

REVIEW

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The outcomes of right-sided and left-sided colonic diverticulitis following non-operative management: a systematic review and meta-analysis

Sih-Shiang Huang¹, Chih-Wei Sung², Hsiu-Po Wang^{3,4} and Wan-Ching Lien^{1,5*}

Abstract

Background: There is no sufficient overview of outcomes in right-sided and left-sided colonic diverticulitis (CD) following non-operative management. This systematic review was conducted to evaluate the recurrence/treatment failure in right-sided and left-sided CD.

Methods: A systematic review was conducted following PRISMA guidelines. MEDLINE, Embase, and Cochrane Library from inception to Dec 2021 were searched. The study characteristics, recurrence/treatment failure, and risk factors for recurrence/treatment failure were extracted. Proportional meta-analyses were performed to calculate the pooled recurrent/treatment failure rate of right-sided and left-sided CD using the random effect model. Logistic regression was applied for the factors associated with the recurrence/treatment failure.

Results: Thirty-eight studies with 10,129 patients were included, and only two studies comprised both sides of CD. None of the studies had a high risk of bias although significant heterogeneity existed. The pooled recurrence rate was 10% (95% CI 8–13%, $I^2 = 86%$, $p < 0.01$) in right-sided and 20% (95% CI 16–24%, $I^2 = 92%$, $p < 0.01$) in left-sided CD. For the uncomplicated CD, the pooled recurrence rate was 9% (95% CI 6–13%, $I^2 = 77%$, $p < 0.01$) in right-sided and 15% (95% CI 8–27%, $I^2 = 97%$, $p < 0.01$) in the left-sided. Age and gender were not associated with the recurrence of both sides. The treatment failure rate was 5% (95% CI 2–10%, $I^2 = 84%$, $p < 0.01$) in right-sided and 4% (95% CI 2–7%, $I^2 = 80%$, $p < 0.01$) in left-sided CD. The risk factors for recurrence and treatment failure were limited.

Conclusion: Non-operative management is effective with low rates of recurrence and treatment failure for both right-sided and left-sided CD although left-sided exhibits a higher recurrence. The recurrence rates did not differ between patients receiving antibiotics or not in uncomplicated CD. Age and sex were not associated with the recurrence although other risk factors were dispersing. Further risk factors for recurrence and treatment failure would be investigated for precise clinical decision-making and individualized strategy.

Keywords: Colonic diverticulitis, Right-sided, Left-sided, Non-operative management, Recurrence, Treatment failure

Introduction

Acute colonic diverticulitis (CD), referring to the inflammation of the diverticula, is one of the common diagnoses for patients with abdominal pain [1]. The incidence of CD has been increasing over time, i.e. the percentage of acute admissions was increasing by 16% in males

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and 12% in females during 10 years in England [2] and a 26% increase in presentations from 1998 to 2005 in the United States [3]. Although CD exhibits a low mortality rate, it would lead to enormous morbidity including pelvic abscess, intestinal perforation, bowel fistula, bowel obstruction, peritonitis, or sepsis [4]. A substantial percentage of recurrence occurs following an acute episode of CD despite complete remission [5, 6]. Also, certain patients experienced treatment failure and proceeded to surgery.

The characteristics of right-sided CD differ from left-sided in many respects. Most of the right-sided diverticula are solitary, containing all bowel layers (true diverticula). Right-sided CD occurs more frequently in Asians with fewer complications [7–9]. By contrast, left-sided CD occurs mainly in the western population. However, there is no sufficient overview of recurrence/treatment failure in the right-sided and left-sided CD in the literature [10]. Therefore, this systematic review was conducted to evaluate the recurrence/treatment failure in the right-sided and left-sided CD following non-operative management.

Materials and methods

The systematic review was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The review protocol was registered in PROSPERO (CRD42021278200). Ethical committee review was waived at the study institution.

Data resources and study selection

We performed a literature review in 3 databases, MEDLINE, Embase, and Cochrane Library, searching for relevant studies from inception to Dec 2021. We used boolean combinations of keywords including “diverticulitis” or “diverticulosis” combined with “recurrent” or “recurrence” or “relapsed” or “location”. Our search was limited to the English language only. Two authors (Huang SS and Sung CW) reviewed the titles and abstracts to extract eligible studies, which were those that reported recurrent rates of left-sided or right-sided diverticulitis. A manual search of the reference lists of the included articles was also conducted to include other relevant studies. Also, we excluded articles that did not record the locations of the diverticulitis. A third author (Lien WC) made the final decision regarding discrepancies. We excluded case reports, case series, duplicate articles, editorials, and studies involving surgical interventions.

Data extraction and quality assessment

Full-text articles were screened for eligible studies reporting the recurrent rates of left-sided or right-sided CD. We also extracted the population number, baseline

characteristics, severity score of diverticulitis, duration of antibiotic treatment, percutaneous drainage, length of hospital stay, length of follow-up time, and mortality. Two authors (Huang SS and Sung CW) performed quality assessments using the revised Cochrane tool for assessing the risk of bias in randomized trials (RoB 2 tool) [12] and the Newcastle–Ottawa Scale (NOS) [13]. The RoB 2 tool is one of the most commonly used tools for risk of bias assessment in randomized trials. The NOS is a standard tool for quality assessment of nonrandomized studies in systematic review and meta-analysis.

