOS) to evaluate the risk of bias,  
44  
45 136 respectively. For single-arm cohort studies, we will use a modified tool to assess the  
46  
47 137 risk of bias of eligible studies based on the Agency for Healthcare Research and Quality  
48  
49 138 (AHRQ) tool.[16] The risk of bias will be evaluated by one investigator (CW) and double  
50  
51 139 checked by one methodologist (ZYL). Any disagreement will be resolved by discussion  
52  
53 140 with a senior investigator (WD). Detailed criteria of the modified AHRQ tool are shown  
54  
55 141 in Supplemental Table S2. Results from risk of bias assessment will be tabulated shown.

### 58 142 Statistical analysis

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4 143 We will firstly describe the basic characteristics and risk of bias of eligible studies. If  
5  
6 144 studies with different designs were eligible, they will be reported and synthesized  
7  
8 145 separately. The eligible studies will be assessed in terms of heterogeneity by evaluating  
9  
10 146 the clinical and methodological differences qualitatively, and if there was significant  
11  
12 147 heterogeneity, quantitative synthesis will be abandoned.

13  
14 148 This planned systematic review aims to collect evidence from randomized clinical trials  
15  
16 149 and observational studies, however, we anticipate that the data of resection rate will be  
17  
18 150 mostly reported in single-arm cohort studies, lacking comparison between randomly  
19  
20 151 allocated intervention groups. Considering the potential clinical and methodological  
21  
22 152 heterogeneity among eligible observational studies, random-effects model will be used  
23  
24 153 to combine the effect.[17] The curative resection rate and all the secondary outcomes  
25  
26 154 with 95% CI will be pooled as proportion with logit transformation if there were enough  
27  
28 155 data supporting for the synthesis.[18] Clopper-Pearson interval method will be used to  
29  
30 156 estimate the CI in each individual study.[19]

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32  
33 157 The between-study variance will be estimated using the restricted maximum-likelihood  
34  
35 158 estimator.[20] We will measure heterogeneity between studies using  $I^2$  statistics and an  
36  
37 159  $I^2$  value larger than 50% will be considered as substantial heterogeneity.[21]

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39  
40 160 There is no planned assessment for reporting bias in this systematic review since the  
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42 161 hypothesis behind the commonly applied methods for detecting reporting bias may not  
43  
44 162 be satisfied in the meta-analysis for single-armed rate or proportions.[22]

45  
46  
47 163 Subgroup analysis will be conducted with regards to lesion size, lesion location,  
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49 164 duration of the disease, submucosal fibrosis and different types of IBD (UC and CD).  
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51 165 Post-hoc subgroup analysis will be conducted if there is evidence that some important  
52  
53 166 sources contribute to the statistical heterogeneity. The potential sources of  
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55 167 heterogeneity will be further assessed using multiple random-effects meta-regression  
56  
57 168 to explore the independent contribution of each variable to the main outcome. Results  
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59 169 from post-hoc subgroup analysis will be interpreted as hypothesis-generating rather

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4 170 than definite evidence for subgroup difference.  
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6 171 Sensitivity analysis using different transformation methods (log transformation,  
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8 172 Freeman-Tukey Double arcsine transformation, Arcsine transformation, or raw  
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10 173 proportion without transformation) will be conducted to check if the main findings are  
11  
12 174 robust. All the statistical analysis will be completed in R (R Foundation for Statistical  
13  
14 175 Computing, Vienna, Austria, version 3.5.2) with two-sided  $\alpha$  of 0.05.  
15  
16

17 176 Grading the quality of evidence  
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19  
20 177 The quality of evidence for all the outcomes will be assessed using the Grading of  
21  
22 178 Recommendations Assessment, Development and Evaluation (GRADE) working  
23  
24 179 group methodology.[23] Detailed evaluation methods will follow the recommendations  
25  
26 180 from GRADE working group.  
27

28  
29 181 Role of funding source, ethics, conflict of interest, and dissemination  
30

31 182 This systematic review and meta-analysis is funded by Peking Union Medical College  
32  
33 183 (100232017). The sponsor has no role in study design, data collection, data analysis,  
34  
35 184 and results interpretation. A formal ethical approval is waived since there is no  
36  
37 185 individual data involved in the analysis and all the combined results will be retrieved  
38  
39 186 from study-level data. This is a research protocol for a systematic review and the data  
40  
41 187 are not collected yet, hence, there is no data published in a data repository. The results  
42  
43 188 will be disseminated through peer-reviewed publications or conference abstracts.  
44  
45

46 189 **Competing Interest statement**  
47

48  
49 190 All the authors declared that there was no conflict of interest.  
50

51  
52 191 **Patient and Public Involvement**  
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54 192 Patients and or public are not involved.  
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56

