Systematic Review and Meta-Analysis

Medicine

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Urolithiasis in patients with inflammatory bowel disease

A systematic review and meta-analysis of 13,339,065 individuals

Aldukhayel Abdulrhman, MD[a,*], Adil Alsweed, MD[b], May Rashed Alotaibi, MBBS[c], Abdullah Yousef Aldakhil, MBBS[d], Shahad Fahad Alahmadi, MBBS[e], Saud Musallum Albishri, MBBS[f], Nurah Ibrahem Alhmed, MBBS[g]

Abstract

Background: This study aimed to summarize the current literature regarding the prevalence of renal stones in patients with inflammatory bowel disease (IBD). Moreover, we aimed to evaluate the risk factors of urolithiasis in patients with IBD and the difference between patients with IBD and healthy controls in terms of urinary profile.

Methods: On February 23, 2022, a computerized search was conducted on PubMed, OVID via MEDLINE, Web of Science, and Scopus using relevant keywords. Three independent reviewers performed 2-stage screening and data extraction. The National Institutes of Health tools were employed for quality assessment. Review Manager 5.4 software was used to calculate the mean difference (MD) between IBD patients and non-IBD in terms of urine profile using the Inverse-variance model and to estimate the odds ratio of reported risk factors for renal stones with the Generic Inverse-Variance model.

Results: Thirty-two articles (n = 13,339,065 patients) were included. The overall prevalence of renal stones in patients with IBD was 6.3%, 95% Confidence interval (4.8%–8.3%). The prevalence of urolithiasis was more common in Chron's disease vs Ulcerative colitis (7.9% vs 5.6%) and in old studies (1964–2009) than in more recent studies (2010–2022) (7.3% vs 5.2%), respectively. Compared to non-IBD patients, patients with IBD were associated with significantly lower urine volume (MD = –518.84 mL/day, $P < .00001$), calcium 24-hour urine (MD = –28.46 mg/day, $P < .0001$), citrate 24-hour urine (MD = –144.35 mg/day, $P < .00001$), sodium 24-hour urine (MD = –23.72 mg/day, $P = .04$), and magnesium 24-hour urine (MD = –33.25 mg/day, $P < .00001$).

Conclusion: The overall prevalence of renal stones in patients with IBD was comparable to the general population. Patients with Chron's disease were associated with a higher prevalence of urolithiasis compared to Ulcerative colitis. Drugs that induce renal calculi should be stopped in high-risk patients.

Abbreviations: BMI = body mass index, CD = Chron's disease, CI = confidence interval, IBD = inflammatory bowel disease, MD = mean difference, NIH = National Institutes of Health, OR = odds ratio, UC = ulcerative colitis.

Keywords: chron's disease, IBD, nephrolithiasis, renal calculi, ulcerative colitis, urolithiasis

1. Introduction

Ulcerative colitis (UC) and Chron's disease (CD) are the most common forms of inflammatory bowel disease (IBD), which affect more than 1.4 million people in the United States.[1] Several extraintestinal manifestations of IBD have been reported, including the formation of renal calculi, either urolithiasis or nephrolithiasis, which occurs in up to 25% to 30% of patients with IBD.[2,3] IBD is linked with malabsorption secondary to bowel resection, primary malabsorption, chronic dehydration, and metabolic disorders, all of which contribute to the development of urinary calculi.[4,5] A lack of treatment might result in an increased risk of recurrent stone formation and impaired renal function.

Urolithiasis occurs when mineral crystals accumulate in the urinary tract, ureters, and urinary bladder.[6] The prevalence of urolithiasis in the general population varies depending on the

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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[a] Department of Family and Community Medicine, Qassim University, College of Medicine, Buraidah, Saudi Arabia, [b] PHC Physician, Ministry of Health, Qassim, Saudi Arabia, [c] College of Medicine, Almaarefa University, Riyadh, Saudi Arabia, [d] College of Medicine, Qassim University, Qassim, Saudi Arabia, [e] College of Medicine, Al-Rayan Colleges, Medina, Saudi Arabia, [f] College of Medicine, Jeddah University, Jeddah, Saudi Arabia, [g] College of Medicine, Ibn Sina National College, Jeddah, Saudi Arabia.