Data analysis

To calculate the pooled recurrence/treatment failure rates of right-sided and left-sided diverticulitis, proportional meta-analyses were performed. The pooled recurrence and treatment failure rates were presented with proportions and 95% confidence intervals (CIs). The Dersimonian-Laird random effects model with Hartung-Knapp variance correction was applied to improve the estimation [14, 15]. Forest plots were drawn to inspect the results visually and heterogeneity across the included studies was estimated with the Higgins statistics (I^2) [16]. Logistic regression was applied for the factors associated with the recurrence/treatment failure. All analyses were performed using R 4.1.1 software (R Foundation for Statistical Computing, Vienna, Austria). A p -value of <0.05 was considered statistically significant.

Results

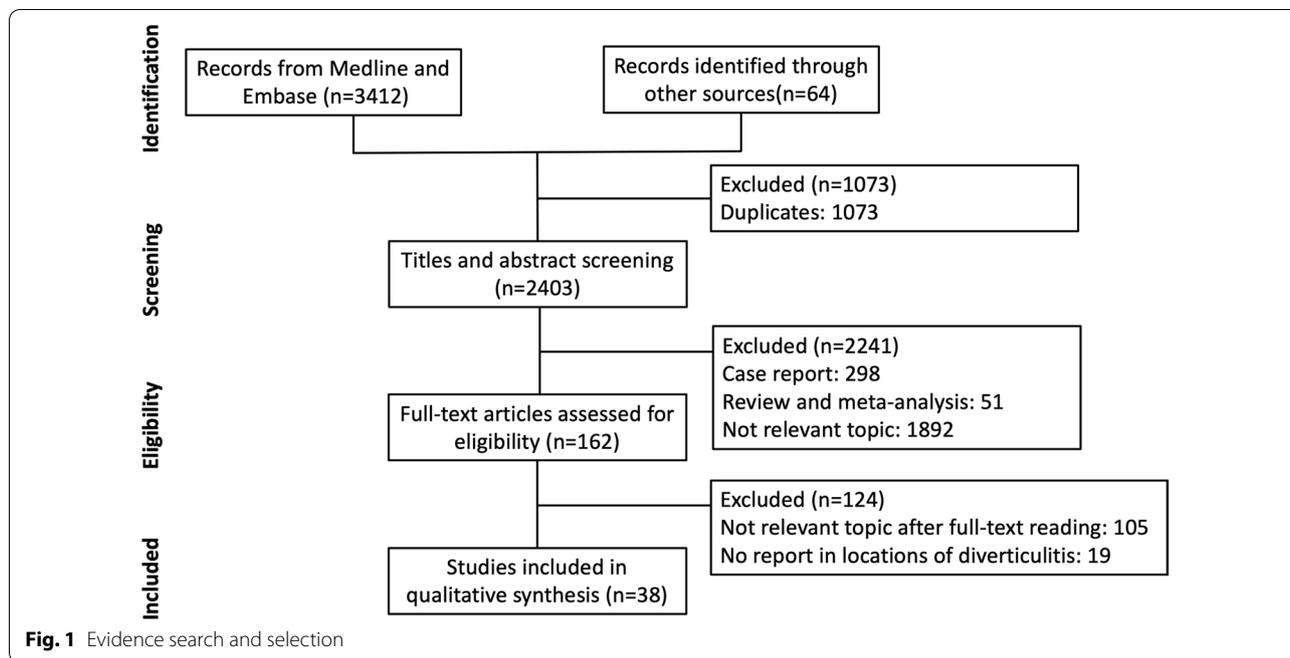
Article selection, characteristics, and quality of the included studies

The initial search identified 3,412 studies from MEDLINE and Embase and 64 studies from manual search (Fig. 1). After removing 1,073 duplicates, 2,403 articles were screened through the titles and abstract; 2,241 articles were excluded after initial screening and the remaining 162 studies were retrieved for full-text review. Finally, 38 studies with 10,129 patients were included in this study, and 2 studies comprised both sides of CD [17, 18].

Twenty-one studies investigated the recurrence of right-sided CD and 19 studies were for left-sided CD. The detailed information was listed in Table 1. Two randomized clinical trials for the right side and 3 for the left side were evaluated by the RoB 2 tool and no high risk of potential bias was detected (Fig. 2). Nineteen cohort studies for the right side and 16 for the left side were assessed by the NOS and none of the studies had a high risk of bias (Fig. 3).

Right-sided CD

A total of 3,931 patients were included and most of them were from the eastern population [8, 9, 17–35].



The mean age was 41.4 years, with 57% being males. The median follow-up period ranged from 4 to 90 months and it was lacking in 3 studies [19, 25, 32]. Notably, only 4 studies were conducted outside of eastern Asia [23, 29–31]. Seventeen studies came from eastern Asia (13 from South Korea, 2 from Japan, 1 from China, and 1 from Taiwan), and the mean age ranged from 35 to 46 years.

Ten studies reported the details of antibiotic treatment: 7 with 2nd or 3rd generation of cephalosporin plus metronidazole [19, 23, 27, 28, 31, 33, 34] and 3 with adding aminoglycoside [22, 26, 36]. The duration ranged from 1 to 14 days. Twenty-seven (0.7%) patients received percutaneous drainage.