57 193 **DISCUSSION**  
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4 194 There exist technical difficulties for endoscopic resection of non-polypoid dysplasia  
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6 195 due to indefinite margin and submucosal fibrosis. Our meta-analysis will evaluate the  
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8 196 overall en-bloc/complete/curative resection rate and implement subgroup analysis  
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10 197 according to potential influence factors such as lesion size, inflammatory activity to  
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12 198 select patients who may benefit more from endoscopic therapy. In another aspect,  
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14 199 taking into account the lack of evidence in natural history for non-polypoid dysplasia  
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16 200 after endoscopic resection especially for metachronous dysplasia and CRC incidence  
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18 201 rate,[6] this planned systematic review and meta-analysis will provide useful  
19  
20 202 information of long-term prognosis. We will also compare our results with the evidence  
21  
22 203 from polypoid dysplasia which was cited by ECCO[8] and SENIC[6] guidelines which  
23  
24 204 may help to make reasonable therapeutic strategies for management of non-polypoid  
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26 205 dysplasia in IBD. Besides, endoscopic resection has advantage for less complication  
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28 206 risk and confirms to patients' preference,[24] therefore, if endoscopic resection is  
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30 207 reasonable for management of non-polypoid dysplasia, it could be recommended as  
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32 208 primary management. However, this systematic review may have some potential  
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34 209 limitations. The best evidence evaluating the effect of endoscopic resection should  
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36 210 come from randomized controlled trials comparing the endoscopic resection versus  
37  
38 211 other therapies in patients with non-polypoid dysplasia in inflammatory bowel disease.  
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40 212 However, based on our pilot literature search, few studies, if any, have addressed this  
41  
42 213 problem in a randomized design. The data synthesis from a single-arm cohort studies  
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44 214 or other relevant data sources may be highly sensitive to the selection of population and  
45  
46 215 the practice setting, hence, there may be significant heterogeneity between studies.  
47  
48 216 Moreover, the potential limited follow-up may be insufficient to observe enough cases  
49  
50 217 for some long-term outcome events such as CRC incidence rate, local recurrence rate,  
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52 218 and overall survival. The underlying heterogeneity regarding to clinical and  
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54 219 methodological considerations should be evaluated using subgroup analysis or meta-  
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56 220 regression. Nevertheless, the number of eligible studies are expected to be small given  
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58 221 the relatively late application of this technique in practice, limiting our ability of  
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4 222 analyzing the impact factor of the treatment effectiveness.  
5

6 223 **CONTRIBUTION**  
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8  
9 224 WD is the guarantor of this systematic review and launched this research. CW and ZY  
10  
11 225 completed the pilot literature search and will conducted the formal literature search and  
12  
13 226 screening. ZYL designed the data extraction form, the tool for risk of bias assessment,  
14  
15 227 and data synthesis plan. CW and ZY will extract the data. ZYL will conduct the  
16  
17 228 quantitative synthesis. WD, CW, ZY, and ZYL will interpret the results. All the authors  
18  
19 229 contributed to the drafting of the manuscript and approved the publication.  
20  
21

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23

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26  
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28  
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30  
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33 235 College) for providing critical comments for the overall design and manuscript.  
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**Supplementary Table 1. Literature search strategy in Medline.**

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*)).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*)).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

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**Supplementary Table 2. Detailed criteria to assess the risk of bias.**

<b>Domain</b>	<b>Item</b>	<b>Response</b>
Selection bias	1. Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2. Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2. Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	the registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1. Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1. Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

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Domain	Item	Response
	2. Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of valid and reliable participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	3. Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	1. Were the potential outcomes pre-specified by	Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are

Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

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# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.



1		#2	If registered, provide the name of the registry (such as	Page 2.
2			PROSPERO) and registration number	
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6	Contact	#3a	Provide name, institutional affiliation, e-mail address of	Title page.
7			all protocol authors; provide physical mailing address of	
8			corresponding author	
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14	Contribution	#3b	Describe contributions of protocol authors and identify	Page 8.
15			the guarantor of the review	
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20		#4	If the protocol represents an amendment of a previously	Page 2.
21			completed or published protocol, identify as such and	
22			list changes; otherwise, state plan for documenting	
23			important protocol amendments	
24				
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29	Sources	#5a	Indicate sources of financial or other support for the	Page i and 7.
30			review	
31				
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35	Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
36				
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38	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and / or	Page 7.
39			institution(s), if any, in developing the protocol	
40	or funder			
41				
42				
43	Rationale	#6	Describe the rationale for the review in the context of	Page 1 to 2.
44			what is already known	
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48	Objectives	#7	Provide an explicit statement of the question(s) the	Page 2.
49			review will address with reference to participants,	
50			interventions, comparators, and outcomes (PICO)	
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56	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.
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design, setting, time frame) and report characteristics  
(such as years considered, language, publication status)  
to be used as criteria for eligibility for the review

