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Complete List of Authors:	Du, Qiang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Yang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Zhang, Jianhao; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Liu, Xueting; Sichuan University West China Hospital, Department of Evidence-Based Medicine and Clinical Epidemiology Wang, Yong; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Lie; Sichuan University West China Hospital, Department of Gastrointestinal Surgery; Sichuan University West China Hospital, Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center
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Laparoscopic versus open left hemicolectomy for left-sided colon cancer: protocol for a systematic review and meta-analysis

Qiang Du[#1], Yang Yang[#1], Jianhao Zhang[1], Xueting Liu[2], Yong Wang[1*], Lie Yang[1,3*]

[1]Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[2]Department of Evidence-Based Medicine and Clinical Epidemiology, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[3]Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.

[#]Contributed equally to this manuscript.

*Corresponding author:

Lie Yang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China; Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China; Tel: +86 28 85164035; Fax: +86 28 85164035; E-mail: lie_222@163.com.

Yong Wang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China. E-mail :wydoctor1974@aliyun.com.

ABSTRACT

Introduction: Laparoscopic colectomy has been widely used clinically due to its minimally invasive advantages, and many studies have also demonstrated its safety and efficacy. However, the efficacy of laparoscopic left hemicolectomy remains unclear due to the differences in pathogenesis and surgical details between left and right colon cancers. Therefore, we plan to conduct a systematic review and meta-analysis to investigate whether laparoscopic techniques can be safely used in left hemicolectomy.

Method and analysis: This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. A systematic search was performed for all articles related to laparoscopic left hemicolectomy in PubMed, Web of Science, Medline, EMBASE, and the Cochrane Library from inception to November 5, 2021. Article screening and data extraction were performed independently by two authors and cross-checked after completion. The literature to be included will use corresponding tools for bias risk assessment. Subgroup analyses and sensitivity analyses will be used to explore potential heterogeneity.

Ethics and dissemination: Because this systematic review is based on studies with published results and does not involve intervention in patients, no ethical review is required. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42022291526.

Strength and limitations of this study:

To the best of our knowledge, this will be the first meta-analysis to compare surgical approaches for left hemicolectomy.

Subgroup and sensitivity analyses will be used to explore potential heterogeneity.

Both the quality of the included literature and the final outcomes will be evaluated.

Restriction of publication language to English only is a limitation of this study.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignant tumor and the third leading cause of tumor-related deaths worldwide. [1] [2]At present, surgery is still the main treatment for CRC, and laparoscopic surgery has become widely accepted due to its minimally invasive advantages. Although laparoscopic rectal cancer surgery remains controversial, laparoscopic colon cancer surgery has been recommended early by the National Comprehensive Cancer Network (NCCN) guidelines,[3] mainly based on several large multicenter RCTs, including the Australasian Laparoscopic Colon Cancer Study (ALCCaS) Trial,[4] the Clinical Outcomes of Surgical Therapy (COST) study,[5] the Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (MRC CLASICC) trial and the Colon Cancer Laparoscopic or Open Resection (COLOR) Study.[6] [7] These trials have demonstrated that laparoscopic colectomy is superior to conventional open surgery in terms of short-term outcomes, such as surgical incision length, intraoperative bleeding, and postoperative functional recovery, while also demonstrating that the adequacy of tumor removal is not threatened and that tumor-related long-term outcomes are not significantly different from those of open surgery.[8-11] In addition, these results have also been verified by the Cochrane Database of Systematic Reviews.[12] [13]

However, left-sided colon cancer has been underrepresented in these trials, as the patients who underwent left hemicolectomy accounted for a very low proportion in the included cases, such as 113 (10.4%) in the COLOR study,[10] 59 (7.4%) and 64 (7.4%) in the CLASICC trial and COST study,[5] [7] respectively, and even fewer in the ALCCaS and Barcelona trials, with only 22 (3.7%) and 5 (2.3%),[11] [14] respectively. Compared to right hemicolectomy or transverse colectomy, left hemicolectomy has quite different anatomic features and surgical procedures, with a challenge in the mobilization of splenic flexure. Furthermore, it has been widely accepted that right and left colon cancers are two different diseases based on their differences in embryonic origin, genetic characteristics, and biological behaviors and therefore may have different survival outcomes.[15-18] Therefore, the safety and prognosis of the treatment of left and right colon cancer should be evaluated separately by site, but the existing clinical trials are not representative of left hemicolectomy, so there is an urgent need to study

this topic.

At present, several clinical trials have been conducted specifically on laparoscopic left hemicolectomy,[19 20] and even results from RCTs have been published,[21 22] but these results lack a pooling to form evidence-based medical evidence. Therefore, the purpose of this study was to synthesize the published results to fill the evidence gap for laparoscopic techniques for left hemicolectomy and to remind future investigators conducting colon cancer-related studies to stratify the final results based on the different locations of the tumor if there are inconsistencies between the results of this study and those of the whole colon.

MATERIALS AND METHODS

This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines.[23 24] According to the guidelines, our study has been registered on the website of the International Prospective Register of Systematic Reviews (PROSPERO).[25] The registration number is CRD42022291526.

Inclusion criteria:

Population: All patients with left-sided colon cancer confirmed by preoperative imaging and pathology who underwent left hemicolectomy with mobilization of splenic flexure were the target population of our study.

Intervention: The intervention in the experimental group was laparoscopic left hemicolectomy. In this meta-analysis, the definition of left hemicolectomy mainly included four aspects. First, ligation of the corresponding vessels, such as the inferior mesenteric vein (IMV), was performed. Second, mobilization and pull-down of splenic flexure were observed. Third, resection of the distal transverse colon, splenic flexure, descending colon, sigmoid, etc. Finally, either an intracorporeal anastomosis or an extracorporeal anastomosis is performed for colocolonic anastomosis or colorectal anastomosis. Slight adjustments during the procedure to suit the actual situation are considered acceptable.

