The prevalence of pouch fistulas in ulcerative colitis following restorative proctocolectomy: a systematic review and meta-analysis

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Background/Aims: One complication of restorative proctocolectomy with ileo-anal pouch anastomosis is fistula formation in the pouch. Fistulas can be associated with significant morbidity and pouch failure. We conducted a systematic review with meta-analysis to try and understand the prevalence of pouch fistulas in patients with ulcerative colitis following restorative proctocolectomy. Methods: The Embase, Embase Classic, and PubMed databases were searched between January 1979 and April 2022. Studies were included if there were cross-sectional, case-controlled, population-based or cohort studies reporting on prevalence of pouch fistulas in ulcerative colitis. Studies had to report the number of patients with pouch fistulas using either clinical, endoscopic, or radiological diagnosis in an adult population. Results: Thirty-three studies screened met the inclusion criteria. The pooled prevalence of developing at least 1 fistula was 0.05 (95% confidence interval [CI], 0.04–0.07). The pooled prevalence of pouch failure in patients with pouch fistula was found to be 0.24 (95% CI, 0.19–0.30). The pooled prevalence of developing a pouch fistula at 3 years, 5 years and more than 5 years was 0.04 (95% CI, 0.02–0.07), 0.05 (95% CI, 0.02–0.07), and 0.05 (95% CI, 0.02–0.10), respectively. Conclusions: This is the first systematic review and meta-analysis to report the prevalence of pouch fistula. It also provides a pooled prevalence of pouch failure in these patients. These results can help to shape future guidelines, power future studies, and help counsel patients. (Intest Res, Published online )

Key Words: Ulcerative colitis; Fistula; Restorative proctocolectomy; Pouch

INTRODUCTION

Restorative proctocolectomy with ileo-anal pouch anastomosis (IPAA) refers to the operation in where the patient’s own small bowel can be used as a reservoir to allow “natural defecation” without the need for a long-term ostomy following removal of a diseased large bowel. This has become a popular quality of life operation for those with ulcerative colitis (UC) who have not responded to medical therapy and in some patients with familial adenomatous polyposis.¹ Despite good functional outcomes, complications can occur with the pouch to include inflammatory, mechanical, psychological, and functional. One of these complications include fistulas in the pouch itself.

The cause of pouch fistulas is multifactorial to include ischemia, post-surgical dehiscence and Crohn’s disease (CD) of the pouch.² Whereas some of this may be unavoidable, counseling about the incidence of pouch fistulas remains an important part of the pre-surgical work up as pouch fistulas can have a significant impact on the quality of life of patients who have undergone restorative proctocolectomy. They can cause

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persistent discharge and foul odors, which can result in social stigma and embarrassment. Additionally, they can lead to skin irritation, infection, and difficulty with wound healing. Pouch fistulas most commonly occur between the pouch and vagina; pouch and bladder; pouch and anal anastomosis; and pouch and seminal vesicles.\(^3\)

The management of pouch fistulas can be challenging, and utilizes various surgical and non-surgical treatments. Surgical interventions include revision of the pouch and closure of the fistula, whereas non-surgical treatments include topical and systemic antibiotics, wound care, and fistula plugging. Failure of these treatments can result in removal or diversion of the pouch and is termed pouch failure.\(^4\)

The prevalence of pouch fistulas varies in the literature. We, therefore, conducted a systematic review with meta-analysis to understand the prevalence of pouch fistulas following restorative proctocolectomy and pouch failure in those with pouch fistulas after colectomy for UC.

**METHODS**

We searched Embase, Embase Classic, and PubMed from 1978 to April 2022 to identify all studies that reported the prevalence of pouch fistulas following restorative proctocolectomy in adults (≥90%) of all participants (≥18 years of age). We included studies that were population-based studies, case-controlled studies, cohort studies, and cross-sectional surveys that reported the prevalence of pouch fistulas.

We included cross-sectional, case-controlled studies, population-based, and cohort studies reporting on prevalence of pouch fistulas in patients who had undergone restorative proctocolectomy for UC. Studies had to report the number of patients with pouch fistulas using either clinical, endoscopic or radiological diagnosis in an adult population.

