Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 7

Systematic Review and Meta-Analysis on Colorectal Cancer Found on Colonic Evaluation after CT-Confirmed Acute Diverticulitis in the Asian Population

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Received: 02 Sep 2023
Accepted: 16 Oct 2023
Published: 24 Oct 2023
J Short Name: COO

Citation:

Chang JHE, Systematic Review and Meta-Analysis on Colorectal Cancer Found on Colonic Evaluation after CT-Confirmed Acute Diverticulitis in the Asian Population. Clin Onco. 2023; 7(3): 1-6

Keywords:

Computed Tomography; MeSH; Colon cancer

1. Abstract

1.1. Introduction: Computed Tomography (CT) findings of acute diverticulitis may mimic features of malignancy and current guidelines advocate colonic evaluation after an episode of acute diverticulitis, as risk of malignancy is higher in patients with advanced age and complicated diverticulitis. However, the benefits have not yet been determined in Asian population. We reviewed 4 studies conducted in Asian patients, comprising of 902 patients to evaluate the role of routine colonic evaluation after CT-proven acute diverticulitis.

1.2. Methods: Medline, EMBASE, and the Cochrane library were searched for articles published up to November 2022. A combination of both 'MeSH' and non-'MeSH' key terms using Boolean operators, were used: "colonic neoplasms", "colorectal cancer", "colon cancer", "colonic cancer", "colonoscopy", and "diverticulitis". Any randomised or non-randomised, English-language article that analyzed incidence of colorectal cancer after performing colonoscopy in patients with previous diverticulitis was included.

1.3. Results: 4/429 publications were eligible for inclusion. 372 patients were evaluated. 4.03%(15/372) were found to have colorectal malignancy. The pooled colorectal cancer (CRC) detection rate was 1.64%(95% CI,0.00-0.0593). The pooled proportion of CRC detected after an episode of uncomplicated diverticulitis is 3.44 (95% CI 0.0148-0.0609). The proportion of CRC detected after an episode of complicated diverticulitis is 14.29(95% CI,0.0201-0.3308).

1.4. Conclusion: There may be benefit in selecting Asian patients with complicated diverticulitis to undergo colonoscopy. There is also a high polyp pick up rate, which may have benefit in early removal of possible underlying pre-malignant polyps. However, further larger scales studies are required to improve the quality of data and enable us to formulate practice recommendations.

2. Introduction

Acute colonic diverticulitis is a common cause of surgical admission diagnosed clinically and mostly aided with a Computed Tomography (CT) scans of the abdomen and pelvis. It has been noted that CT features of acute diverticulitis may mimic that of underlying colorectal malignancy. Diverticulitis is also considered a risk factor for colorectal cancer (CRC) in some studies [1]. The current guidelines by the American Society of Colon and Rectal Surgeons and American Gastroenterology Association recommend colonic evaluation after acute diverticulitis. A recent meta-analysis performed in 2020 by Koo et al [2] also suggested that colonic evaluation is advised in patients with advanced age and complicated diverticulitis as its benefits in picking up CRC outweighs the risk involved in colonoscopy. However, majority of these reports have been based on Western patients and studies. In the Asian population, diverticulitis is more prevalent in younger patients, in the right colon, is less severe and associated with lower recurrence rate [3-8]. There has also been an increase in right-sided diverticular disease in Asian patients by up to 45% in the last few years [9], hence determining the need and role for routine colonic evaluation

in these patients may help us better understand how they should be followed up. Few articles have explored the benefits and necessity of routine colonic evaluation post-acute diverticulitis in Asian patients. The aim of our meta-analysis is to evaluate the role of colonoscopy in Asian patients with CT-proven acute diverticulitis.

3. Materials and Methods

3.1. Literature Search

The review was conducted in accordance with the Cochrane Handbook of Systematic Reviews and Meta-analysis and the PRISMA statement guidelines. An electronic search using Medline, EMBASE, and Cochrane Library databases up to November 30, 2021, to identify all the relevant articles was performed. A combination of both Medical Subject Headings and non-Medical Subject Headings key terms using Boolean operators were used on Medline, including 'colonic neoplasms', 'colorectal cancer', 'colon cancer', 'colonic cancer' and 'diverticulitis'. A manual search of the reference lists of included studies was performed to identify additional relevant articles. Only studies performed in Asian countries were selected.

3.2. Outcome Measures

The primary outcome measure is the incidence rate of CRC diagnosed in Asian patients with previous CT proven diverticulitis that had undergone complete colonic evaluation within a year as part of routine follow-up.