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8	Information	#9	Describe all intended information sources (such as	Page 3.
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10	sources		electronic databases, contact with study authors, trial	
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12			registers or other grey literature sources) with planned	
13				
14			dates of coverage	
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18	Search strategy	#10	Present draft of search strategy to be used for at least	Page 4.
19				
20			one electronic database, including planned limits, such	
21				
22			that it could be repeated	
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26	Study records -	#11a	Describe the mechanism(s) that will be used to manage	Page 4.
27	data		records and data throughout the review	
28				
29				
30	management			
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33	Study records -	#11b	State the process that will be used for selecting studies	Page 4.
34	selection process		(such as two independent reviewers) through each	
35				
36			phase of the review (that is, screening, eligibility and	
37				
38			inclusion in meta-analysis)	
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43	Study records -	#11c	Describe planned method of extracting data from reports	Page 4.
44	data collection		(such as piloting forms, done independently, in	
45				
46			duplicate), any processes for obtaining and confirming	
47	process		data from investigators	
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53	Data items	#12	List and define all variables for which data will be sought	Page 4.
54				
55			(such as PICO items, funding sources), any pre-planned	
56				
57			data assumptions and simplifications	
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1	Outcomes and	#13	List and define all outcomes for which data will be	Page 3.
2			sought, including prioritization of main and additional	
3	prioritization		outcomes, with rationale	
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9	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias	Page 5.
10			of individual studies, including whether this will be done	
11	individual studies		at the outcome or study level, or both; state how this	
12			information will be used in data synthesis	
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19	Data synthesis	#15a	Describe criteria under which study data will be	Page 6.
20			quantitatively synthesised	
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24		#15b	If data are appropriate for quantitative synthesis,	Page 6.
25			describe planned summary measures, methods of	
26			handling data and methods of combining data from	
27			studies, including any planned exploration of	
28			consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
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36		#15c	Describe any proposed additional analyses (such as	Page 6 and 7.
37			sensitivity or subgroup analyses, meta-regression)	
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42		#15d	If quantitative synthesis is not appropriate, describe the	Page 6.
43			type of summary planned	
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47	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such	Page 6 and 7.
48			as publication bias across studies, selective reporting	
49			within studies)	
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55	Confidence in	#17	Describe how the strength of the body of evidence will	Page 7.
56			be assessed (such as GRADE)	
57	cumulative			
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1 evidence

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8 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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# BMJ Open

## Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a systematic review protocol

Journal:	<i>BMJ Open</i>
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SCHOLARONE™  
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4 1 **TITLE**

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6 2 Endoscopic resection for non-polypoid dysplasia in inflammatory bowel disease: a  
7  
8 3 systematic review protocol  
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13 5 **AUTHORSHIP**

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## 1 **ABSTRACT**

### 2 **Introduction**

3 Non-polypoid low-grade dysplasia (LGD) in inflammatory bowel disease is associated  
4 with medium increased risk of colorectal cancer, while treatment recommendations  
5 remain controversial. We aim to evaluate the efficacy and safety of endoscopic  
6 treatment for the non-polypoid dysplasia in patients with inflammatory bowel disease.

### 7 **Methods and analysis**

8 Medline, Embase, Cochrane Library, the Scopus, Web of Science, and clinical trials  
9 registry from database inception to the search date will be used to retrieve the eligible  
10 studies. Studies that report the curative resection rate or any of other secondary  
11 outcomes of endoscopic treatment in patients with non-polypoid dysplasia in  
12 inflammatory bowel disease will be included in the analysis. We will conduct  
13 quantitative synthesis if the eligible studies are homogeneous judging from clinical and  
14 methodological perspectives.

### 15 **Ethics and dissemination**

16 Ethical approval for this study was waived by the Ethics Committee of Peking Union  
17 Medical College Hospital because there is no individual data involved in the analysis,  
18 and all the combined results will be retrieved from study-level data. We plan to  
19 disseminate results through peer-reviewed journals or conference abstracts.

### 20 **Registration number**

21 CRD42019120413.

### 22 **Keywords**

23 Non-polypoid dysplasia, inflammatory bowel diseases, endoscopy, systematic review,  
24 protocol.

## 1 **Strengths and limitations of this study**

- 2 ➤ The planned quantitative synthesis addressing the endoscopic resection for non-  
3 polypoid in inflammatory bowel disease will overcome the limited statistical power  
4 in the previous original studies.
- 5 ➤ There is no restriction on population, study design, or publication characteristics  
6 providing an overall evidence map for clinical practice.
- 7 ➤ Limited evidences from randomised controlled trials may weaken the confidence  
8 of the study conclusion.