Comparison: Traditional open left hemicolectomy.

Outcome: The outcomes assessed in this systematic review and meta-analysis included perioperative outcomes (operative time, estimated blood loss, length of incision, time to resume oral diet, time to peristalsis), postoperative outcomes (length of hospital stay, number of harvested lymph nodes, 30-day mortality, postoperative complications), and oncological outcomes (tumor recurrence, 5-year overall survival, and 5-year disease-free survival). In this study, oncologic outcomes were considered primary outcomes, with perioperative and postoperative outcomes as secondary outcomes.

Study design: All randomized controlled and nonrandomized controlled clinical studies comparing laparoscopic left hemicolectomy with open left hemicolectomy for which full text was available were included.

Exclusion criteria:

1. Studies that included tumors from other colorectal locations but did not analyse the left hemicolectomy separately or for which data from the left hemicolectomy were not extractable were not included.
2. Benign colorectal disease or emergency surgery will be excluded.
3. No splenic flexure mobilization will also be excluded.
4. Noncomparative studies and non-English publications were excluded.

Study Selection

We systematically searched the PubMed, Web of Science, Medline, EMBASE, and Cochrane Library databases for all literature comparing laparoscopic and open surgical approaches for left hemicolectomy from inception to November 5, 2021. Searches were carried out using medical subject headings (MeSH) and free text words in combination with the search strategy. We used the following keywords: “colon cancer”, “left hemicolectomy”, “laparoscopy” and “open”. All possible forms of these keywords will be used to ensure the comprehensiveness of the search. Additionally, we enriched our retrieval results with several methods, such as the similar articles function in PubMed, cross-checking references of the

retrieved literature, searching ClinicalTrials (https://www.clinicaltrials.gov/), etc.

Search Terms for PubMed

#1 ((((((((((((((((((Colonic Neoplasms) OR (Neoplasm, Colonic)) OR (Neoplasms, Colonic)) OR (Colon Neoplasms)) OR (Colon Neoplasm)) OR (Neoplasm, Colon)) OR (Neoplasms, Colon)) OR (Cancer of Colon)) OR (Colon Cancers)) OR (Colon Cancer)) OR (Cancer, Colon)) OR (Cancers, Colon)) OR (Cancer of the Colon)) OR (Colonic Cancer)) OR (Cancer, Colonic)) OR (Cancers, Colonic)) OR (Colonic Cancers)) OR (Colon Adenocarcinoma)) OR (Adenocarcinoma, Colon)) OR (Adenocarcinomas, Colon)) OR (Colon Adenocarcinomas)

#2 open surgery

#3 ((((((((((((((Laparoscopy) OR (Celioscopy)) OR (Peritoneoscopy)) OR (Surgical Procedures, Laparoscopic)) OR (Laparoscopic Surgical Procedure)) OR (Procedure, Laparoscopic Surgical)) OR (Procedures, Laparoscopic Surgical)) OR (Surgery, Laparoscopic)) OR (Laparoscopic Surgical Procedures)) OR (Laparoscopic Surgery)) OR (Laparoscopic Surgeries)) OR (Surgeries, Laparoscopic)) OR (Laparoscopic Assisted Surgery)) OR (Laparoscopic Assisted Surgeries)) OR (Surgeries, Laparoscopic Assisted)) OR (Surgery, Laparoscopic Assisted)) OR (Surgical Procedure, Laparoscopic)

#4 (left hemicolectomy) OR (left colectomy)

#5 #2 AND #3

#6 #1 AND #4 AND #5

The management of the literature search records will be carried out in EndNote X9.1. Two authors (QD and JZ) independently performed an initial screening of the titles and abstracts of the search results and assessed the eligibility of the articles. After removing duplicates and irrelevant literature, the two authors will assess the eligibility of the articles according to the inclusion criteria after reading the full text of the remaining articles separately. Any controversial points arising during this process will be referred to a third author (LY) and discussed until the dispute is resolved. The specific literature screening process will be summarized in a flow diagram.

Data Extraction

Data to be collected, such as study details (first author, year of publication, study design, follow-up period, type of outcome), patient demographics (age, sex, American Society of Anesthesiologists (ASA) score, tumor stage, etc.), and the outcomes of interest mentioned above will be consolidated into a piloting spreadsheet. Additionally, we will extract the effect estimates of the outcome of interest for statistical analysis. If there were multiple representations of the data, we preferred to use the data after adjusting for confounding factors. To reduce bias and reduce errors in data extraction, the same two investigators (QD and JZ) independently extracted data from the included literature, cross-checked after extraction, and disagreements were resolved by discussion and, if necessary, by asking a third author (LY) to resolve. Because this analysis was based on the intention-to-treat principle, all patients who were converted from the laparoscopic group to the conventional open surgery group remained in the laparoscopic group for analysis. We will also use sensitivity analyses to assess the impact of including studies that do not report intention-to-treat on overall outcomes.

There are currently several RCTs, such as COST, CLASICC, ALCCaS, and COLOR, comparing laparoscopic and open colectomy, and we believe that inclusion of their data would enhance the quality of our evidence for this study. We will be sending emails to the authors of these trials asking for stratified data on left hemicolectomy.

Statistical Analysis

Statistically, it is not possible to combine the median with the mean value, and only data expressed as the mean and standard deviation can be used for meta-analysis. In this study, we will not use the median to estimate the mean, as other studies have done, because we believe this would not be worth the cost. The weighted mean difference (WMD) or standardized mean difference (SMD) and corresponding 95% confidence interval (CI) were used for the analysis of continuous variables. The dichotomous variables were analysed using risk ratio (RR) values with 95% CIs. Considering the characteristics of survival analysis, we will first

attempt to extract survival analysis-related data from the included studies and then calculate the pooled hazard ratio (HR). HR and 95% CI will be extracted directly from the article, and if not reported in the article, we consider using software such as Engauge Digitizer to obtain the required data from Kaplan–Meier curves following the method provided by Parmar et al.[26] Finally, the obtained data will be integrated into the spreadsheet designed by Tierney et al. to calculate the HR and 95% CI.[27] If the data were insufficient or the HR was not available for other reasons, then the pooled OR values of OS and DFS were calculated separately.