We excluded those papers who reported exclusively patients with familial adenomatous polyposis or in those papers where it was not able to extract the patients reported exclusively for UC. To identify published abstracts, we hand searched conference proceedings from United European Gastroenterology, European Crohn’s and Colitis Organisation, British Society of Gastroenterology, and Digestive Disease Week through April 2022.

We searched the medical literature using the terms in Supplementary Table 1 using both as medical subject headings (MeSH) and free-text terms. No language restrictions were applied. We hand searched references from eligible studies for any further studies to be included. Studies that appeared potentially eligible but did not have the required data we emailed the authors for clarification. The eligibility of studies was independently assessed by 2 authors (S.W.L. and I.D.) against the pre-agreed inclusion criteria. All disagreements went to a third reviewer for a consensus (D.S.).

We collected data on author, year, country, method to define presence of acute or chronic pouchitis; number of patients providing complete data; number of male or female patients; type of pouch, number of patients with active acute pouchitis; number of patients with chronic pouchitis, number of patients with CD of the pouch, number of patients with inflammatory pouch condition (pouchitis, cuffitis, and pre-pouch ileitis) number of patients with fistula, location of fistula, timing of fistula in relation to surgery for restorative proctocolectomy, median follow-up, method to diagnose fistula and outcomes following diagnosis of fistula. For papers that reported the management and outcomes of these fistulas we included these as a narrative analysis.

We compared prevalence of fistula according to type of pouch, sex, presence of pouchitis and disease activity using an odds ratio, with a 95% confidence interval (CI). We assessed the quality of studies using the Joanna Briggs Institute (JBI)-Prevalence Critical Appraisal Checklist for studies reporting prevalence and incidence data independently by 2 authors (S.W.L. and I.D.). We combined the proportion of patients with fistulas in each study to calculate the pooled prevalence for each study. We performed sub-analysis of individual types of fistula to find a prevalence for all of these. We then performed a random effects model in order to pool the data to provide an estimate of the prevalence of pouch fistulas. Heterogeneity was assessed using the \(I^2\) statistic. Heterogeneity was considered low for an \(I^2\) value of 0% to 30%, moderate for 30% to 70% and significant for >70%. Publication bias was assessed by funnel plot inspection, Egger’s test, and Begg’s test. All statistics were generated using R with the package “meta.” Egger’s test assesses publication bias by using funnel plots. They calculate the linear regression of the intervention effect estimates on their standard errors weighted by their inverse variance. The presence of an asymmetric funnel plot indicates publication bias.

Data was extracted by 2 independent reviewers (S.W.L. and I.D.) using a Microsoft Excel spreadsheet. Discrepancies were resolved with a third reviewer (D.S.). Studies excluded during full text review is provided in Supplementary Table 2. We combined the proportion of individuals with fistulas in each study to give a pooled prevalence for all studies.
The systematic review followed a prior defined protocol with comprehensive search of multiple electronic databases including conference proceedings and followed steps as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for reporting systematic reviews. The systematic review was registered with PROSPERO, and was assigned an ID of CRD42022325073.

RESULTS

The search revealed 20,002 studies. After screening there were 34 studies remaining for analysis (Fig. 1). These studies reported on 14,343 patients with 1,103 patients developing pouch fistulas. The characteristics of the studies are displayed in Table 1. All 34 studies met our threshold of scoring at least 7 out of 9 on the JBI-Prevalence Critical Appraisal Checklist (Supplementary Table 3).

1. Any Fistula Prevalence

Thirty-four studies reported on 14,343 patients with 1,103 of these patients having at least 1 fistula. This produced a pooled prevalence of 0.06 (95% CI, 0.04–0.08) with significant heterogeneity ($I^2 = 90\%$) (Fig. 2). Eggers’ test indicates the presence of funnel plot asymmetry suggesting publication bias ($P = 0.01$) (Supplementary Fig. 1).