** Correspondence: Abdulrhman Aldukhayel, Department of Family and Community Medicine, Qassim University, College of Medicine, Buraidah, Saudi Arabia (e-mail: m_dkhiel@qu.edu.sa).*

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geographic region and the population studied. In general, the global prevalence of urolithiasis is estimated to be around 1% to 20%, with higher prevalence rates in industrialized countries.[7] In the United States, for example, the prevalence of kidney stones has been reported to be approximately 8.8%.[8] IBD and urolithiasis have long been known to be linked; historical studies revealed that IBD patients had 2- to 3-folded greater rates of symptomatic stone development than the general population.[9] Surgery is the primary treatment option for patients with IBD who are unable to respond to pharmacological therapy (antibiotics and biologics, immunomodulators, and anti-inflammatory drugs).[10,11] Even after surgery for IBD, the risk of urolithiasis remains to be higher. Studies associating IBD with an increased incidence of urolithiasis or nephrolithiasis tend to be outdated or based on a small number of patients.[12–16] A previous meta-analysis showed that up to 22% of IBD patients had urinary complications. Moreover, they demonstrated that patients with IBD had an increased risk ratio (RR) of contracting nephrolithiasis compared to those without IBD (RR = 3.85, 95% confidence interval [CI]: 3.08–4.82). However, this study did not investigate the urinary profile, stone composition, and risk factors of renal stones in patients with IBD. Therefore, this systematic review and meta-analysis aimed to summarize the current literature regarding the prevalence of renal stones in patients with IBD. Moreover, we aimed to evaluate the risk factors of urolithiasis in patients with IBD and the difference between patients with IBD and healthy controls in terms of urinary profile.

2. Methods

We have followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist and Cochrane Handbook for Systematic Reviews of Interventions in reporting this study.[17,18]

2.1. Eligibility criteria

We included the observational studies (case-control, cohort, and cross-sectional) that reported data (prevalence, risk factors, urine profile, and stone composition) regarding the development of renal stones (urolithiasis and nephrolithiasis) in patients with IBD (UC or CD). There were no restrictions regarding country, race, age, gender, or associated comorbidities. We excluded case reports, conference abstracts, and non-English studies.

2.2. Information sources and search strategy

On February 23, 2022, we searched the following databases: MEDLINE via PubMed and OVID, Scopus, and Web of Science, using the relevant keywords to identify the relevant citations. Table S1, Supplemental Digital Content, http://links.lww.com/MD/J100 shows the detailed search term for each database. These databases were searched from inception to the date of search. Moreover, the reference lists of all included citations were searched. The retrieved citations were imported to EndNote X9 software, and duplications were removed.

2.3. Selection process

Using Microsoft Excel software, a screening sheet was created. Study ID, publication year, title, abstract, keywords, digital object identifier, and URL are all included. The selection process was undertaken using a 2-step screening technique by 3 independent reviewers (M.R.A, A.Y.A, and S.F.A). Step 1 was screening the title and abstract of all studies found via the literature search to determine which studies might proceed to step 2 (Full-text screening), where reviewers would read and assess whether each research met eligibility criteria. Any disagreement between the reviewers was solved by the judgment of the study supervisor (A.A).

2.4. Data items and collection process

Four independent reviewers extracted the following data from the included studies to an offline preprepared Excel sheet: Demographic data of the included patients (age, gender, and residency), study characteristics (studies groups, study duration, total sample size, country, and main findings), outcomes (prevalence of renal stones, urine profile of IBD patients, risk factors of developing renal stones, and stone composition).

2.5. Risk of bias and quality assessment

Using the National Institutes of Health (NIH) quality assessment tool for observational cohort, case-control, and cross-sectional studies, 2 authors (S.M.A and N.I.A) independently evaluated the risk of bias and the quality of each included article. Reviewers can critically evaluate the internal validity of research using this tool. Studies were deemed "good," "fair," or "poor." In the case when the authors disagreed on a rating, a third author (A.A) resolved any disagreements.