Statistical heterogeneity among the studies was calculated by the chi-squared ($\chi 2$) test and I-squared (I^2) test.[28] We considered that high heterogeneity existed if the value of $P< 0.1$ or $I^2 > 50\%$. If there was high heterogeneity, a random-effects model was applied. Otherwise, a fixed-effects model was used. We will conduct subgroup analyses based on different study design types so that we can explore the potential causes of heterogeneity and reduce it as accurately as possible. Sensitivity analysis will be performed to determine the robustness of the results by sequentially excluding one study at a time. $P < 0.05$ was considered statistically significant. Software such as RevMan 5.4 and STATA 16 will be used for statistical processing. Publication bias will be estimated by visual assessment of funnel plots if ≥10 studies are available. If the extracted data are not suitable for pooling, a systematic narrative synthesis will be presented in textual form.

Risk Of Bias Assessment

Quality assessment will be carried out by two authors (QD and JZ), and discrepancies will be resolved through discussion. If consensus was not reached, then the third author (LY) was consulted for arbitration. The risk of bias in randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool,[29] which includes six aspects: randomization, allocation concealment, application of blinding, integrity of outcome data, selective reporting, and other biases. For each, we will use high risk, low risk, or unclear risk to assess the results. The methodological quality of nonrandomized controlled trials will be evaluated using the Newcastle–Ottawa Scale (NOS),[30] which consists of three aspects: patient selection, comparability of cohorts, and assessment of outcome. The total score is 9 stars, and each

article is classified as low quality (0-5 stars) or high quality (6-9 stars). The final results will be summarized in a table.

Evidence Quality Evaluation

The quality of evidence for each outcome will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[31] with four levels: high, moderate, low, and very low.

Patient And Public Involvement

Since this study is a secondary study based on other studies, there will be no direct patient or public involvement in this study.

Ethics And Dissemination

Because no patients were involved, ethical approval was not required. The final results of this research will be submitted to a peer-reviewed journal or presented at relevant conferences, and any deviations from this protocol will be recorded and explained in the final report.

SUMMARY

It has been more than 30 years since laparoscopic technology was first applied to colorectal surgery.[32] Although the risk of incomplete tumor removal was once questioned, laparoscopic technology has particularly unique advantages over traditional open surgery and is now widely used in clinical practice. However, in the existing studies, the proportion of left hemicolectomy is very small, which is not enough to support the application of laparoscopy in left colon cancer. Our review will provide a reference for the clinical use of laparoscopic left hemicolectomy.

There may also be some limitations in our review. First, as the types of studies included include both RCTs and non-RCTs, there is a high potential for heterogeneity between studies. Second, we include only studies published in English, and we may have lost data published in

other languages to some extent, resulting in bias.

Contributors: The original idea was conceived by LY. QD and YY drafted the manuscript for this protocol. QD, YY, JHZ, YW, LY participated in the design of the study and the setting of the inclusion and exclusion criteria. QD and YY design the search strategy, and XTL will be responsible for the modifications. QD and JHZ will perform the literature screening and data extraction. YW and LY will review the overall work. All authors have read and approved the publication of the protocol.

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Provenance and peer review: Not commissioned; externally peer reviewed.

ORCID iDs

Qiang Du: https://orcid.org/0000-0002-7283-1140

Lie Yang: https://orcid.org/0000-0003-1178-7147

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously	n/a

		completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4、5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4、5
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	5

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	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6
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	7
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	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7、8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

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Complete List of Authors:	Du, Qiang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Yang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Zhang, Jianhao; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Liu, Xueting; Sichuan University West China Hospital, Department of Evidence-Based Medicine and Clinical Epidemiology Wang, Yong; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Lie; Sichuan University West China Hospital, Department of Gastrointestinal Surgery; Sichuan University West China Hospital, Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center
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Laparoscopic versus open left hemicolectomy for left-sided colon cancer: protocol for a systematic review and meta-analysis

Qiang Du[#1], Yang Yang[#1], Jianhao Zhang[1], Xueting Liu[2], Yong Wang[1*], Lie Yang[1,3*]

[1]Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[2]Department of Evidence-Based Medicine and Clinical Epidemiology, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[3]Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.

[#]Contributed equally to this manuscript.

*Corresponding author:

Lie Yang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China; Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China; Tel: +86 28 85164035; Fax: +86 28 85164035; E-mail: lie_222@163.com.

Yong Wang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China. E-mail :wydoctor1974@aliyun.com.

ABSTRACT

Introduction: Laparoscopic colectomy has been widely used clinically due to its minimally invasive advantages, and many studies have also demonstrated its safety and efficacy. However, the efficacy of laparoscopic left hemicolectomy remains unclear due to the differences in pathogenesis and surgical details between left and right colon cancers. Therefore, we plan to conduct a systematic review and meta-analysis to investigate whether laparoscopic techniques can be safely used in left hemicolectomy.

Method and analysis: This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. A systematic search was performed for all articles related to laparoscopic left hemicolectomy in PubMed, Web of Science, Medline, EMBASE, and the Cochrane Library from inception to November 5, 2021. Article screening and data extraction were performed independently by two authors and cross-checked after completion. The literature to be included will use corresponding tools for bias risk assessment. Subgroup analyses and sensitivity analyses will be used to explore potential heterogeneity.

Ethics and dissemination: Because this systematic review is based on studies with published results and does not involve intervention in patients, no ethical review is required. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42022291526.

Strength and limitations of this study:

To the best of our knowledge, this will be the first meta-analysis to compare surgical approaches for left hemicolectomy.