## 12 INTRODUCTION

13 Inflammatory Bowel Disease (IBD) is a chronic relapsing disease including Ulcerative  
14 Colitis (UC) and Crohn's Disease (CD). The annual incidence of IBD is 37.0-  
15 39.4/100,000 person-years in western countries and 11.3/10,000 person-years in the  
16 Asian area.[1] Patients with long-term IBD have an increased risk of colorectal cancer  
17 (CRC), and most cases of CRC are believed to arise from dysplasia.[2] Here, dysplasia  
18 refers to an unequivocal neoplastic alteration of the colonic epithelium without  
19 evidence of tissue invasion, which is characterized by specific cytological and/or  
20 architectural changes to the epithelium, and CRC refers to lesions that show histological  
21 evidence of invasion through the muscularis mucosa into the submucosa.[3] Besides,  
22 the colitis-associated dysplasia should be distinguished from sporadic neoplasm by  
23 comprehensive judgement based on the site, morphology and histological feature of the  
24 lesion according to the European consensus.[4] The cumulative incidence of neoplasia  
25 (sporadic adenoma, UC associated dysplasia, and CRC) in long-standing UC patients  
26 was 4.1% at 10 years, 14.1% at 20 years, 28.0% at 30 years, and 38.9% at 40 years,  
27 with CRC risk of 0.1%, 2.9%, 6.7%, 10.0%, respectively.[5] The hazard ratio of  
28 developing CRC in IBD patients with dysplasia compared to IBD patients without  
29 dysplasia was 7.8 for low-grade dysplasia (LGD) and 33.1 for high-grade dysplasia  
30 (HGD).[5] Therefore, timely surveillance and early treatment of precancerous lesions  
31 (dysplasia) are essential to prevent CRC in IBD.

32 The SCENIC consensus classified IBD-dysplasia into visible and non-visible lesions,  
33 with visible lesions further divided into polypoid dysplasia (protruding from the  
34 mucosa into the lumen  $\geq$  2.5 mm) and non-polypoid dysplasia ( $<$  2.5 mm or no  
35 protrusion above the mucosa) dysplasia.[6] There is a strong association between HGD  
36 and CRC (synchronous[7] or metachronous[5]), justifying colectomy as a reasonable  
37 treatment for patients with IBD-HGD. With regards to LGD, polypoid LGD is believed  
38 to be an indication for endoscopic resection, due to technical feasibility and much lower

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4 39 risk of recurrence. Treatment recommendations for non-polypoid LGD, however,  
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6 40 remain controversial,[8] since non-polypoid LGD has medium risk (e.g., between  
7  
8 41 polypoid LGD[9] and HGD[5]) to develop CRC[10] but requires much higher  
9  
10 42 endoscopic skill to resect it.

11  
12 43 Endoscopic resection techniques for non-polypoid LGD consist of endoscopic mucosal  
13  
14 44 resection (EMR) and endoscopic submucosal dissection (ESD). The safety of  
15  
16 45 endoscopic resection for polypoid LGD has been confirmed by meta-analysis with post-  
17  
18 46 operation CRC risk of as low as 5/1,000 person-years.[9] Data about CRC risk after  
19  
20 47 resection of non-polypoid dysplasia in IBD are scarce. The submucosal fibrosis and  
21  
22 48 obscure margin of non-polypoid dysplasia in IBD are responsible for technical  
23  
24 49 difficulties in endoscopic resection.[11] With the development of endoscopic  
25  
26 50 techniques, several studies started to fill the gap on endoscopic resection in the  
27  
28 51 management of non-polypoid dysplasia.[12]

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30  
31 52 The small sample sizes and heterogeneity of these studies compromised the reliability  
32  
33 53 of their conclusions. Therefore, it is crucial to perform a systematic review collecting  
34  
35 54 and evaluating available studies and to establish a body of evidence for IBD patients  
36  
37 55 with non-polypoid dysplasia undergoing endoscopic resection.

## 38 39 40 56 **Objectives**

41  
42  
43 57 This research protocol aims to evaluate the efficacy (curative resection rate, for example)  
44  
45 58 and safety (such as recurrence, bleeding, and perforation) of endoscopic treatment for  
46  
47 59 the non-polypoid dysplasia in patients with IBD.

## 48 49 50 60 **METHODS AND ANALYSIS**

51  
52 61 The protocol was registered on the PROSPERO website (CRD42019120413) and  
53  
54 62 reported in compliance with PRISMA-P statement.[13] Any further amendments in the  
55  
56 63 protocol and conducting of this systematic review will be recorded and submitted to the  
57  
58 64 PROSPERO website and reported in the future publications.

## 65 **Inclusion criteria for study selection**

### 66 Types of studies

67 Eligible studies may include retrospective or prospective cohort studies (single-arm or  
68 multiple exposure groups), consecutive case series, cross-sectional studies, or  
69 randomized controlled trials that reported at least one of the primary outcomes (curative  
70 resection rate) and secondary outcomes (en-bloc resection rate, CRC incidence rate,  
71 local recurrence rate, metachronous recurrence rate, rate of postoperative bleeding and  
72 perforation during the procedure, rate of submucosal fibrosis, and overall survival).