2.6. Data synthesis

The prevalence of developing renal stones was calculated using the random-effects model with a 95% CI. Using the I^2 statistic, we calculated the percentage of heterogeneity and inconsistency between studies, with values of 25%, 50%, and 75% deemed low, moderate, and high, respectively. The random-effect model was employed if the heterogeneity was considerable and $I^2 > 50\%$; otherwise, the fixed-effect model was utilized.[19] Comprehensive Meta-analysis was used for all statistical analyses (Comprehensive Meta-analysis; USA: version 3.3.070). To resolve heterogeneity, sensitivity analysis was performed by removing 1 study in each scenario, which is known as sequential sensitivity analysis. Furthermore, subgroup analysis was performed to minimize the risk of inconsistency. To assess the difference between IBD patients and non-IBD in terms of urine profile, we used the Review Manager 5.4 software to calculate the mean difference (MD) between both groups using the Inverse-variance model. Moreover, we applied the Generic Inverse-Variance model to estimate the odds ratio (OR) of reported risk factors for renal stones. Publication bias was assessed based on the criteria of Egger test, and a funnel plot was generated for the forest plots that included 10 studies or more.[20]

3. Results

3.1. Study selection

Based on our literature search, we found a total of 1180 relevant citations. After removing duplication, 779 articles underwent title/abstract screening. Then, 735 studies were deemed ineligible to our criteria. The full-text screening was performed on 44 articles, and only 12 studies were excluded. Finally, 32 articles (n = 13,339,065 patients) were included in the qualitative (systematic review) and quantitative synthesis (meta-analysis).[12–16,21–47] Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included studies.

3.2. Characteristics of included studies and patients

Regarding the year of publication of the included studies, it ranged from 1962 to 2021. Eleven studies were conducted in the United States of America (USA), 3 in Denmark, 3 in Germany, 2 in Japan, 2 in Switzerland, and one in each of the following