Subgroup and sensitivity analyses will be used to explore potential heterogeneity.

Both the quality of the included literature and the final outcomes will be evaluated.

Restriction of publication language to English only is a limitation of this study.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignant tumor and the third leading cause of tumor-related deaths worldwide. [1] [2]At present, surgery is still the main treatment for CRC, and laparoscopic surgery has become widely accepted due to its minimally invasive advantages. Although laparoscopic rectal cancer surgery remains controversial, laparoscopic colon cancer surgery has been recommended early by the National Comprehensive Cancer Network (NCCN) guidelines,[3] mainly based on several large multicenter RCTs, including the Australasian Laparoscopic Colon Cancer Study (ALCCaS) Trial,[4] the Clinical Outcomes of Surgical Therapy (COST) study,[5] the Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (MRC CLASICC) trial and the Colon Cancer Laparoscopic or Open Resection (COLOR) Study.[6] [7] These trials have demonstrated that laparoscopic colectomy is superior to conventional open surgery in terms of short-term outcomes, such as surgical incision length, intraoperative bleeding, and postoperative functional recovery, while also demonstrating that the adequacy of tumor removal is not threatened and that tumor-related long-term outcomes are not significantly different from those of open surgery.[8-11] In addition, these results have also been verified by the Cochrane Database of Systematic Reviews.[12] [13]

However, left-sided colon cancer has been underrepresented in these trials, as the patients who underwent left hemicolectomy accounted for a very low proportion in the included cases, such as 113 (10.4%) in the COLOR study,[10] 59 (7.4%) and 64 (7.4%) in the CLASICC trial and COST study,[5] [7] respectively, and even fewer in the ALCCaS and Barcelona trials, with only 22 (3.7%) and 5 (2.3%),[11] [14] respectively. Compared to right hemicolectomy or transverse colectomy, left hemicolectomy has quite different anatomic features and surgical procedures, with a challenge in the mobilization of splenic flexure. Furthermore, it has been widely accepted that right and left colon cancers are two different diseases based on their differences in embryonic origin, genetic characteristics, and biological behaviors and therefore may have different survival outcomes.[15-18] Therefore, the safety and prognosis of the treatment of left and right colon cancer should be evaluated separately by site, but the existing clinical trials are not representative of left hemicolectomy, so there is an urgent need to study this topic.

At present, several clinical trials have been conducted specifically on laparoscopic left hemicolectomy,[19 20] and even results from RCTs have been published,[21 22] but these results lack a pooling to form evidence-based medical evidence. Therefore, the purpose of this study was to synthesize the published results to fill the evidence gap for laparoscopic techniques for left hemicolectomy and to remind future investigators conducting colon cancer-related studies to stratify the final results based on the different locations of the tumor if there are inconsistencies between the results of this study and those of the whole colon.

MATERIALS AND METHODS

This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines.[23 24] According to the guidelines, our study has been registered on the website of the International Prospective Register of Systematic Reviews (PROSPERO).[25] The registration number is CRD42022291526.

Inclusion criteria:

Population: All patients with left-sided colon cancer confirmed by preoperative imaging and pathology who underwent left hemicolectomy with mobilization of splenic flexure were the target population of our study.

Intervention: The intervention in the experimental group was laparoscopic left hemicolectomy. In this meta-analysis, the definition of left hemicolectomy mainly included four aspects. First, ligation of the corresponding vessels, such as the inferior mesenteric vein (IMV), was performed. Second, mobilization and pull-down of splenic flexure were observed. Third, resection of the distal transverse colon, splenic flexure, descending colon, sigmoid, etc. Finally, either an intracorporeal anastomosis or an extracorporeal anastomosis is performed for colocolonic anastomosis or colorectal anastomosis. Slight adjustments during the procedure to suit the actual situation are considered acceptable.

Comparison: Traditional open left hemicolectomy.

Outcome: The outcomes assessed in this systematic review and meta-analysis included perioperative outcomes (operative time, estimated blood loss, length of incision, time to resume oral diet, time to peristalsis), postoperative outcomes (length of hospital stay, number of harvested lymph nodes, 30-day mortality, postoperative complications), and oncological outcomes (tumor recurrence, 5-year overall survival, and 5-year disease-free survival). In this study, oncologic outcomes were considered primary outcomes, with perioperative and postoperative outcomes as secondary outcomes. In this study, tumor recurrence was defined as any recurrence confirmed by imaging or pathology, including local recurrence and systemic recurrence. DFS was defined as the duration from the date of surgery to confirmed recurrence or death from any cause, and OS was defined as the duration from the date of surgery to the date of proven death from any cause.

Study design: All randomized controlled and nonrandomized controlled clinical studies comparing laparoscopic left hemicolectomy with open left hemicolectomy for which full text was available were included.

Exclusion criteria:

1. Studies that included tumors from other colorectal locations but did not analyse the left hemicolectomy separately or for which data from the left hemicolectomy were not extractable were not included.
2. Benign colorectal disease or emergency surgery will be excluded.
3. No splenic flexure mobilization will also be excluded.
4. Noncomparative studies and non-English publications were excluded.

Study Selection

We systematically searched the PubMed, Web of Science, Medline, EMBASE, and Cochrane Library databases for all literature comparing laparoscopic and open surgical approaches for left hemicolectomy from inception to November 5, 2021. Searches were carried out using medical subject headings (MeSH) and free text words in combination with the search strategy. We used the following keywords: “colon cancer”, “left hemicolectomy”, “laparoscopy” and

"open". All possible forms of these keywords will be used to ensure the comprehensiveness of the search. Additionally, we enriched our retrieval results with several methods, such as the similar articles function in PubMed, cross-checking references of the retrieved literature, searching ClinicalTrials (https://www.clinicaltrials.gov/), etc.