2. Pouch-Vaginal Fistula Prevalence

Twelve studies reported on 707 female patients with 47 of these patients reported to have a pouch-vaginal fistula. This produced a pooled prevalence of 0.06 (95% CI, 0.04–0.10) with low heterogeneity ($I^2 = 37.4\%$) (Fig. 3). Eggers’ test indicates the presence of funnel plot asymmetry suggesting publication bias ($P = 0.02$) (Supplementary Fig. 2).

3. Pouch-Anal Anastomosis Fistula Prevalence

Ten studies reported on 1,998 patients with 134 of these patients reported to have a pouch–anal anastomosis fistula. This produced a pooled prevalence of 0.06 (95% CI, 0.03–0.09) with moderate heterogeneity ($I^2 = 64\%$) (Fig. 4). Eggers’ test indicates the presence of funnel plot asymmetry suggesting publication bias ($P = 0.03$) (Supplementary Fig. 3).

4. Prevalence of Pouch Failure in Patients with Pouch Fistulas

Fourteen studies reported on 325 patients with pouch fistula with 82 of those developing pouch failure. This produced a
pooled prevalence of 0.25 (95% CI, 0.19–0.32) with low heterogeneity ($I^2 = 15.6\%$) (Fig. 5). Eggers’ test does not indicate the presence of funnel plot asymmetry suggesting absence of publication bias ($P=0.8$) (Supplementary Fig. 4).

### 5. Prevalence of Pouch Fistulas with Time

Four studies reported on 655 patients with pouch follow-up at 3 years. Twenty-five of those patients were reported to have developed a pouch fistula. This produced a pooled prevalence of 0.04 (95% CI, 0.02–0.07) with low heterogeneity ($I^2 = 33\%$).