### 73 Types of participants

74 Patients diagnosed with IBD and non-polypoid dysplasia should be confirmed by  
75 clinical, endoscopic, and histological evaluation. Here, dysplasia refers to an  
76 unequivocal neoplastic alteration of the colonic epithelium without evidence of tissue  
77 invasion, which is characterized by specific cytological and/or architectural changes to  
78 the epithelium[3]. Due to the update of terminology,[6] the term non-polypoid  
79 dysplasia here includes flat dysplasia, Paris 0-II lesions, and laterally spreading tumors  
80 (lesions reach a large (>10 mm) lateral diameter without increasing their height or  
81 protrusion above the mucosa).[6,14] To avoid missing eligible studies, we will carefully  
82 check the definition of DALM and will only include those that fulfill the criteria of non-  
83 polypoid dysplasia, since the term DALM is confusing and is used to describe all  
84 irregular, diffuse masses or plaque lesions in actively or previously inflamed areas of  
85 the colon.

### 86 Types of interventions

87 The endoscopic resection includes EMR and ESD for non-polypoid dysplasia in IBD.

### 88 Types of outcome measures

89 The primary outcome in our systematic review is curative resection rate (R0 resection

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4 90 with submucosal invasion <1,000 mm, absent lymphovascular involvement) of non-  
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6 91 polypoid dysplasia.[15] The secondary outcomes in this systematic review include en-  
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8 92 bloc resection rate, R0 resection rate (en-bloc resection with negative horizontal and  
9  
10 93 vertical margin), CRC incidence rate, local recurrence rate, metachronous recurrence  
11  
12 94 rate, rate of postoperative bleeding and perforation during the procedure, rate of  
13  
14 95 submucosal fibrosis, and overall survival.

## 16 96 **Literature search for identification of studies**

17  
18  
19 97 Potentially relevant studies will be searched using Medline, Embase, the Cochrane  
20  
21 98 Controlled Register of Trials (CENTRAL), the Scopus, Web of Science, and  
22  
23 99 clinicaltrials.gov registry from database inception up to 1 July 2019. Free text and  
24  
25 100 MeSH terms relevant to endoscopy, inflammatory bowel disease, and dysplasia will be  
26  
27 101 used in the literature search. We will not use any filter for study design. Hand search of  
28  
29 102 the bibliographies of relevant review and systematic review articles will be also  
30  
31 103 conducted. We will set no language limitation in the literature search. The detailed  
32  
33 104 literature search strategy is shown in Supplemental Table S1.

## 36 105 **Data collection and analysis**

### 39 106 Selection of studies

40  
41  
42 107 Records retrieved from the literature search will be imported into Endnote, and  
43  
44 108 duplicated citations will be removed. Two investigators (CW and ZY) will  
45  
46 109 independently assess the eligibility of the studies by reading the title, abstract, and full  
47  
48 110 texts of potentially eligible studies will be used to determine the final eligibility.  
49  
50 111 Disagreement during the literature screening and inclusion process will be resolved by  
51  
52 112 discussion with a methodologist (ZYL) and a gastroenterologist (WD). In each stage,  
53  
54 113 we will record reasons for excluding citation in the Endnote library.

### 56 114 Data extraction and management

57  
58  
59 115 Data will be extracted into an Excel extraction form by one investigator (CW) and  
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4 116 double-checked by one methodologist (ZYL). We will retrieve the following  
5  
6 117 information from each eligible study:

7  
8 118 1) basic information of the study: author, publication year, design, sample size;

9  
10  
11 119 2) patient characteristics: age, sex, duration of disease, inflammatory  
12  
13 120 endoscopic/histological activity, lesion size, lesion location, submucosal fibrosis,  
14  
15 121 different types of IBD (UC and CD) and primary sclerosing cholangitis (PSC);

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18 122 3) detailed information of the endoscopic equipment for surveillance and techniques  
19  
20 123 for therapy: WLE, CE, NBI, EMR, ESD, etc;

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22  
23 124 4) outcome data: number of patients with en-bloc/R0/curative resection, postoperative  
24  
25 125 bleeding and perforation, submucosal fibrosis, CRC incidence, local recurrence, and  
26  
27 126 metachronous recurrence, and overall survival in long-term follow-up.

28  
29 127 We will make the most extensive use of all the available materials of the relevant studies,  
30  
31 128 including but not limited to the publications, unpublished reports, information from  
32  
33 129 study registries, and online appendices. If the vital information is unavailable in the  
34  
35 130 above sources, we will try to contact the investigators to get the relevant data through  
36  
37 131 email. We will transform all the extracted data into the International System of Units.