3.3. Selection of Studies and Data Extraction

Two reviewers independently screened and assessed all the studies for inclusion. The studies were first screened based on titles and abstracts for preliminary inclusion. The full-text articles were then retrieved for further detailed review for confirmation for study inclusion. Conflicts were resolved by consensus or by appeal to a third author.

A data sheet was used to extract the following data from text, tables, and figures in each study: first author, year, and type of publication; age; sex; comorbidities of patients; incidence of CRC. Individual participant data from the respective articles were not collected because the data would not change the estimates of CRC detection rates. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram has been included to depict the flow of the screening process (Figure 1).

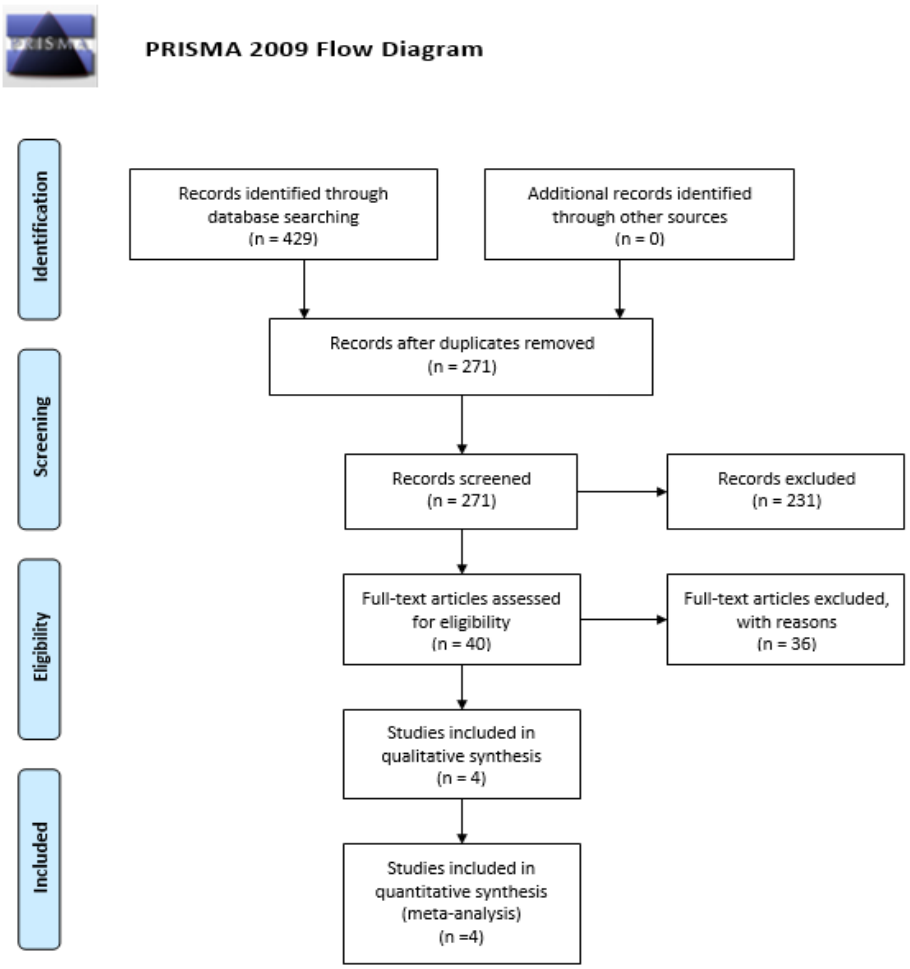

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

3.4. Risk of Bias and Quality Assessment

A risk of bias and quality assessment was conducted independently by 2 reviewers for included studies using the Newcastle Ottawa Scale. Consensus was obtained, with any conflicts resolved either by mutual agreement or by appeal to a third reviewer. Publication bias was assessed using funnel plots. Funnel plots were constructed to assess for publication bias by graphing the study inverse of SE (1/SE) versus the log odds of CRC detection, wherein:

$$SE = \sqrt{\frac{1}{Denominator} + \frac{1}{Denominator - Numerator}}$$

Log odds = ln (*NumeratorDenominator-Numerator*

3.5. Data Analysis

We undertook meta-analysis of CRC incidence by calculating the exact (Clopper-Pearson) confidence intervals for CRC incidence rates, and using the variance-stabilizing Freeman-Tukey double arcsine transformation to achieve approximate normality of the data. The pooled estimate was then computed using the random effects model with inverse variance weighting, and then back-transformed using the *metaprop* package in Stata. $P < 0.05$ was considered to indicate nominal statistical significance.