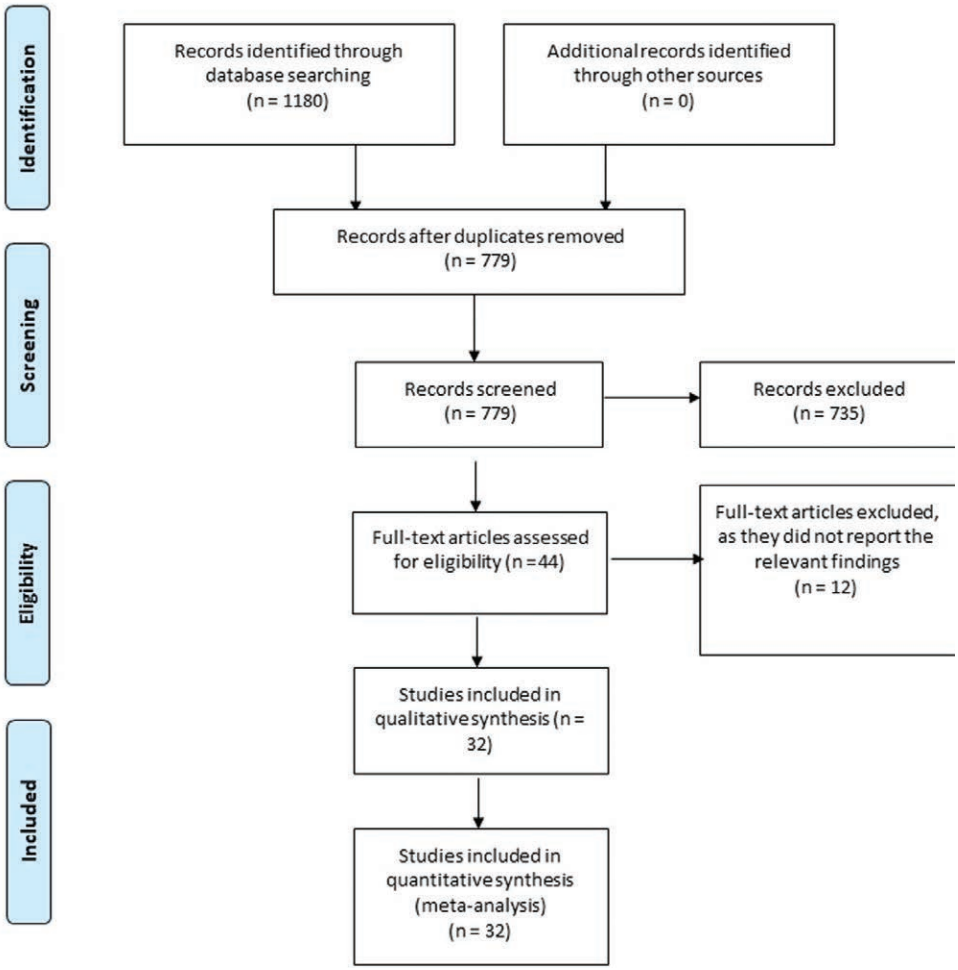

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

countries Brazil, Greece, Korea, Sweden, Australia, Tunisia, Poland, Scotland, and Spain. The majority of the included studies were cohort (25 studies), and 7 studies were case-control studies. The mean age of the included patients was 42 years (range 8–82) years. More than half of the patients (52.86%) are males across the included studies. The mean body mass index (BMI) was reported only in 6 studies, and it was found to be within the normal range. Among all patients, only 4331 patients underwent bowel surgery. Table 1 summarizes the baseline characteristics of included studies and patients.

3.3. Quality of the included studies

Based on the NIH quality assessment tool for observational cohort studies, about 60% of the studies were deemed as "Good," and 40% of the studies were deemed as "Fair." In terms of case-control studies, 28.6% were deemed as "Good," and 71.4% were deemed as "Fair." There were no "Poor" studies. Figure S1, Supplemental Digital Content, http://links.lww.com/MD/J101 shows the detailed quality assessment based on the NIH tool.

3.4. Prevalence of renal stones in IBD patients

The overall prevalence of renal stones in patients with IBD was 6.3%, 95% CI (4.8% to 8.3%), Figure 2. The pooled data were heterogeneous (I^2 = 97.70%, P < .001). To resolve the heterogeneity, sensitivity analysis was performed and demonstrated that Cury et al, 2013, Hueppelshaeuser et al 2012[41], and Ishii et al 2009[42] had the highest effect on the overall effect estimate[39]; by excluding them, the overall prevalence reduced to 5.7%, 5.9%, and 5.7%, respectively, Figure 3. A significant publication bias was detected based on the funnel plot (Fig. 4) and Egger test (P = .017). Trim and fill analysis showed that by trimming 5 studies, the overall prevalence would be 8.1% (5.3% to 12.1%).

After performing the subgroup analysis to minimize the inconsistency, the random-effect estimate analysis showed that the prevalence of renal stones in CD patients was higher than patients with UC and un-specified IBD [7.9%, 95% CI (3.1%–18.7%), I^2 = 95.83%, P < .001], [5.6%, 95% CI (3.9%–7.8%), I^2 = 81.62%, P < .001], and [5.6%, 95% CI (3.8%–8.1%), I^2 = 98.45%, P < .001], respectively. Based on the sone location, the random-effect model showed that urolithiasis, nephrolithiasis, and both in patients with IBD was [7.1%, 95% CI (3.2%–15.2%), I^2 = 99.56%, P < .001], [2.1%, 95% CI (0.3%–12.8%), I^2 = 99.65%, P < .001], and [11.0%, 95% CI (6.5%–18.1%), I^2 = 50.52%, P = .132], respectively. A subgroup analysis based on the study design demonstrated that the overall prevalence of renal stones in case-control studies was lower than in cohort studies [4.1%, 95% CI (3.0%–5.6%), I^2 = 49%, P = .097] and [6.9%, 95% CI (5.0%–9.4%), I^2 = 98%, P < .001]. Regarding UC, the prevalence of urolithiasis was 6.8%, 95% CI (3.3%–13.4%), nephrolithiasis 4.2%, 95% CI (2.1%–8.1%), and both 9%, 95% CI (2.1%–31.0%). Regarding CD, the prevalence of urolithiasis was 7.1%, 95% CI (3.6%–13.6%), nephrolithiasis 4.6%, 95% CI (3.6%–5.8%), and both 11.9%, 95% CI (8.4%–16.6%). Based on

Table 1

Summary of included studies and patients.