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40 132 Risk of bias assessment

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42  
43 133 If relevant evidence is available, we will use the Cochrane Collaboration's tool for  
44  
45 134 assessing the risk of bias in randomised controlled trials and the Newcastle-Ottawa  
46  
47 135 Scale (NOS) to evaluate the risk of bias in two-armed cohort studies, respectively. For  
48  
49 136 single-arm cohort studies, we will use a modified tool to assess the risk of bias of  
50  
51 137 eligible studies based on the Agency for Healthcare Research and Quality (AHRQ)  
52  
53 138 tool.[16] The risk of bias will be evaluated by one investigator (CW) and double-checked  
54  
55 139 by one methodologist (ZYL). Any disagreement will be resolved by discussion with a  
56  
57 140 senior investigator (WD). Detailed criteria of the modified AHRQ tool are shown in  
58  
59 141 Supplemental Table S2.  
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4 142 Statistical analysis  
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6 143 We will first describe the basic characteristics and the risk of bias of eligible studies. If  
7  
8 144 eligible studies are in different designs, they will be reported and synthesized separately.  
9

10 145 We will assess the eligible studies in terms of heterogeneity by evaluating the clinical  
11  
12 146 and methodological differences qualitatively, and if there is significant heterogeneity,  
13  
14 147 the quantitative synthesis will be abandoned.  
15

16  
17 148 This planned systematic review aims to collect evidences from randomized clinical  
18  
19 149 trials and observational studies. However, we anticipate that the data of interested  
20  
21 150 outcomes will be mostly reported in single-arm cohort studies, lacking comparison  
22  
23 151 between randomly allocated intervention groups. Considering the potential clinical and  
24  
25 152 methodological heterogeneity among eligible observational studies, we will use a  
26  
27 153 random-effects model to combine the effect.[17] The curative resection rate and all the  
28  
29 154 secondary outcomes with 95% CI will be pooled as proportion with logit transformation  
30  
31 155 if there are enough data supporting for the synthesis.[18] Clopper-Pearson interval  
32  
33 156 method will serve to estimate the 95% CI in each study.[19]  
34

35  
36 157 The between-study variance will be estimated using the restricted maximum-likelihood  
37  
38 158 estimator.[20] We will measure heterogeneity between studies using  $I^2$  statistics, and  
39  
40 159 an  $I^2$  value larger than 50% will be defined as substantial heterogeneity.[21]  
41

42  
43 160 We do not plan to assess reporting bias in this systematic review since the hypothesis  
44  
45 161 behind the commonly applied methods for detecting reporting bias may not apply to  
46  
47 162 single-arm rates or proportions.[22]  
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49  
50 163 Subgroup analysis will be conducted with regards to lesion size, lesion location,  
51  
52 164 duration of the disease, submucosal fibrosis, and different types of IBD (UC and CD).  
53

54 165 We will perform post-hoc subgroup analysis if there is evidence that some crucial  
55  
56 166 sources contribute to the statistical heterogeneity. The potential sources of  
57  
58 167 heterogeneity will be further assessed using multiple random-effects meta-regression  
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4 168 to explore the independent contribution of each variable to the main outcome. Results  
5  
6 169 from post-hoc subgroup analysis will be interpreted as hypothesis-generating rather  
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8 170 than definite evidence for subgroup difference.  
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11 171 Sensitivity analysis using different transformation methods (log transformation,  
12  
13 172 Freeman-Tukey Double arcsine transformation, Arcsine transformation, or raw  
14  
15 173 proportion without transformation) will be conducted to check if the main findings are  
16  
17 174 robust. All the statistical analysis will be completed in R (R Foundation for Statistical  
18  
19 175 Computing, Vienna, Austria, version 3.5.2) with two-sided  $\alpha$  of 0.05.  
20

21 176 Grading the quality of evidence  
22

23  
24 177 The quality of evidence for all the outcomes will be assessed using the Grading of  
25  
26 178 Recommendations Assessment, Development and Evaluation (GRADE) working  
27  
28 179 group methodology.[23] Detailed evaluation methods will follow the recommendations  
29  
30 180 from GRADE working group.  
31

### 32 181 **Patient and Public Involvement**

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35 182 Patients or public are not involved in the design and conception of this study.  
36  
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### 38 183 **Ethics and dissemination**

39  
40  
41 184 Formal ethical approval is waived since there is no individual data involved in the  
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43 185 analysis, and all the combined results will be retrieved from study-level data. This is a  
44  
45 186 research protocol for a systematic review and the data are not collected yet, hence, there  
46  
47 187 is no data published in a data repository. The results will be disseminated through peer-  
48  
49 188 reviewed publications or conference abstracts.  
50