### Table 1. Characteristics of Studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Country</th>
<th>Sex (M:F)</th>
<th>Total patients</th>
<th>Patients with fistula</th>
<th>Median follow-up (yr)</th>
<th>Patients with pouch failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen et al. (2012)</td>
<td>UK</td>
<td>60:42</td>
<td>102</td>
<td>13</td>
<td>NA</td>
<td>NA</td>
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<td>Carcamo et al. (2020)</td>
<td>Chile</td>
<td>49:67</td>
<td>116</td>
<td>22</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>Cho et al. (2012)</td>
<td>South Korea</td>
<td>35:18</td>
<td>55</td>
<td>2</td>
<td>4.2</td>
<td>NA</td>
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<tr>
<td>Davies et al. (2006)</td>
<td>UK</td>
<td>35:52</td>
<td>87</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Dayton et al. (2002)</td>
<td>USA</td>
<td>339:226</td>
<td>565</td>
<td>9</td>
<td>6.5</td>
<td>7</td>
</tr>
<tr>
<td>ElHak et al. (2014)</td>
<td>Egypt</td>
<td>NA</td>
<td>107</td>
<td>3</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Hahnloser et al. (2007)</td>
<td>USA</td>
<td>1,023:862</td>
<td>1,885</td>
<td>264</td>
<td>NA</td>
<td>113</td>
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<tr>
<td>Heimann et al. (2022)</td>
<td>USA</td>
<td>249:226</td>
<td>475</td>
<td>44</td>
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<td>38</td>
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<tr>
<td>Helavirta et al. (2020)</td>
<td>Finland</td>
<td>282:209</td>
<td>491</td>
<td>12</td>
<td>11</td>
<td>53</td>
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<tr>
<td>Ho et al. (2006)</td>
<td>USA</td>
<td>135:195</td>
<td>330</td>
<td>20</td>
<td>NA</td>
<td>8</td>
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<tr>
<td>Ide et al. (2017)</td>
<td>Japan</td>
<td>120:114</td>
<td>248</td>
<td>6</td>
<td>NA</td>
<td>11</td>
</tr>
<tr>
<td>Ikeuchi et al. (2010)</td>
<td>Japan</td>
<td>540:460</td>
<td>1,000</td>
<td>16</td>
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<td>28</td>
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<tr>
<td>Johnson et al. (2001)</td>
<td>Norway</td>
<td>41:31</td>
<td>64</td>
<td>7</td>
<td>NA</td>
<td>6</td>
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<tr>
<td>Kjaer et al. (2016)</td>
<td>Denmark</td>
<td>18:30</td>
<td>447</td>
<td>58</td>
<td>NA</td>
<td>34</td>
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<tr>
<td>Körsgen et al. (1996)</td>
<td>UK</td>
<td>NA</td>
<td>180</td>
<td>21</td>
<td>NA</td>
<td>17</td>
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<tr>
<td>Krausz et al. (2005)</td>
<td>Israel</td>
<td>91:83</td>
<td>174</td>
<td>10</td>
<td>5.4</td>
<td>4</td>
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<tr>
<td>Kuwabara et al. (2021)</td>
<td>Japan</td>
<td>199:121</td>
<td>320</td>
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<td>NA</td>
<td>2</td>
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<tr>
<td>Lavryk et al. (2019)</td>
<td>USA</td>
<td>1,615:1,182</td>
<td>2,797</td>
<td>216</td>
<td>NA</td>
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<td>Lepistö et al. (2002)</td>
<td>Finland</td>
<td>281:206</td>
<td>486</td>
<td>45</td>
<td>NA</td>
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<tr>
<td>Lightner et al. (2017)</td>
<td>USA</td>
<td>1,020:855</td>
<td>1,875</td>
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<td>16.1</td>
<td>94</td>
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<td>Lim et al. (2021)</td>
<td>Australia</td>
<td>121:91</td>
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<td>26</td>
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<tr>
<td>Lorenzo et al. (2016)</td>
<td>Italy</td>
<td>124:61</td>
<td>185</td>
<td>32</td>
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<td>Macaluso et al. (2017)</td>
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<td>NA</td>
<td>71</td>
<td>11</td>
<td>9.2</td>
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<tr>
<td>Mennigen et al. (2012)</td>
<td>Germany</td>
<td>80:50</td>
<td>130</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Parra et al. (2019)</td>
<td>Brazil</td>
<td>20:34</td>
<td>54</td>
<td>5</td>
<td>NA</td>
<td>5</td>
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<tr>
<td>Ryoo et al. (2014)</td>
<td>South Korea</td>
<td>28:44</td>
<td>72</td>
<td>11</td>
<td>6.9</td>
<td>2</td>
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<tr>
<td>Shimada et al. (2020)</td>
<td>Japan</td>
<td>131:93</td>
<td>224</td>
<td>1</td>
<td>6.3</td>
<td>13</td>
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<tr>
<td>Tan et al. (2014)</td>
<td>Australia</td>
<td>82:60</td>
<td>142</td>
<td>9</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Teixeira et al. (2003)</td>
<td>Brazil</td>
<td>40:40</td>
<td>80</td>
<td>1</td>
<td>9</td>
<td>1</td>
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<tr>
<td>Tuilchinsky et al. (2008)</td>
<td>Israel</td>
<td>57:63</td>
<td>120</td>
<td>13</td>
<td>5.4</td>
<td>NA</td>
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<tr>
<td>Villamil et al. (2011)</td>
<td>Puerto Rico</td>
<td>46:42</td>
<td>88</td>
<td>9</td>
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<tr>
<td>Zárate et al. (2008)</td>
<td>Chile</td>
<td>46:61</td>
<td>107</td>
<td>2</td>
<td>NA</td>
<td>4</td>
</tr>
<tr>
<td>Zittan et al. (2017)</td>
<td>Canada</td>
<td>437:321</td>
<td>758</td>
<td>26</td>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>

NA, not available.
Eggers’ test was unable to be calculated due to a paucity of studies.

When assessing the prevalence of fistula at 5 years, 21 studies reported on 6,667 patients. Four hundred and twelve of those patients were reported to have developed a pouch fistula. This produced a pooled prevalence of 0.05 (95% CI, 0.02–0.07) with significant heterogeneity ($I^2 = 89\%$) (Supplementary Fig. 6). Eggers’ test does not indicate the presence of funnel plot asymmetry suggesting absence of publication bias ($P=0.05$) (Supplementary Fig. 7).