Search Terms for PubMed

#1 ((((((((((((((((((Colonic Neoplasms) OR (Neoplasm, Colonic)) OR (Neoplasms, Colonic)) OR (Colon Neoplasms)) OR (Colon Neoplasm)) OR (Neoplasm, Colon)) OR (Neoplasms, Colon)) OR (Cancer of Colon)) OR (Colon Cancers)) OR (Colon Cancer)) OR (Cancer, Colon)) OR (Cancers, Colon)) OR (Cancer of the Colon)) OR (Colonic Cancer)) OR (Cancer, Colonic)) OR (Cancers, Colonic)) OR (Colonic Cancers)) OR (Colon Adenocarcinoma)) OR (Adenocarcinoma, Colon)) OR (Adenocarcinomas, Colon)) OR (Colon Adenocarcinomas)

#2 open surgery

#3 ((((((((((((((Laparoscopy) OR (Celioscopy)) OR (Peritoneoscopy)) OR (Surgical Procedures, Laparoscopic)) OR (Laparoscopic Surgical Procedure)) OR (Procedure, Laparoscopic Surgical)) OR (Procedures, Laparoscopic Surgical)) OR (Surgery, Laparoscopic)) OR (Laparoscopic Surgical Procedures)) OR (Laparoscopic Surgery)) OR (Laparoscopic Surgeries)) OR (Surgeries, Laparoscopic)) OR (Laparoscopic Assisted Surgery)) OR (Laparoscopic Assisted Surgeries)) OR (Surgeries, Laparoscopic Assisted)) OR (Surgery, Laparoscopic Assisted)) OR (Surgical Procedure, Laparoscopic)

#4 (left hemicolectomy) OR (left colectomy)

#5 #2 AND #3

#6 #1 AND #4 AND #5

The management of the literature search records will be carried out in EndNote X9.1. Two authors (QD and JZ) independently performed an initial screening of the titles and abstracts of the search results and assessed the eligibility of the articles. After removing duplicates and irrelevant literature, the two authors will assess the eligibility of the articles according to the inclusion criteria after reading the full text of the remaining articles separately. Any controversial points arising during this process will be referred to a third author (LY) and

discussed until the dispute is resolved. The specific literature screening process will be summarized in a flow diagram.

Data Extraction

Data to be collected, such as study details (first author, year of publication, study design, follow-up period, type of outcome), patient demographics (age, sex, American Society of Anesthesiologists (ASA) score, tumor stage, etc.), and the outcomes of interest mentioned above will be consolidated into a piloting spreadsheet. Additionally, we will extract the effect estimates of the outcome of interest for statistical analysis. If there were multiple representations of the data, we preferred to use the data after adjusting for confounding factors. To reduce bias and reduce errors in data extraction, the same two investigators (QD and JZ) independently extracted data from the included literature, cross-checked after extraction, and disagreements were resolved by discussion and, if necessary, by asking a third author (LY) to resolve. Because this analysis was based on the intention-to-treat principle, all patients who were converted from the laparoscopic group to the conventional open surgery group remained in the laparoscopic group for analysis. We will also use sensitivity analyses to assess the impact of including studies that do not report intention-to-treat on overall outcomes.

There are currently several RCTs, such as COST, CLASICC, ALCCaS, and COLOR, comparing laparoscopic and open colectomy, and we believe that inclusion of their data would enhance the quality of our evidence for this study. We will be sending emails to the authors of these trials asking for stratified data on left hemicolectomy. Meanwhile，for the missing data of other studies, we will also send an email to ask for.

Statistical Analysis

Statistically, it is not possible to combine the median with the mean value, and only data expressed as the mean and standard deviation can be used for meta-analysis. In this study, we will not use the median to estimate the mean, as other studies have done, because we believe this would not be worth the cost. The weighted mean difference (WMD) or standardized mean difference (SMD) and corresponding 95% confidence interval (CI) were used for the analysis

of continuous variables. The dichotomous variables were analysed using risk ratio (RR) values with 95% CIs. Considering the characteristics of survival analysis, we will first attempt to extract survival analysis-related data from the included studies and then calculate the pooled hazard ratio (HR). HR and 95% CI will be extracted directly from the article, and if not reported in the article, we consider using software such as Engauge Digitizer to obtain the required data from Kaplan–Meier curves following the method provided by Parmar et al.[26] Finally, the obtained data will be integrated into the spreadsheet designed by Tierney et al. to calculate the HR and 95% CI.[27] If the data were insufficient or the HR was not available for other reasons, then the pooled OR values of OS and DFS were calculated separately.

Statistical heterogeneity among the studies was calculated by the chi-squared ($\chi 2$) test and I-squared (I^2) test.[28] We considered that high heterogeneity existed if the value of $P < 0.1$ or $I^2 > 50\%$. When the heterogeneity was 0, the fixed-effects model was used, and when the heterogeneity was between 0-50%, the random-effects model was used. We will conduct subgroup analyses, based on different study design types, and meta-regression so that we can explore the potential causes of heterogeneity and reduce it as accurately as possible when heterogeneity exceeded 50%. If the heterogeneity is too high, then qualitative analysis was performed. Sensitivity analysis will be performed to determine the robustness of the results by sequentially excluding one study at a time. $P < 0.05$ was considered statistically significant. Software such as RevMan 5.4 and STATA 16 will be used for statistical processing. Publication bias will be estimated by visual assessment of funnel plots if ≥10 studies are available. If the extracted data are not suitable for pooling, a systematic narrative synthesis will be presented in textual form.

Risk Of Bias Assessment

Quality assessment will be carried out by two authors (QD and JZ), and discrepancies will be resolved through discussion. If consensus was not reached, then the third author (LY) was consulted for arbitration. The risk of bias in randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool,[29] which includes six aspects: randomization, allocation concealment, application of blinding, integrity of outcome data, selective reporting, and other

biases. For each, we will use high risk, low risk, or unclear risk to assess the results. The methodological quality of nonrandomized controlled trials will be evaluated using the Newcastle–Ottawa Scale (NOS),[30] which consists of three aspects: patient selection, comparability of cohorts, and assessment of outcome. The total score is 9 stars, and each article is classified as low quality (0-5 stars) or high quality (6-9 stars). The final results will be summarized in a table.