We used the random effect model for analysis and the pooled recurrence rate was 10% (95% CI 8–13%) (Fig. 4A). Subgroup analysis showed a recurrence rate of 9% (95% CI 6–13%) within the uncomplicated diverticulitis (Fig. 4B). High heterogeneity was observed between the studies. We also performed a subgroup analysis investigating the relationship between the use of antibiotics and recurrence. The result demonstrated no significant difference in recurrence rates between the antibiotics and antibiotics-free group (9% vs. 8%, $p = 0.85$).

Further analysis demonstrated that age ($p = 0.184$) and gender ($p = 0.932$) were not related to the recurrence. The reported factors associated with recurrence were limited. Park et al. reported that patients with multiple diverticula outside the right-sided colon were associated with a higher risk of recurrence [20]. Kim et al. presented

that smoking and longer hospital stay may be the risk factors for recurrence [8].

Also, 8 of the 21 included studies reported the rate of treatment failure, and the pooled results showed a failure rate of 5% (95% CI 2–10%) (Fig. 4C). Patients would proceed to surgical intervention following treatment failure. The risk factors related to failure in non-operative management were limited. Park et al. reported that elderly (age > 50 years), recurrent episodes, and elevated C-reactive protein levels were risk factors of failure in conservative treatment [19]. Multiple diverticula were also related to the treatment failure [34].

Left-sided CD

A total of 6,198 patients were included, and most of them were from the western population [17, 18, 36–52]. The mean age was 61.4 years and 45% were males. The median follow-up period ranged from 6 to 128 months.

Only 4 studies reported the regimen of antibiotic treatment: one with cephalosporin plus metronidazole for at least 7 days [42], one with ampicillin/sulbactam for at least 7 days [40], one with amoxicillin/clavulanic acid for 10 days [37], one with ampicillin, metronidazole, and aminoglycoside for 5 days [36]. Twenty-six (0.4%) patients underwent percutaneous drainage.

The recurrence rates in the included studies were varying. In patients with sigmoid diverticulitis, Mueller et al. reported the highest recurrence rate of 47% (78/167), and 17% (13/78) of them required surgery [43]. Frileux et al. reported a recurrence rate of 43% (55/128) [44] and

Table 1 The detailed information of the included studies

Author	Design*	period	brief conclusion
Right-sided diverticulitis			
Mizuki et al. [17]	RCS	1998–2009	The rate of recurrence did not differ between left-sided and right-sided diverticulitis (20% vs 27%, $p = NS^*$)
Chen et al. [21]	RCS	2013–2020	Right-sided diverticulitis with non-operative treatment had a low recurrence rate (2%)
Moon et al. [22]	RCS	2001–2005	Conservative treatment should be considered a safe and effective option for acute right-sided diverticulitis as its low rate of recurrence (3.6%) and treatment failure (0%)
Issa et al. [23]	RCS	2005–2007	The current study supports conservative therapy for right-sided diverticulitis due to a low recurrence rate (7%) and treatment failure rate (0%)
Ha et al. [24]	RCS	2005–2012	Conservative treatment had a low recurrence rate (10%) in patients with acute right-sided diverticulitis
Park et al. [25]	RCS	1998–2007	Conservative treatment is primarily required for right-sided diverticulitis, and the recurrence rate was 8%. The rate of treatment failure was 1%
Kim et al. [26]	RCS	2008–2009	Conservative treatment with antibiotics should be the treatment of choice for right-sided diverticulitis which had a recurrence rate of 13%
Park et al. [27]	PCS	2007–2009	Outpatient management for uncomplicated right-sided diverticulitis had a similar recurrence rate compared with inpatient management (10% vs 11%, $p = NS^*$). No treatment failure was noted in both groups
Park et al. [20]	PCS	2004–2012	The recurrence rate for medical treatment of right-sided diverticulitis was 19%; of those, diverticula located only in the right colon and a single diverticulum had a lower recurrence rate
Park et al. [19]	RCS	2017–2019	In medical treatment for right-sided diverticulitis, 9% ended up with treatment failure. Elderly (Age > 50), recurrent episodes, and elevated C-reactive protein levels are factors associated with treatment failure. The recurrence rate was 13% in the conservative treatment success group
Kim et al. [28]	RCT	2014–2018	The overall recurrence rate of medical treatment for right-sided diverticulitis was 9%. No significant differences were shown between the antibiotics and the non-antibiotics group in the recurrence rate (10% vs 8%, $p = NS^*$) and the treatment failure rate (2% vs. 5%, $p = NS^*$)
Kim et al. [8]	RCS	2001–2014	The recurrence rate was 11% in right-sided diverticulitis. Smoking and longer hospital stay were the risk factors for recurrence
Park et al. [9]	RCS	2002–2012	16% of the included patients had a recurrence of right-sided diverticulitis. Multiple diverticula and intraperitoneally located diverticulitis may have a higher recurrence rate
Courtot et al. [29]	RCS	2003–2017	The article consisted of western populations, right-sided diverticulitis had a recurrence rate of 10.4% and treatment failure rate of 6%
Schneider et al. [30]	RCS	2005–2013	The recurrence rate of right-sided diverticulitis was 16.7%. In Caucasians, right-sided diverticulitis occurred in younger and thinner patients compared to left-sided
Destek et al. [31]	RCS	2014–2017	The overall rate of recurrence was 21.1% in acute right-sided diverticulitis
Lee et al. [18]	RCS	2011–2017	The recurrence rate of left-sided diverticulitis was higher than right-sided (19.1% vs 6.9%, $p = 0.003$). In addition, compared to left-sided, right-sided diverticulitis presented as younger age and less advanced modified Hinchey stages
Matsushima et al. [32]	RCS	1994–2005	Conservative therapy had a low recurrence rate of 8.4% in acute right-sided diverticulitis
Park et al. [33]	RCS	2000–2007	The overall recurrence rate was 2%. However, patients who had a pericolic abscess showed a high recurrence rate of 20%
Park et al. [34]	RCT	2011–2014	No significant differences were shown between one-day versus four-day antibiotics treatment strategy in recurrence (10.3% vs 9.0%, $p = NS^*$) and treatment failure (17.2% vs 21.3%, $p = NS^*$)
Yang et al. [35]	RCS	1994–2004	The recurrence rate of acute right-sided diverticulitis was 12.6%. For recurrent diseases, conservative treatment was still safe and efficient
Left-sided diverticulitis			
Daniels et al. [36]	RCT	2010–2014	The recurrence rate was low (3% vs 3%, $p = NS^*$) in both strategies with or without antibiotics within 6 months of follow-up. The rate of treatment failure was 7% and 11% in the antibiotics group and observation group respectively
Pisanu et al. [8]	RCS	2006–2011	The rate of recurrence was similar (6% vs 20%, $p = NS^*$) between the older and younger groups. No patient suffered from treatment failure under medical treatment in this study
Mizuki et al. [17]	RCS	1998–2009	The rate of recurrence did not differ between left-sided and right-sided diverticulitis (20% vs 27%, $p = NS^*$)
Santos et al. [37]	RCT	2018–2020	Conservative treatment of complicated sigmoid diverticulitis had a high recurrence rate (27%) within 6 months
Holmer et al. [38]	PCS	2004–2007	The rate of treatment failure was low (4%). However, conservative treatment had a much higher recurrence than the surgical intervention (33% vs 4%, $p < 0.001$)
Mizrahi et al. [39]	RCS	1998–2008	Conservative treatment for sigmoid diverticulitis had a recurrence rate of 21%, but no emergent surgery was required during long-term follow-up