Study ID	Country	Groups	Sample size	Study design	Outcome	Age	Gender (male%)	BMI (mean ± SD)	Number of atient who underwent bowel surgery
Torricelli 2020	US	IBD	34	Case–control	Urine parameters and stone composition	58.4 ± 12	55.88	26.6 ± 6.6	34 (100)
		Control	34			58.5 ± 12.0	55.88	26.5 ± 6.5	-
RUDZIŃSKI 2021	Poland	UT+	110	Cohort	Association between UT and IBD and stone composition	57 ± 16	53.64	NR	110 (100)
		UT-	349			56 ± 17	44.41		349 (100)
Miyajima 2021	Japan	UT+	34	Case–control	Risk factors of urolithiasis and stone composition	44.5 (22–66)	82.35	NR	29 (85.3)
		UT-	1037			42.0 (11–90)	68.56		586 (56.5)
Herzog 2018	Switzerland	CD	481	Cohort	Association between UT and age at disease onset of IBD	<10 to > 40	48.86	NR	159 (33.056)
Stark 2017	US	CD	19,730	Cohort	Association between UT and IBD and risk factors of urolithiasis	16.09 ± 0.03	49.94	NR	NR
		UC	11,177			15.7 ± 0.05	47.07		
		Non-IBD	8,797,615			13.63 ± 0.01	50.22		
Fagagnini 2017	Switzerland	CD	1333	Cohort	Association between UT and IBD and Risk factors of urolithiasis	NR	45.46	23.5 (21.1-26.5)	562 (42.2)
		UC	990				52.63	24.2 (21.7-26.9)	99 (10)
Varda 2015	US	IBD	14,352	Cohort	Association between UT and IBD	<30 to > 80	59.70	NR	NR
		Non-IBD	3,573,527				61.10		
Kima 2015	Korea	CD	387	Cohort	Prevalence of UT in CD and Risk factors for urolithiasis	35 (19-72)	25.06	NR	176 (45.48)
Cury 2013	Brazil	CD	93	Cohort	Prevalence of UT in IBD and Risk factors for urolithiasis	41	48.39	NR	2 (2)
		UC	75			43	25.33		0 (0)
Boussorra 2013	Tunisia	CD	184	Cohort	Prevalence of UT in CD	34.7	51.63	NR	NR
Hueppelshaeuser 2012	Germany	CD	46	Cohort	Prevalence of UT in CD and urine parameters	6 to 62	63.04	NR	15 (32.61)
Ishii 2009	Japan	UT+	39	Cohort	Prevalence of CD and stone composition	NR	76.92	NR	39 (100)
		UT-	59				77.97		59 (100)
PARKS 2003	NR	IBD	126	Cohort	Prevalence of UT in IBD and urine parameters	44 ± 1	84.92		96 (76.19)
MCCONNELL 2002	Scotland	CD	25	Case–control	Prevalence of UT in IBD and urine parameters	39 (18-65)	40.00	NR	11 (44)
		UC	15			47 (32-71)	40.00		1 (6.67)
		Non-IBD	17			36 (24-47)	64.71		Control
Christodoulou 2002	Greece	CD	37	Cohort	Prevalence of UT in IBD	40.2 ± 11.4	59.46	NR	NR
		UC	215			54.1 ± 10.1	57.67		
SOTO 2001	Spain	CD	42	Case–control	Urine parameters and stone composition	15 to 72	52.38	NR	11 (26.19)
		Control	18			25 to 65	44.44		Control
Bohles 1988	Germany	CD	86	Case–control	Prevalence of UT in CD and urine parameters	31.2 ± 10.55	61.63	NR	NR
		Control	53			32.37 ± 16.67	71.70		
ANDERSSON 1987	Sweden	CD	107	Cohort	Prevalence of UT in CD	NR	51.40	NR	107 (100)
KNUDSEN 1978	Denmark	CD	140	Cohort	Prevalence of UT in IBD	34 (11-73)	37.86	NR	46 (32.86)
		UC	88			42 (12-74)	55.68		25 (28.41)
Fleckenstein 2010	Denmark	CD	140	Cohort	Prevalence of UT in IBD	39 (11-79)	37.86	NR	NR
		UC	88			39 (10-74)	55.68		
Shield 1976	US	UC	233	Cohort	Prevalence of UT in IBD	36.2	55.36	NR	148 (63.52)
Greenstein 1976	US	IBD	700	Cohort	Prevalence of UT in UC	NR	NR	NR	NR
		UC	202						
Farmer 1974	US	CD	80	Case–control	Prevalence of UT in IBD and urine parameters	36.5	52.50	NR	41 (51.25)
		UC	18			41.5	55.56		10 (55.56)
		Control	27			NR	NR		Control
Bennett 1972	Australia	UC	458	Cohort	Prevalence of UT in UC	NR	NR	NR	333 (72.71)
Gelzayd 1969	US	IBD	885	Cohort	Prevalence of UT in UC and stone composition	25.23	NR	NR	NR
		UC	677			27			
Grossman 1967	US	IBD	1100	Case–control	Prevalence of UT in UC	NR	2.18	NR	827 (75.2)
		UC	761				1.97		544 (71.5)
Dreen 1962	US	UC	583	Cohort	Prevalence of UT in UC	NR	NR	NR	NR
Simoneaux 1996	NR	CD	90	Cohort	Prevalence of UT in CD	NR	NR	NR	NR
Siener 2013	Germany	UT+	10	Cohort	Prevalence of UT in CD	56.1 ± 12.6	60.00	25.5 ± 4.1	2 (20)
		UT-	41			48.2 ± 14.2	29.27	24.3 ± 4.5	10 (24.39)