Evidence Quality Evaluation

The quality of evidence for each outcome will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[31] with four levels: high, moderate, low, and very low.

Patient And Public Involvement

Since this study is a secondary study based on other studies, there will be no direct patient or public involvement in this study.

Ethics And Dissemination

Because no patients were involved, ethical approval was not required. The final results of this research will be submitted to a peer-reviewed journal or presented at relevant conferences, and any deviations from this protocol will be recorded and explained in the final report.

Contributors: The original idea was conceived by LY. QD and YY drafted the manuscript for this protocol. QD, YY, JHZ, YW, LY participated in the design of the study and the setting of the inclusion and exclusion criteria. QD and YY design the search strategy, and XTL will be responsible for the modifications. QD and JHZ will perform the literature screening and data extraction. YW and LY will review the overall work. All authors have read and approved the publication of the protocol.

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ORCID iDs

Qiang Du: https://orcid.org/0000-0002-7283-1140

Lie Yang: https://orcid.org/0000-0003-1178-7147

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously	n/a

		completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4、5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4、5
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	5

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	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6
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	7
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	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7、8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

BMJ Open

Laparoscopic versus open left hemicolectomy for left-sided colon cancer: protocol for a systematic review and meta-analysis

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Complete List of Authors:	Du, Qiang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Yang; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Zhang, Jianhao; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Liu, Xueting; Sichuan University West China Hospital, Department of Evidence-Based Medicine and Clinical Epidemiology Wang, Yong; Sichuan University West China Hospital, Department of Gastrointestinal Surgery Yang, Lie; Sichuan University West China Hospital, Department of Gastrointestinal Surgery; Sichuan University West China Hospital, Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center
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Laparoscopic versus open left hemicolectomy for left-sided colon cancer: protocol for a systematic review and meta-analysis

Qiang Du[#1], Yang Yang[#1], Jianhao Zhang[1], Xueting Liu[2], Yong Wang[1*], Lie Yang[1,3*]

[1]Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[2]Department of Evidence-Based Medicine and Clinical Epidemiology, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, Sichuan Province, China.

[3]Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.

[#]Contributed equally to this manuscript.

*Corresponding author:

Lie Yang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China; Institute of Digestive Surgery, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China; Tel: +86 28 85164035; Fax: +86 28 85164035; E-mail: lie_222@163.com.

Yong Wang, Department of Gastrointestinal Surgery, West China Hospital of Sichuan University, No. 37 Guoxue Lane, Chengdu, 610041, China. E-mail :wydoctor1974@aliyun.com.

ABSTRACT

Introduction: Laparoscopic colectomy has been widely used clinically due to its minimally invasive advantages, and many studies have also demonstrated its safety and efficacy. However, the efficacy of laparoscopic left hemicolectomy remains unclear due to the differences in pathogenesis and surgical details between left and right colon cancers. Therefore, we plan to conduct a systematic review and meta-analysis to investigate whether laparoscopic techniques can be safely used in left hemicolectomy.

Method and analysis: This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. A systematic search was performed for all articles related to laparoscopic left hemicolectomy in PubMed, Web of Science, Medline, EMBASE, and the Cochrane Library from inception to November 5, 2021. Article screening and data extraction were performed independently by two authors and cross-checked after completion. The literature to be included will use corresponding tools for bias risk assessment. Subgroup analyses and sensitivity analyses will be used to explore potential heterogeneity.

Ethics and dissemination: Because this systematic review is based on studies with published results and does not involve intervention in patients, no ethical review is required. The results of this study will be published in a peer-reviewed journal.

PROSPERO registration number: CRD42022291526.

Strength and limitations of this study:

To the best of our knowledge, this will be the first meta-analysis to compare surgical approaches for left hemicolectomy.

Subgroup and sensitivity analyses will be used to explore potential heterogeneity.

Both the quality of the included literature and the final outcomes will be evaluated.

Restriction of publication language to English only is a limitation of this study.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed malignant tumor and the third leading cause of tumor-related deaths worldwide. [1] [2]At present, surgery is still the main treatment for CRC, and laparoscopic surgery has become widely accepted due to its minimally invasive advantages. Although laparoscopic rectal cancer surgery remains controversial, laparoscopic colon cancer surgery has been recommended early by the National Comprehensive Cancer Network (NCCN) guidelines,[3] mainly based on several large multicenter RCTs, including the Australasian Laparoscopic Colon Cancer Study (ALCCaS) Trial,[4] the Clinical Outcomes of Surgical Therapy (COST) study,[5] the Medical Research Council Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (MRC CLASICC) trial and the Colon Cancer Laparoscopic or Open Resection (COLOR) Study.[6] [7] These trials have demonstrated that laparoscopic colectomy is superior to conventional open surgery in terms of short-term outcomes, such as surgical incision length, intraoperative bleeding, and postoperative functional recovery, while also demonstrating that the adequacy of tumor removal is not threatened and that tumor-related long-term outcomes are not significantly different from those of open surgery.[8-11] In addition, these results have also been verified by the Cochrane Database of Systematic Reviews.[12] [13]

However, left-sided colon cancer has been underrepresented in these trials, as the patients who underwent left hemicolectomy accounted for a very low proportion in the included cases, such as 113 (10.4%) in the COLOR study,[10] 59 (7.4%) and 64 (7.4%) in the CLASICC trial and COST study,[5] [7] respectively, and even fewer in the ALCCaS and Barcelona trials, with only 22 (3.7%) and 5 (2.3%),[11] [14] respectively. Compared to right hemicolectomy or transverse colectomy, left hemicolectomy has quite different anatomic features and surgical procedures, with a challenge in the mobilization of splenic flexure. Furthermore, it has been widely accepted that right and left colon cancers are two different diseases based on their differences in embryonic origin, genetic characteristics, and biological behaviors and therefore may have different survival outcomes.[15-18] Therefore, the safety and prognosis of the treatment of left and right colon cancer should be evaluated separately by site, but the existing clinical trials are not representative of left hemicolectomy, so there is an urgent need to study this topic.