Table 1 (continued)

Author	Design*	period	brief conclusion
Chabok et al. [40]	RCT	2003–2010	The rate of recurrence did not differ between antibiotics and non-antibiotics groups (16% vs 16%, $p = NS^*$) in the treatment of left-sided diverticulitis. Also, the rate of treatment failure was similar between antibiotics and non-antibiotics groups (1% vs. 0.3%, $p = NS^*$)
Reisman et al. [42]	RCS	1987–1997	The rate of recurrence was 30%. No significant difference in recurrence was found between older (> 60 years) and younger (≤ 60 years) patients, whether treated conservatively or surgically
Muller et al. [41]	RCS	1985–1991	Although the recurrence rate of sigmoid diverticulitis was reported high (47%), lethal complications were still rare. Also, the rate of treatment failure was 0%
Frileux et al. [43]	RCS	1995–2002	The recurrence rate of sigmoid diverticulitis was high (43%), but recurrence attacks were rarely severe. Operative treatment was not advised after the first attack of diverticulitis
Lopez-Borao et al. [44]	RCS	1998–2008	The overall recurrence rate of diverticulitis was 20.5%. The rate of treatment failure was 6.9%. Younger age (< 45 years) was not a risk of recurrence
Binda et al. [45]	RCS	1996–1999	The rate of recurrence was higher in medical treatment than in operative treatment (17.2% vs 5.8%, $p < 0.001$). Risk factors for recurrence included medical treatment, younger age (< 40 years), and a history of at least 3 episodes of acute diverticulitis. In addition, the overall treatment failure rate was 6.9%
Biondo et al. [46]	RCS	1994–2008	The rate of recurrence was 20.7%. No significant differences were shown between the immunosuppressed patients and the nonimmunosuppressed patients (21.5% vs 20.5%, $p = NS^*$)
Unlü et al. [47]	RCS	2004–2012	The recurrence rate of acute sigmoid diverticulitis was 24.4%. The younger group (≤ 50 years) was not associated with a higher recurrence rate than the older group (25.6% vs 23.8%, $p = NS^*$)
Buchs et al. [48]	PCS	2007–2011	The overall recurrence rate was 16.4% in uncomplicated sigmoid diverticulitis. A high level of serum C-reactive protein (> 240 mg/L) was associated with early recurrence (< 6 months) ($p = NS^*$)
Trenti et al. [49]	RCS	1994–2011	The recurrence rate of acute diverticulitis was 14.8% in this study. The univariate analysis showed higher recurrence in patients under chronic corticoid therapy ($p = 0.043$) and the presence of more than 1 abscess ($p < 0.001$)
Brochmann et al. [50]	RCS	2013–2014	The recurrence rate of uncomplicated left-sided diverticulitis was 6.7%, and the treatment failure rate was 3.6%. No significant differences were shown between the patients treated with antibiotics and those without antibiotics (10.9% vs 4.6%, $p = NS^*$)
Lee et al. [18]	RCS	2011–2017	The recurrence rate of left-sided diverticulitis was higher than right-sided (19.1% vs 6.9%, $p = 0.003$). In addition, compared to left-sided, right-sided diverticulitis presented as younger age and less advanced modified Hinchey stages
Meyer et al. [51]	RCS	2005–2009	In Hinchey 1a diverticulitis, the overall recurrence rate was 23.9%. The presence of extraluminal air on computed tomography did not show a higher recurrence rate (17.9% vs 25.3%, $p = NS^*$)

* RCS Retrospective cohort study, PCS Prospective cohort study, RCT Randomized clinical trial, NS Non-significant

Holmer et al. reported 33% (13/40) [40]. By contrast, several studies reported successful results with recurrence rates of 3–6% following conservative treatment [37, 38, 51].