## 51 189 **DISCUSSION**

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54 190 Indefinite margins and submucosal fibrosis add to technical difficulties for endoscopic  
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56 191 resection of non-polypoid dysplasia. Our meta-analysis will evaluate the overall en-  
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58 192 bloc/R0/curative resection rate and implement subgroup analysis according to potential  
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4 193 influence factors such as lesion size, inflammatory activity to select patients who may  
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6 194 benefit most from endoscopic therapy. Given that the incidence of metachronous  
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8 195 dysplasia and CRC remains largely unknown in non-polypoid dysplasia after endoscopic  
9  
10 196 resection,[6] this planned systematic review and meta-analysis will provide useful  
11  
12 197 information on long-term prognosis. We will also compare our results with the evidence  
13  
14 198 from polypoid dysplasia which was cited by ECCO[8] and SENIC[6] guidelines, which  
15  
16 199 may help clinicians make reasonable therapeutic strategies for management of non-  
17  
18 200 polypoid dysplasia in IBD. Besides, endoscopic resection has the advantage of less  
19  
20 201 complication risk and patient preference,[24] therefore, if endoscopic resection proves  
21  
22 202 reasonably effective and safe for management of non-polypoid dysplasia, it may  
23  
24 203 become the first-choice therapy in such patients. However, this systematic review has  
25  
26 204 some potential limitations. The best evidence evaluating the effect of endoscopic  
27  
28 205 resection should come from randomised controlled trials comparing the endoscopic  
29  
30 206 resection versus other therapies in patients with non-polypoid dysplasia in IBD.  
31  
32 207 However, based on our pilot literature search, few studies, if any, have addressed this  
33  
34 208 problem in a randomised design. The data synthesis from single-arm cohort studies or  
35  
36 209 other relevant data sources may be highly sensitive to the selection of population and  
37  
38 210 the practice setting. Hence, we are justified to expect significant heterogeneity across  
39  
40 211 studies. Moreover, the potentially limited follow-up periods may be insufficient to  
41  
42 212 observe long-term outcome events such as CRC incidence, local recurrence, and overall  
43  
44 213 survival. The underlying heterogeneity regarding clinical and methodological  
45  
46 214 considerations should be evaluated using subgroup analysis or meta-regression.  
47  
48 215 Nevertheless, the number of eligible studies is expected to be small, given the relatively  
49  
50 216 late application of endoscopic techniques in practice, limiting our ability to analyze  
51  
52 217 influencing factors for treatment effectiveness.

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4 219 **AUTHORS' CONTRIBUTIONS**  
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6 220 WD is the guarantor of this systematic review and launched this research. CW and ZY  
7  
8 221 completed the pilot literature search and will conduct the formal literature search and  
9  
10 222 screening. ZYL designed the data extraction form, the tool for risk of bias assessment,  
11  
12 223 and data synthesis plan. CW and ZY will extract the data. ZYL will conduct the  
13  
14 224 quantitative synthesis. WD, CW, ZY, and ZYL will interpret the results. All the authors  
15  
16 225 contributed to the drafting of the manuscript and approved the publication.  
17  
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29  
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38  
39 235 analysis, and result interpretation.  
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41  
42 236 **COMPETING INTERESTS**  
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44  
45 237 The authors declare that they have no conflict of interest.  
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47 308 preferences and physician recommendations. *Inflamm Bowel Dis*  
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49 309 2010;**16**:1658–62.  
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**Supplementary Table 1. Literature search strategy in Medline.**

#	Term
1	Exp Inflammatory bowel disease/
2	Crohn*.mp.
3	Ulcerative colitis*.mp
4	IBD.mp.
5	Inflammatory bowel disease*.mp.
6	OR/1-5
7	Exp Colonic Neoplasms/
8	(dysplas* OR neoplas* OR adenom* OR polyp*).mp.
9	DALM.mp.
10	colit* AND associat* AND (lesion* OR mass*).mp.
11	OR/7-10
12	6 AND 11
13	exp Endoscopic Mucosal Resection/
14	(endoscop* AND (therap* OR dissect* OR resect* OR treat*).mp./ (endoscop* ADJ5 (therap* OR dissect* OR resect* OR treat*).mp.
15	(ESD OR EMR OR EPMR OR ER).mp.
16	OR/13-15
17	12 AND 16

**Supplementary Table 2. Detailed criteria to assess the risk of bias.**

Domain	Item	Response
Selection bias	1. Did the study apply clear inclusion/exclusion criteria in the selection of participants?	Low risk, the study reported clear and appropriate inclusion/exclusion criteria; high risk, the criteria used in the study may lead to bias in the estimation of the curative resection rate; unclear, there is no relevant information.
	2. Were the participants representative of the targeted population?	Low risk, the participants were recruited consecutively or using probability sampling method; high risk, the participants in the study were biased from the targeted population; unclear, there is no relevant information.
Performance bias	1. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Low risk, there was no concurrent or unintended intervention, or the existing concurrent intervention is unlikely to influence the resection rate; high risk, there were some concurrent or unintended intervention that may influence the resection rate; unclear, there is no relevant information.
	2. Did variation from the study protocol	Low risk, the reporting results are concordant with the information from registration and study protocol; high risk, there are some changes in the conducting of the study compared with the

Domain	Item	Response
	compromise the conclusions of the study?	the registration or study protocol; unclear, there is no available registration or protocol.
Attrition bias	1. Was the follow-up completed in all subjects?	Low risk, the primary outcome (curative resection) could be assessed in more than or equal to 90% of the participants, or there is solid evidence indicating that those who lose to follow-up were similar with those still staying in the cohort; high risk, less than 90% of the participants contributed to the primary outcome; or there is evidence indicating that those who lose to follow-up were different with those still staying in the cohort; unclear, there is no relevant information.
Detection bias	1. Were the outcome assessors blinded to the intervention or exposure status of participants?	Low risk, the outcome assessor were totally blinded to the intervention; high risk, the outcome assessor knew the intervention; unclear, there is no relevant information.