Based on the pooled proportions, the relative risk ($\widehat{\emptyset}$) of CRC detection was calculated as the ratio of the pooled proportions ($\frac{p_1}{p_2}$). The lower (LCL) and upper (UCL) bounds for the 95% confidence intervals were obtained using the Katz-logarithmic method, whereby n_1 and n_2 represent the total number of patients with complicated and uncomplicated diverticulitis respectively (i.e. $n_1=6$ and $n_2=40$), and the P-value was calculated based on the z-score of the natural log-transformed relative risk [10].

4. Results

The systematic search identified a total of 429 publications for possible inclusion. Non-relevant and duplicate publications were excluded based on title and abstract review. 40 publications were reviewed based on their full text and 4 publications were identified to be eligible for inclusion and were published between 2014 and 2022. The 4 studies included were retrospective studies conducted in Asia evaluating patients diagnosed with acute diverticulitis on CT scan. 1 study included only patients with uncomplicated diverticulitis while the other 3 included patients with both complicated and uncomplicated diverticulitis. In these studies, patients who had emergency surgery at index admission, colonoscopy 1 year prior to diagnosis of diverticulitis, previous history of colonic cancer were excluded. The timing for colonic evaluation varied from within 4-8 weeks of initial presentation to within a year of presentation.

5. Risk of Bias

Based on the Newcastle-Ottawa Scale, all 4 studies were of good quality (Table 3).

6. Findings of Malignancy

The study analysis comprised of 902 patients from 2004 to 2022. Out of the total population studied, 530 patients were excluded, as they either did not have colonic evaluation or did not have it within 1 year of diagnosis of acute diverticulitis; hence a total of 372 subjects were evaluated. The summary of methods, study design, nature of diverticulitis, timing and type of colonic evaluation are summarized in Table 1. Of the 372 patients, 13 patients (3.49%) were found to have colorectal malignancy. Of the 13 patients diagnosed with CRC, 10 were right-sided malignancies while 3 were left-sided. Table 2 summarizes the nature of diverticulitis and incidence of malignancy and polyps detected on colonoscopy.

The pooled CRC detection rate in the Asian studies was 1.64% (95% CI, 0.00-5.93). The heterogeneity was significant (I2 =73%, p=0.01) (Figure 2). A pooled population of 263 patients with uncomplicated diverticulitis was included from 2 studies in which 10 were diagnosed to have CRC. The pooled proportion of CRC detected after an episode of uncomplicated diverticulitis is 3.44 (95% CI 0.0148-0.0609),(I2 = 73.6%, p 0.083) (Figure 3).

A pooled population of 21 patients with complicated diverticulitis from only 1 study showed 3 patients were diagnosed to have CRC. The proportion of CRC detected after an episode of complicated diverticulitis is 14.29%.

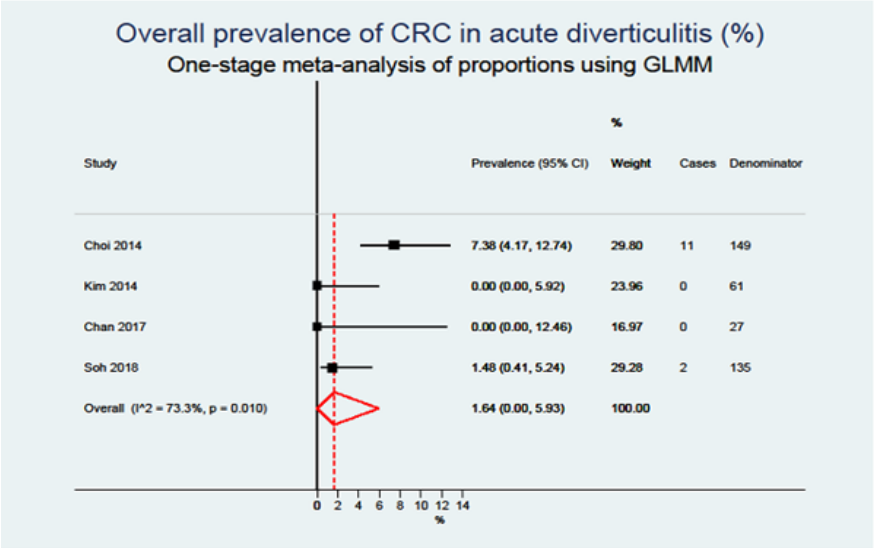

Figure 2: Pooled CRC detection rate in the Asian studies

Table 1: Summary of methods, study design, nature of diverticulitis, timing and type of colonic evaluation are sum Baseline characteristics, nature of disease, methods, and time of colonic evaluation