The pooled recurrence rate was 20% (95% CI 16–24%) using the random effect model (Fig. 5A) and the recurrence rate of uncomplicated CD was 15% (95% CI 8–27%) (Fig. 5B). High heterogeneity existed between the included studies. Moreover, we investigate the effects of antibiotics-free on recurrence. The pooled results showed similar recurrence rates (20% vs. 19%, $p = 0.334$) in patients receiving antibiotics or not.

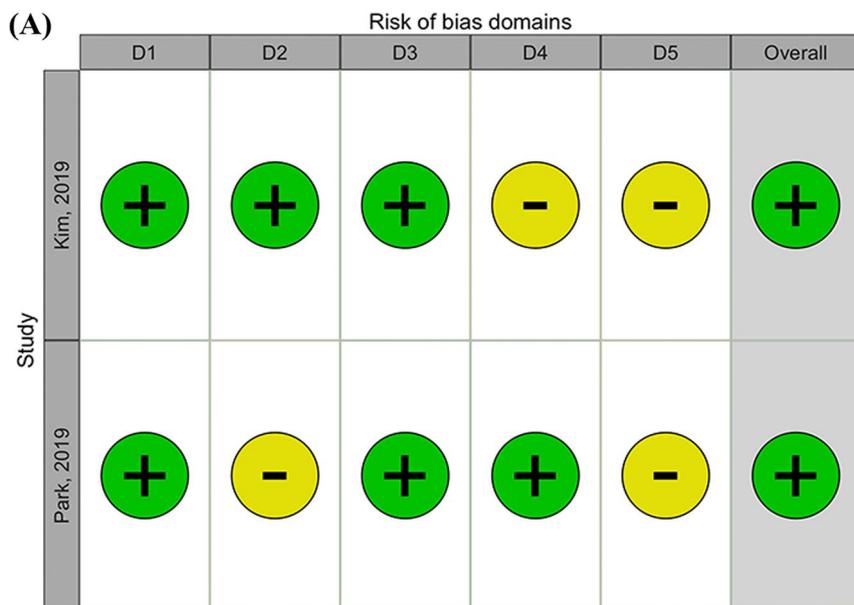
The regression analysis regarding the effects of age and gender on the recurrence was performed. The results showed age ($p = 0.587$) and gender ($p = 0.988$) were not related to the recurrence. Holmer et al. reported that previous recurrent episodes of sigmoid diverticulitis, perforated sigmoid diverticulitis, and conservative treatment were risk factors for recurrent sigmoid diverticulitis [21]. Trenti et al. reported the use of steroids and more than one abscess were associated with recurrence [50].

Eight of the 19 included studies reported the rate of treatment failure, and the pooled results showed a failure rate of 4% (95% CI 2–7%) (Fig. 5C). Patients would proceed to surgery. No other specific risk factors for treatment failure were reported in the included studies.

Discussion

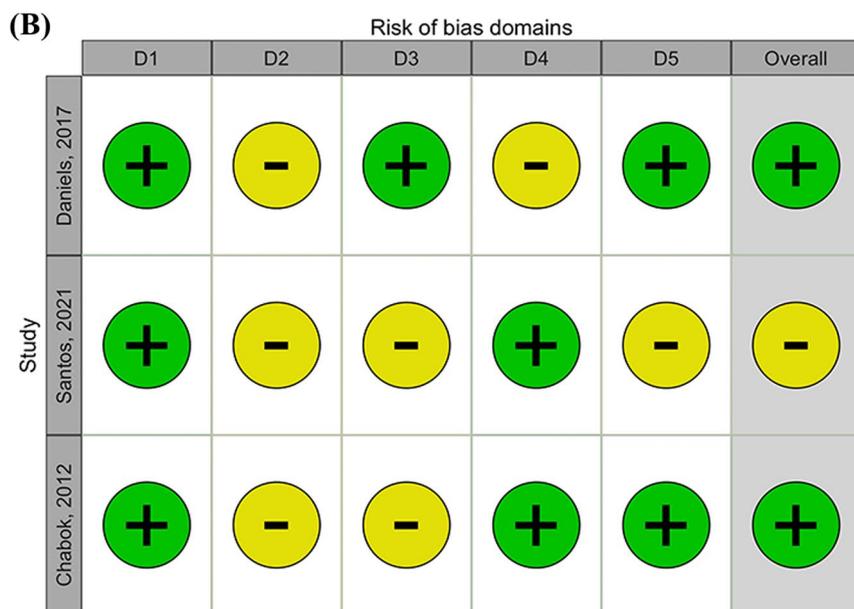
We performed a systematic review and meta-analysis to investigate the recurrence/treatment failure of right-sided and left-sided CD following non-operative management. Thirty-eight comparative studies with a total of 10,129 patients were identified. To the best of our knowledge, this is the largest meta-analysis currently.