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Domain	Item	Response
	2. Were the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who recruited the participants were unaware of the intervention, or objective measures were used in the patients recruiting; high risk, the personnel who recruited the participants were aware of the intervention, or there is evidence that the recruiting of valid and reliable participants will lead to biased estimation of the primary outcome; unclear, there is no relevant information.
	3. Were primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Low risk, the personnel who assessed the outcome were unaware of the intervention, or objective measures were used in the primary outcome; high risk, the personnel who assessed the outcome were aware of the intervention, or there is evidence that the assessment of the primary outcome will lead to biased estimation; unclear, there is no relevant information.
Reporting bias	1. Were the potential outcomes pre-specified by	Low risk, all the predefined outcomes in registration or study protocol were reported in the study; high risk, the investigators selectively reported some predefined outcomes, or there are



Domain	Item	Response
	the researchers? Are all pre-specified outcomes reported?	changes in the outcomes of interest; unclear, there is no available registration or study protocol.

For peer review only

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	Page 2.
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a. This is not an update of a previous review.

1		#2	If registered, provide the name of the registry (such as	Page 2.
2			PROSPERO) and registration number	
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6	Contact	#3a	Provide name, institutional affiliation, e-mail address of	Title page.
7			all protocol authors; provide physical mailing address of	
8			corresponding author	
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14	Contribution	#3b	Describe contributions of protocol authors and identify	Page 8.
15			the guarantor of the review	
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20		#4	If the protocol represents an amendment of a previously	Page 2.
21			completed or published protocol, identify as such and	
22			list changes; otherwise, state plan for documenting	
23			important protocol amendments	
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29	Sources	#5a	Indicate sources of financial or other support for the	Page i and 7.
30			review	
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35	Sponsor	#5b	Provide name for the review funder and / or sponsor	Page i and 7.
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38	Role of sponsor	#5c	Describe roles of funder(s), sponsor(s), and / or	Page 7.
39			institution(s), if any, in developing the protocol	
40	or funder			
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43	Rationale	#6	Describe the rationale for the review in the context of	Page 1 to 2.
44			what is already known	
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48	Objectives	#7	Provide an explicit statement of the question(s) the	Page 2.
49			review will address with reference to participants,	
50			interventions, comparators, and outcomes (PICO)	
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56	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	Page 2 to 3.
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design, setting, time frame) and report characteristics  
(such as years considered, language, publication status)  
to be used as criteria for eligibility for the review

- |                                                                                           |                                         |      |                                                                                                                                                                                                 |         |
|-------------------------------------------------------------------------------------------|-----------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9<br>10<br>11<br>12<br>13<br>14<br>15<br>16<br>17 | Information sources                     | #9   | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage           | Page 3. |
| 18<br>19<br>20<br>21<br>22<br>23<br>24<br>25                                              | Search strategy                         | #10  | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated                                                      | Page 4. |
| 26<br>27<br>28<br>29<br>30<br>31<br>32                                                    | Study records - data management         | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review                                                                                                    | Page 4. |
| 33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42                                  | Study records - selection process       | #11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | Page 4. |
| 43<br>44<br>45<br>46<br>47<br>48<br>49<br>50<br>51<br>52                                  | Study records - data collection process | #11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators          | Page 4. |
| 53<br>54<br>55<br>56<br>57<br>58<br>59<br>60                                              | Data items                              | #12  | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications                                         | Page 4. |

1	Outcomes and	#13	List and define all outcomes for which data will be	Page 3.
2			sought, including prioritization of main and additional	
3	prioritization		outcomes, with rationale	
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9	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias	Page 5.
10			of individual studies, including whether this will be done	
11	individual studies		at the outcome or study level, or both; state how this	
12			information will be used in data synthesis	
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19	Data synthesis	#15a	Describe criteria under which study data will be	Page 6.
20			quantitatively synthesised	
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24		#15b	If data are appropriate for quantitative synthesis,	Page 6.
25			describe planned summary measures, methods of	
26			handling data and methods of combining data from	
27			studies, including any planned exploration of	
28			consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
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36		#15c	Describe any proposed additional analyses (such as	Page 6 and 7.
37			sensitivity or subgroup analyses, meta-regression)	
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42		#15d	If quantitative synthesis is not appropriate, describe the	Page 6.
43			type of summary planned	
44				
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47	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such	Page 6 and 7.
48			as publication bias across studies, selective reporting	
49			within studies)	
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55	Confidence in	#17	Describe how the strength of the body of evidence will	Page 7.
56			be assessed (such as GRADE)	
57	cumulative			
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1 evidence

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