First author, year	Study design	Country	Study size	Diagnosis	Nature of diverticulitis	Right sided CRC	Left sided CRC	Colonic evaluation	Timing
Choi, 2014	RC	South Korea	149	CT	Complicated and uncomplicated	9	2	Colonoscopy	Within 1 year
Kim, 2014	RC	South Korea	61	CT	Complicated and uncomplicated	0	0	Colonoscopy	Within 1 year
Chan, 2017	RC	Singapore	27	CT	Complicated and uncomplicated	0	0	Colonoscopy	4-6 weeks
Soh, 2018	RC	Singapore	135	CT	Uncomplicated	1	1	Colonoscopy	6-8 weeks

RC-retrospective cohort, PC-prospective cohort, PL-prospective longitudinal, RCT-randomised controlled trial, CT-computed tomography scan, CRC –colorectal cancer

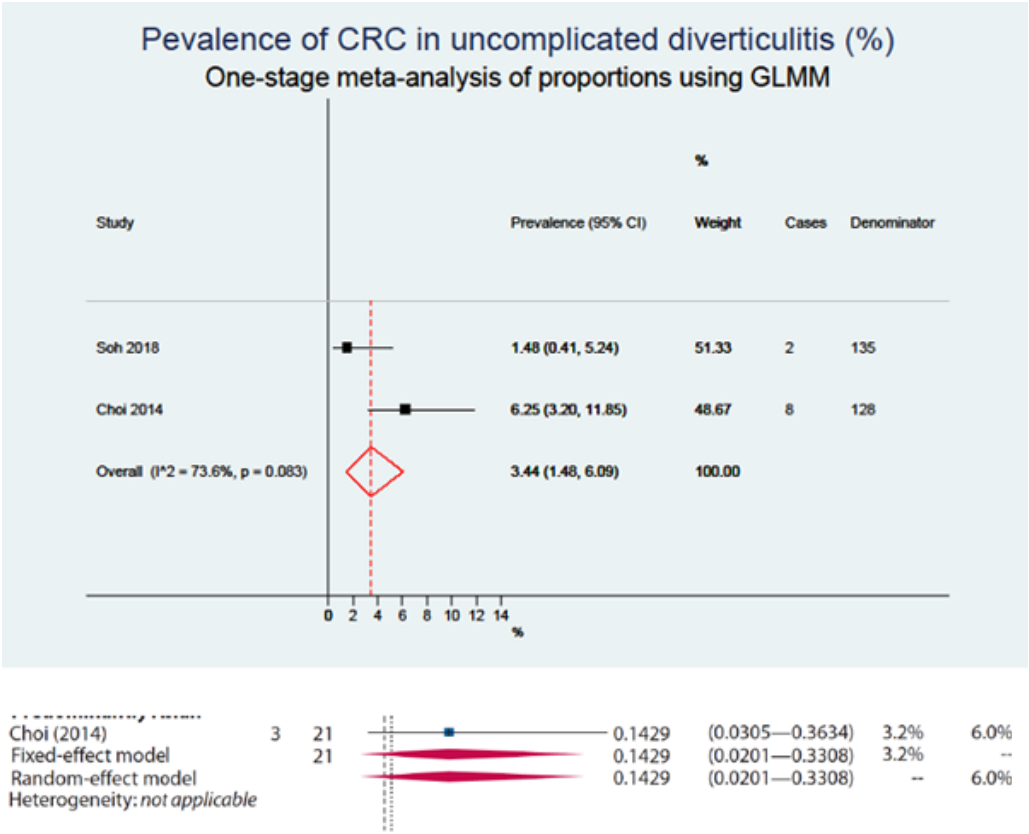

Figure 3: Pooled proportion of CRC detected after an episode of uncomplicated diverticulitis

Table 2: Nature of diverticulitis and incidence of malignancy and polyps detected on colonoscopy
Nature of diverticulitis, incidence of malignancy and polyp detection rate