Fig. 2. Forest plot of studies reporting the prevalence of at least 1 fistula in patients with a pouch.

(Supplementary Fig. 5).
In the assessment of prevalence of pouch fistula at more than 5 years, 8 studies reported on 2,327 patients, with 134 patients developing a fistula during this time. This produced a pooled prevalence of 0.05 (95% CI, 0.02–0.10) with significant heterogeneity ($I^2 = 91\%$) (Supplementary Fig. 8). Eggers’ test was unable to be calculated due to a paucity of studies.

**DISCUSSION**

In this systematic review and meta-analysis, we demonstrated an overall prevalence of 6% for fistula among patients undergoing restorative proctocolectomy with IPAA for UC. When examining specific anatomy of fistulas after IPAA, the prevalence of pouch-vaginal fistula and anal-pouch anastomosis fistula were both 6%. Perhaps most concerning, the prevalence of pouch failure in patients with a pouch fistula was found to be 25%. These estimates can anchor discussions for patients in both the preoperative and postoperative setting and may inform future guidelines.

A recent meta-analysis by Pellino et al.\(^{39}\) in 2022 looking at...
pouch fistula prevalence and failure until 2020 supported our findings on pouch failure rates. Their pouch failure rate was found to be 18% which is similar to our rate of 25%. Their paper added to the literature by reporting on CD development of the pouch. Our meta-analysis is unique as we report a pooled prevalence of pouch fistulas whereas due to their study design they reported that pouch fistula prevalence was between 1.5% and 12%. Our meta-analysis found almost double the number of fistulas.

The management of pouch fistulas involves a combination of surgical and non-surgical interventions. Surgical management is often the first line of treatment for pouch fistulas. Simple fistulas are often managed with seton placement. Failing this or in more complex fistulas options include the creating of a transanal-ileal advancement flap, ileal diversion and fistulectomy. Excision of the pouch and ostomy creation is often the final resort. Medical interventions mainly focus on antibiotic therapy to treat or prevent infections but have limited efficacy. Biologics and small molecules have been shown to be an option when the fistula has been caused by CD development in the pouch. There is a paucity of trials into the management of pouch fistulas. Currently management is centered around multi-disciplinary team meetings using local experience to make decisions. However, such a relatively high prevalence complication deserves a more evidence-based approach and this meta-analysis can help to power these sorely needed future studies.

Our review has multiple strengths, including a large sample size of over 21,000 patients from a variety of countries around the world. This ensured that the results generated are applicable to most if not all population cohorts. In addition, this serves to close a current gap in the literature where such data does not exist. Secondly, we set up an extensive search strategy which included a well-defined inclusion and exclusion criteria as discussed in methods, in order to identify as many relevant studies as possible.

There are several limitations to this study, most of which are inherent to meta-analyses. The studies included were all observational cohort studies with significant heterogeneity with their results which may lead to selection bias. There was a paucity in the number of studies reporting; the type of fistula patients developed; how patients developed fistulas in relation to time; the presence of pouchitis and disease activity; pouch fistula by sex. This may lead to bias in our results. By design, the pediatric population was excluded and thus our results are not applicable to this cohort.

Our review is the first to report a pooled prevalence for pouch fistulas. These findings can help to counsel patients prior to undergoing pouch formation and may shape future guidelines and health policies for fistula surveillance. In addi-
tion, our results can help to power future studies which are sorely needed to improve our understanding of the natural history of pouch fistulas after IPAA for UC. However, caution must be taken due to the high heterogeneity and risk of publication bias in our study.

ADDITIONAL INFORMATION

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability Statement
Not applicable.

Author Contributions
Conceptualization: Kayal M, Barnes EL, Segal JP. Data curation: Lo SW, Dharia I, Sriranganathan D. Formal analysis: Segal JP. Methodology: Dharia I, Segal JP. Supervision: Segal JP. Writing - original draft: Lo SW, Dharia I, Sriranganathan D. Writing - review & editing: Sriranganathan D, Kayal M, Barnes EL, Segal JP. Approval of final manuscript: all authors.

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Supplementary Material
Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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