Our analyses showed that non-operative management was a safe first-line treatment for CDs with low rates of recurrence and treatment failure. The recurrence rate of left-sided CD was significantly higher than that of right-sided CD (20% vs. 10%). There was no significant difference in the recurrence rates of uncomplicated CD (9% vs. 15%) and treatment failure rates (5% vs. 4%) between right-sided and left-sided CD, manifesting as overlapping



Domains:
 D1: Bias due to randomisation.
 D2: Bias due to deviations from intended intervention.
 D3: Bias due to missing data.
 D4: Bias due to outcome measurement.
 D5: Bias due to selection of reported result.

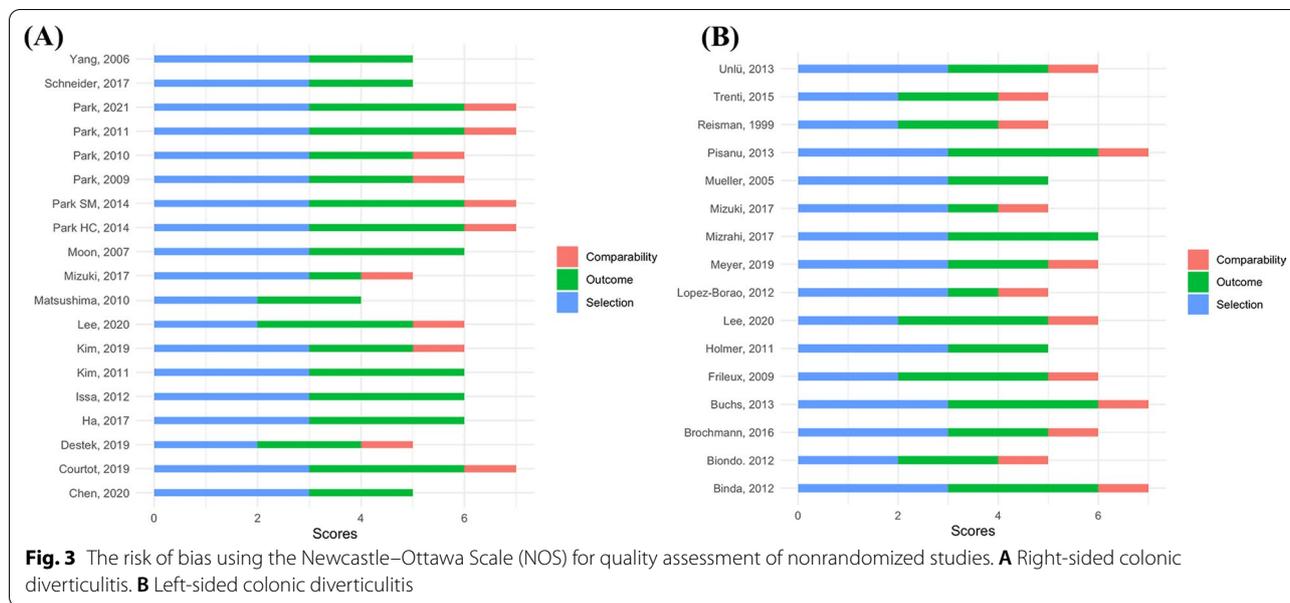
Judgement
 High
 Some concerns
 Low



Domains:
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 D4: Bias due to outcome measurement.
 D5: Bias due to selection of reported result.

Judgement
 High
 Some concerns
 Low

Fig. 2 The risk of bias using the revised Cochrane tool for assessing the risk of bias in randomized trials (RoB 2 tool). **A** Right-sided colonic diverticulitis. **B** Left-sided colonic diverticulitis



in the 95% CI of the pooled data. The pooled results of age, sex, and the use of antibiotics were not related to the recurrence. The other risk factors for recurrence and treatment failure were diverse and limited in the included studies. None of the included studies had a high risk of bias although heterogeneity existed.

Non-operative management includes antibiotic treatment and percutaneous drainage. In this review, the details and duration of antibiotic treatment were not discussed because the data was diverse or lacking. Few patients received percutaneous drainage which indicated the effectiveness of antibiotic treatment only.

In the included studies, a significantly higher recurrence rate was reported among patients with sigmoid diverticulitis [36, 39, 40, 43, 44, 48]. The pooled recurrence rate of left-sided CD would be skewed. The results implied that the sigmoid colon was the most commonly affected location of recurrence, as reported by Sung et al. [52]. However, the locations could not be investigated in this work because most of the studies did not report the exact locations of the CD but only classified it as a left-sided or right-sided CD.

Left-sided CD exhibited a higher recurrence rate than right-sided although there was no difference in the uncomplicated CD. It could be speculated that more recurrences occurred in the left-sided complicated CD. However, the data regarding complicated CD was limited in the included studies so further investigation will be needed.

Although the patients with right-sided CD were younger and had male predominance in our study, as those in a current meta-analysis [10], age and sex were

not associated with the recurrence. The risk factors for recurrence were reported in 9 included studies [8, 9, 19, 20, 33, 46, 49, 50], however, the evidence was scarce and disperse. Radiographic characteristics (e.g. multiple diverticula, more than one abscess), previous recurrent episodes, laboratory data (e.g. C-reactive protein), smoking, long hospital stay, and the use of steroids were noted across different studies.