First author, year	Included patients	Mean/median age	Uncomplicated diverticulitis	Complicated diverticulitis	Patients with malignancy	Patients with advanced adenomas	Patients with non-neoplastic polyps	Right sided CRC	Left sided CRC
Choi, 2014	149	48.6 +/- 16.4	128	21	11 (complicated)	5	42	2	2
Kim, 2014	61	43.3 +/- 15.3	46	15	0	0	19	0	0
Chan, 2017	27	40.5(right sided), 42 (left sided)	NR	NR	0	0	6	0	0
Soh, 2018	135	50.9	135	0	2	2	NR	9	2

NR – No records

Table 3: Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies

Study	Selection				Comparability of cohorts	Outcome			Total score/ Quality
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline		Assessment of outcome	Sufficient follow-up duration	Adequate follow-up	
Choi	*	-	*	*	-	*	*	*	6/Good
Kim	*	-	*	*	-	*	*	*	6/Good
Chan	*	-	*	*	-	*	*	*	6/Good
Soh	*	-	*	*	-	*	*	*	6/Good

Good quality: 3 or 4 (*) in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain or 0 or 1 stars in outcome/exposure domain

7. Discussion

In this systematic review and meta-analysis, the rate of encountering a malignancy with routine colonic evaluation after an episode of acute diverticulitis is 1.64% in a population of 372 patients. This is similar to the detection rate in Koo et al [2] where the detection rate of malignancy is 1.67% in a population of 29348 patients. This is higher than the detection rate of CRC 0.78% (95%, CI 0.13-2.97) in screening patients undergoing colonoscopy seen in a systematic review performed by Niv et al [16]. This suggests that the presence of diverticulitis could raise the likelihood of CRC as compared to the general population, indicating the importance of a follow up scope post diverticulitis.

When stratified to complicated and uncomplicated diverticulitis, we found that it was 4 times as likely to find cancer in the complicated as opposed to uncomplicated group. However, the single Asian study with 21 subjects that demonstrated findings of malignancy in complicated diverticulitis is inadequate for us to draw concrete conclusions.

Current international guidelines suggest routine colonic evaluation in patients after an acute episode of diverticulitis [11,12]. Systematic review and meta- analysis performed by Sharma et al [13] and Koo et al [2] and studies by Rottier et al [14] and Tehranian et al [15] also suggest benefits in routine evaluation in patients who are older and with complicated diverticulitis. However, this data is largely based on the Western population whose severity and location of diverticulitis may differ from that of the Asian population. The aim of our study was to evaluate the role of colonic evaluation in Asian patients with CT-proven acute diverticulitis.

Asian patients predominantly develop right sided diverticulitis which are less severe and in younger patients. The data seen in Western populations hence may not be equally applicable in Asian populations, whose demographics and location of acute diverticulitis differ from that of Western populations.

There are several limitations in the meta-analysis. The retrospective nature of the included studies leads to inevitable selection bias. The study numbers are also small, comprising only of 4 studies, resulting in a smaller sample number with reduced statistical power. There is significant variability in design and methodology in the individual studies resulting in significant heterogeneity, which was addressed using random-effects model analysis. There were a significant number of defaulter rates where 58.8% of patients with acute diverticulitis either did not receive a routine colonoscopy or did not receive it within 1 year of presentation. This may have affected the accuracy in assessing the prevalence of colonic malignancy. Our study also did not look at the pooled proportion rate of polyp pick up. This could be worth looking into as studies have shown that the presence of colonic polyps increases the risk of a patient developing colorectal cancer. It has also been suggested that it takes about 10 years for adenoma to carcinoma transformation to take place [17]. These polyps in patients >50 years

of age would usually be picked up and removed if they followed screening guidelines. However, in our study, the mean age of patients ranged from 40.5-50.9 years. This is much younger than the typical age in which diverticulitis usually occurs, where incidence of diverticulitis usually increases in patients above the age of 60 [18,19]. These patients would not fall under the screening guidelines and it is not known if the combination of chronic inflammation from previous diverticulitis in association with polyps left unremoved till they reach screening ages may lead to an escalation in development of colorectal cancer

8. Conclusion

Currently, there are no comparable meta-analysis and systematic reviews evaluation the role of routine colonoscopy in Asian patients diagnosed with CT-proven acute diverticulitis. This study shows that although the yield of malignancy these patients are low, there may be benefit in selecting patients with complicated diverticulitis to undergo colonoscopy. However, further larger scales studies are required to improve the quality of data and enable us to formulate practice recommendations.

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