At present, several clinical trials have been conducted specifically on laparoscopic left hemicolectomy,[19 20] and even results from RCTs have been published,[21 22] but these results lack a pooling to form evidence-based medical evidence. Therefore, the purpose of this study was to synthesize the published results to fill the evidence gap for laparoscopic techniques for left hemicolectomy and to remind future investigators conducting colon cancer-related studies to stratify the final results based on the different locations of the tumor if there are inconsistencies between the results of this study and those of the whole colon.

MATERIALS AND METHODS

This meta-analysis protocol will be completed and reported according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines.[23 24] According to the guidelines, our study has been registered on the website of the International Prospective Register of Systematic Reviews (PROSPERO).[25] The registration number is CRD42022291526.

Inclusion criteria:

Population: All patients with left-sided colon cancer confirmed by preoperative imaging and pathology who underwent left hemicolectomy with mobilization of splenic flexure were the target population of our study.

Intervention: The intervention in the experimental group was laparoscopic left hemicolectomy. In this meta-analysis, the definition of left hemicolectomy mainly included four aspects. First, ligation of the corresponding vessels, such as the inferior mesenteric vein (IMV), was performed. Second, mobilization and pull-down of splenic flexure were observed. Third, resection of the distal transverse colon, splenic flexure, descending colon, sigmoid, etc. Finally, either an intracorporeal anastomosis or an extracorporeal anastomosis is performed for colocolonic anastomosis or colorectal anastomosis. Slight adjustments during the procedure to suit the actual situation are considered acceptable.

Comparison: Traditional open left hemicolectomy.

Outcome: The outcomes assessed in this systematic review and meta-analysis included perioperative outcomes (operative time, estimated blood loss, length of incision, time to resume oral diet, time to peristalsis), postoperative outcomes (length of hospital stay, number of harvested lymph nodes, 30-day mortality, postoperative complications), and oncological outcomes (tumor recurrence, 5-year overall survival, and 5-year disease-free survival). In this study, 5-year disease-free survival which was defined as the duration from the date of surgery to confirmed recurrence or death from any cause was considered primary outcome, with tumor recurrence, 5-year over survival, perioperative outcomes and postoperative outcomes as secondary outcomes. In this study, tumor recurrence was defined as any recurrence confirmed by imaging or pathology, including local recurrence and systemic recurrence. OS was defined as the duration from the date of surgery to the date of proven death from any cause.

Study design: All randomized controlled and nonrandomized controlled clinical studies comparing laparoscopic left hemicolectomy with open left hemicolectomy for which full text was available were included.

Exclusion criteria:

1. Studies that included tumors from other colorectal locations but did not analyse the left hemicolectomy separately or for which data from the left hemicolectomy were not extractable were not included.
2. Benign colorectal disease or emergency surgery will be excluded.
3. No splenic flexure mobilization will also be excluded.
4. Noncomparative studies and non-English publications were excluded.

Study Selection

We systematically searched the PubMed, Web of Science, Medline, EMBASE, and Cochrane Library databases for all literature comparing laparoscopic and open surgical approaches for left hemicolectomy from inception to November 5, 2021. Searches were carried out using medical subject headings (MeSH) and free text words in combination with the search strategy. We used the following keywords: “colon cancer”, “left hemicolectomy”, “laparoscopy” and

"open". All possible forms of these keywords will be used to ensure the comprehensiveness of the search. Additionally, we enriched our retrieval results with several methods, such as the similar articles function in PubMed, cross-checking references of the retrieved literature, searching ClinicalTrials (https://www.clinicaltrials.gov/), etc.

Search Terms for PubMed

#1 ((((((((((((((((((Colonic Neoplasms) OR (Neoplasm, Colonic)) OR (Neoplasms, Colonic)) OR (Colon Neoplasms)) OR (Colon Neoplasm)) OR (Neoplasm, Colon)) OR (Neoplasms, Colon)) OR (Cancer of Colon)) OR (Colon Cancers)) OR (Colon Cancer)) OR (Cancer, Colon)) OR (Cancers, Colon)) OR (Cancer of the Colon)) OR (Colonic Cancer)) OR (Cancer, Colonic)) OR (Cancers, Colonic)) OR (Colonic Cancers)) OR (Colon Adenocarcinoma)) OR (Adenocarcinoma, Colon)) OR (Adenocarcinomas, Colon)) OR (Colon Adenocarcinomas)

#2 open surgery

#3 ((((((((((((((Laparoscopy) OR (Celioscopy)) OR (Peritoneoscopy)) OR (Surgical Procedures, Laparoscopic)) OR (Laparoscopic Surgical Procedure)) OR (Procedure, Laparoscopic Surgical)) OR (Procedures, Laparoscopic Surgical)) OR (Surgery, Laparoscopic)) OR (Laparoscopic Surgical Procedures)) OR (Laparoscopic Surgery)) OR (Laparoscopic Surgeries)) OR (Surgeries, Laparoscopic)) OR (Laparoscopic Assisted Surgery)) OR (Laparoscopic Assisted Surgeries)) OR (Surgeries, Laparoscopic Assisted)) OR (Surgery, Laparoscopic Assisted)) OR (Surgical Procedure, Laparoscopic)

#4 (left hemicolectomy) OR (left colectomy)

#5 #2 AND #3

#6 #1 AND #4 AND #5

The management of the literature search records will be carried out in EndNote X9.1. Two authors (QD and JZ) independently performed an initial screening of the titles and abstracts of the search results and assessed the eligibility of the articles. After removing duplicates and irrelevant literature, the two authors will assess the eligibility of the articles according to the inclusion criteria after reading the full text of the remaining articles separately. Any controversial points arising during this process will be referred to a third author (LY) and

discussed until the dispute is resolved. The specific literature screening process will be summarized in a flow diagram.