Moreover, the evidence regarding treatment failure was also limited. One study reported that elderly (age > 50 years), recurrent episodes, and elevated C-reactive protein levels were risk factors for failure in conservative treatment [24]. The other study reported multiple diverticula were associated with treatment failure [34].

Further, recent meta-analyses concluded no beneficial impact for antibiotic treatment in the CD [53, 54]. Our results showed the use of antibiotics was not associated with recurrence in both left-sided and right-sided CD. However, all of the studies regarding antibiotic-free treatment included patients with uncomplicated CD only. The interpretation should be cautious and more evidence is needed to investigate the efficacy of antibiotic treatment in CD.

This study has several limitations. First, the included studies were highly heterogeneous with clinical inconsistency. Also, selection bias would exist due to the retrospective nature in more than half of the studies (29/38). However, our study is by far the most comprehensive systematic review regarding the recurrence/treatment failure of left-sided and right-sided CD. None of the included studies had a high risk of bias. Second, the majority of studies regarding left-sided CDs were

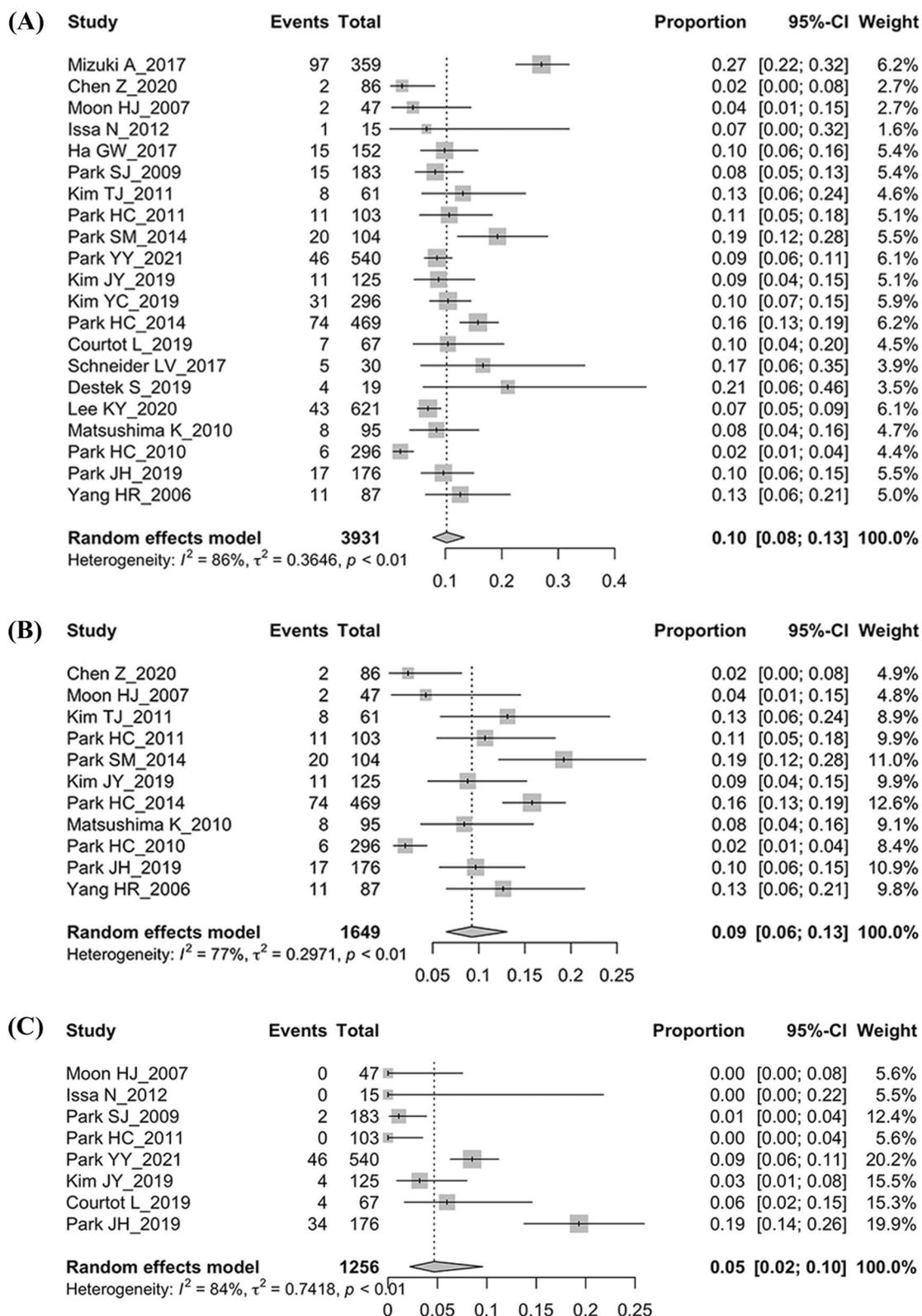
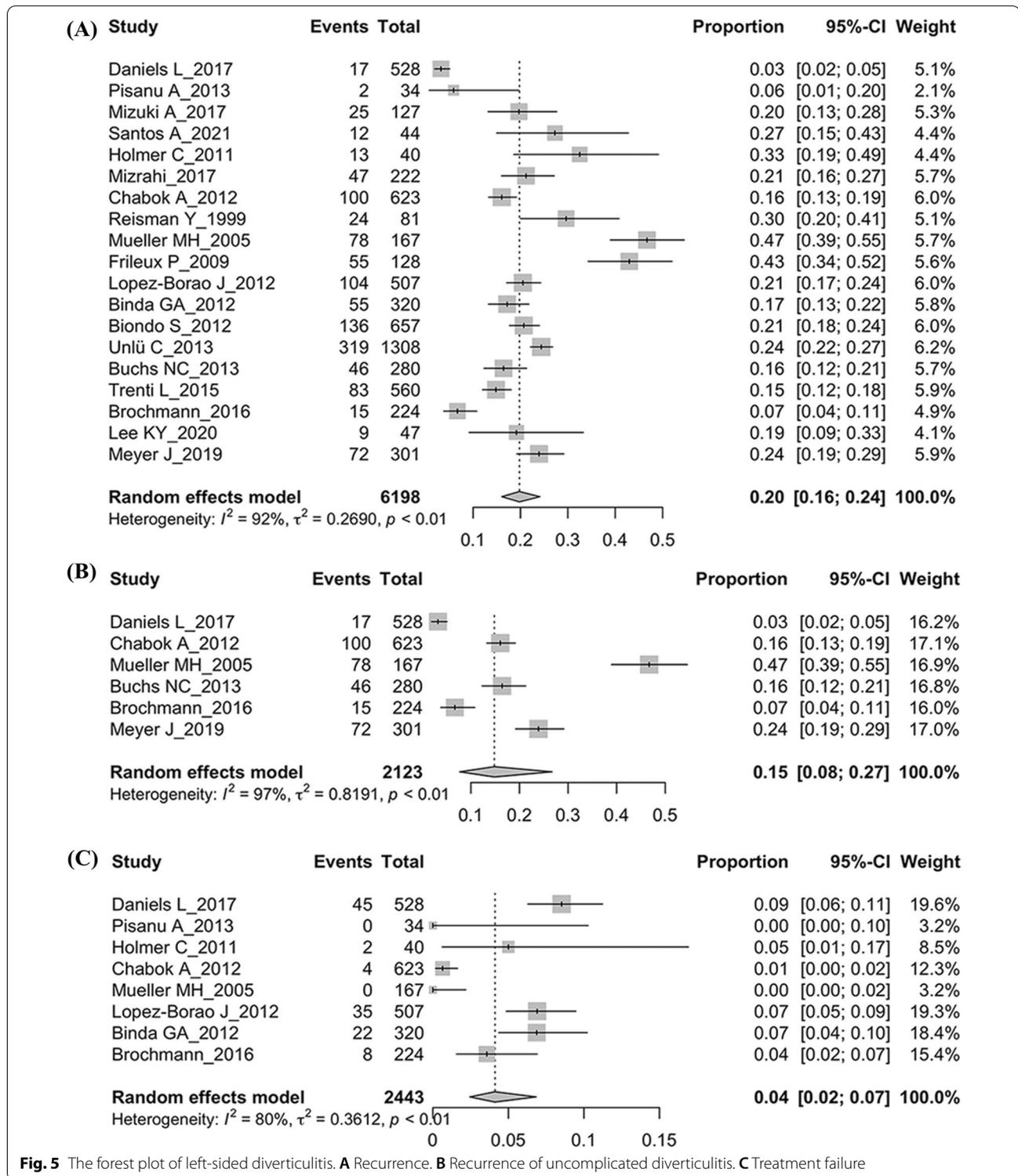


Fig. 4 The forest plot of right-sided diverticulitis. **A** Recurrence. **B** Recurrence of uncomplicated diverticulitis. **C** Treatment failure



conducted in western countries. By contrast, most of the studies discussing right-sided CD were from the Asian population. The results would be extrapolated cautiously to Asian patients with the left-sided CD or vice versa.

Third, the details of comorbidities and severity scores for recurrence and treatment failure were lacking across the studies; thus, risk factors of recurrence and treatment failure other than age and sex cannot be thoroughly

analyzed. Further studies would focus on the risk factors of recurrence and treatment failure and make an individualized treatment strategy.

Conclusion

Non-operative management is effective for right-sided and left-sided CDs with low rates of recurrence and treatment failure although left-sided exhibits a higher rate of recurrence. The recurrence rates did not differ between patients receiving antibiotics or not although current evidence focused on uncomplicated CD. Age and sex were not associated with the recurrence although other risk factors were dispersing. Further investigations should be needed for risk factors for precise clinical decision-making and individualized strategy.

Abbreviations

CD: Colonic diverticulitis; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; RoB 2 tool: Revised cochrane tool for assessing the risk of bias in randomized trials; NOS: Newcastle–Ottawa scale; CI: Confidence interval.

Acknowledgements

None.

Author contributions

SS and WC conceived the study and designed the trial. SS, CW, HP, and WC acquisition of the data. SS, CW, and WC analysis and interpretation of the data. SS and WC drafted the manuscript, and all authors contributed substantially to its revision. HP supervised the study. WC critically revised the manuscript for important intellectual content and took responsibility for the paper as a whole. All authors read and approved the final manuscript.

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Availability of data and materials

All data analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was waived approval by the Institutional Review Board of the Research Ethics Committee of the National Taiwan University Hospital (201907173RIND) due to the hospital policy.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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