Data Extraction

Data to be collected, such as study details (first author, year of publication, study design, follow-up period, type of outcome), patient demographics (age, sex, American Society of Anesthesiologists (ASA) score, tumor stage, etc.), and the outcomes of interest mentioned above will be consolidated into a piloting spreadsheet. Additionally, we will extract the effect estimates of the outcome of interest for statistical analysis. If there were multiple representations of the data, we preferred to use the data after adjusting for confounding factors. To reduce bias and reduce errors in data extraction, the same two investigators (QD and JZ) independently extracted data from the included literature, cross-checked after extraction, and disagreements were resolved by discussion and, if necessary, by asking a third author (LY) to resolve. Because this analysis was based on the intention-to-treat principle, all patients who were converted from the laparoscopic group to the conventional open surgery group remained in the laparoscopic group for analysis. We will also use sensitivity analyses to assess the impact of including studies that do not report intention-to-treat on overall outcomes.

There are currently several RCTs, such as COST, CLASICC, ALCCaS, and COLOR, comparing laparoscopic and open colectomy, and we believe that inclusion of their data would enhance the quality of our evidence for this study. We will be sending emails to the authors of these trials asking for stratified data on left hemicolectomy. Meanwhile，for the missing data of other studies, we will also send an email to ask for.

Statistical Analysis

Statistically, it is not possible to combine the median with the mean value, and only data expressed as the mean and standard deviation can be used for meta-analysis. In this study, we will not use the median to estimate the mean, as other studies have done, because we believe this would not be worth the cost. The weighted mean difference (WMD) or standardized mean difference (SMD) and corresponding 95% confidence interval (CI) were used for the analysis

of continuous variables. The dichotomous variables were analysed using risk ratio (RR) values with 95% CIs. Considering the characteristics of survival analysis, we will first attempt to extract survival analysis-related data from the included studies and then calculate the pooled hazard ratio (HR). HR and 95% CI will be extracted directly from the article, and if not reported in the article, we consider using software such as Engauge Digitizer to obtain the required data from Kaplan–Meier curves following the method provided by Parmar et al.[26] Finally, the obtained data will be integrated into the spreadsheet designed by Tierney et al. to calculate the HR and 95% CI.[27] If the data were insufficient or the HR was not available for other reasons, then the pooled OR values of OS and DFS were calculated separately.

Statistical heterogeneity among the studies was calculated by the chi-squared ($\chi 2$) test and I-squared (I^2) test.[28] We considered that high heterogeneity existed if the value of $P < 0.1$ or $I^2 > 50\%$. When the heterogeneity was 0, the fixed-effects model was used, and when the heterogeneity was between 0-50%, the random-effects model was used. We will conduct subgroup analyses, based on different study design types, and meta-regression so that we can explore the potential causes of heterogeneity and reduce it as accurately as possible when heterogeneity exceeded 50%. If the heterogeneity is too high, then qualitative analysis was performed. Sensitivity analysis will be performed to determine the robustness of the results by sequentially excluding one study at a time. $P < 0.05$ was considered statistically significant. Software such as RevMan 5.4 and STATA 16 will be used for statistical processing. Publication bias will be estimated by visual assessment of funnel plots if ≥10 studies are available. If the extracted data are not suitable for pooling, a systematic narrative synthesis will be presented in textual form.

Risk Of Bias Assessment

Quality assessment will be carried out by two authors (QD and JZ), and discrepancies will be resolved through discussion. If consensus was not reached, then the third author (LY) was consulted for arbitration. The risk of bias in randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool,[29] which includes six aspects: randomization, allocation concealment, application of blinding, integrity of outcome data, selective reporting, and other

biases. For each, we will use high risk, low risk, or unclear risk to assess the results. The methodological quality of nonrandomized controlled trials will be evaluated using the Newcastle–Ottawa Scale (NOS),[30] which consists of three aspects: patient selection, comparability of cohorts, and assessment of outcome. The total score is 9 stars, and each article is classified as low quality (0-5 stars) or high quality (6-9 stars). The final results will be summarized in a table.

Evidence Quality Evaluation

The quality of evidence for each outcome will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[31] with four levels: high, moderate, low, and very low.

Patient And Public Involvement

Since this study is a secondary study based on other studies, there will be no direct patient or public involvement in this study.

Ethics And Dissemination

Because no patients were involved, ethical approval was not required. The final results of this research will be submitted to a peer-reviewed journal or presented at relevant conferences, and any deviations from this protocol will be recorded and explained in the final report.

Contributors: The original idea was conceived by LY. QD and YY drafted the manuscript for this protocol. QD, YY, JHZ, YW, LY participated in the design of the study and the setting of the inclusion and exclusion criteria. QD and YY design the search strategy, and XTL will be responsible for the modifications. QD and JHZ will perform the literature screening and data extraction. YW and LY will review the overall work. All authors have read and approved the publication of the protocol.

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Provenance and peer review: Not commissioned; externally peer reviewed.

ORCID iDs

Qiang Du: https://orcid.org/0000-0002-7283-1140

Lie Yang: https://orcid.org/0000-0003-1178-7147

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Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
Amendments			
	#4	If the protocol represents an amendment of a previously	n/a

		completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	10
Sponsor	#5b	Provide name for the review funder and / or sponsor	10
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	10
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4、5
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	4、5
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	5

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	6
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6
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)	6
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	7
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	7
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	7、8
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	8
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9