(*Continued*)

Table 1

(*Continued*)

Study ID	Country	Groups	Sample size	Study design	Outcome	Age	Gender (male%)	BMI (mean ± SD)	Number of atient who underwent bowel surgery
McAuliffe 2015	US	IBD	44,574	Cohort	Prevalence of UT in IBD	18 to 80	49.39	NR	NR
Herbert 2022	US	CD	1778	Cohort	Prevalence of UT in IBD and Risk factors for urolithiasis	46.6 ± 19.7	40.66	NR	NR
		UC	1326			46.9 ± 19.7	42.91		
Dimke 2020	Denmark	IBD	75,236	Cohort	Prevalence of UT in IBD	NR	45.62	NR	NR
		Non-IBD	767,403				45.90		

BMI = body mass index, CD = Chron's disease, IBD = Inflammatory bowel disease, NR = Not reported, UC = Ulcerative colitis, US = United States, UT = Urolithiasis.

the year of publications, the overall prevalence of renal stones generated from studies that were published from inception to the end of 2009 was higher than the studies published from 2010 to 2022 [7.3%, 95% CI (4.8%–11.0%), $I^2 = 92.23\%$, $P < .001$] vs [5.2%, 95% CI (3.5%–7.5%), $I^2 = 98.51\%$, $P < .001$], respectively (Table 2).

3.5. Urine profile of IBD patients vs non-IBD

Patients with IBD were associated with significantly lower urine volume (MD = –518.84 mL/day, 95% CI: –707.36 to –330.33, $P < .00001$) compared to non-IBD patients. The pooled data were homogenous ($I^2 = 0\%$, $P = .77$). Moreover, IBD patients were associated with significantly lower calcium 24-hour urine level (MD = –28.46 mg/day, 95% CI: –41.67 to –15.25, $P < .0001$), lower citrate 24-hour urine level (MD = –144.35 mg/day, 95% CI: -–198.96 to –89.75, $P < .00001$), lower sodium 24-hour urine level (MD = –23.72 mg/day, 95% CI: –46.24 to –1.19, $P = .04$), and lower magnesium 24-hour urine level (MD = –33.25 mg/day, 95% CI: –44.16 to –22.34, $P < .00001$), compared to non-IBD patients. On the other hand, both IBD and non-IBD patients showed comparable findings in terms of phosphate 24-hour urine level (MD = 261.88 mg/day, 95% CI: –89.94 to 613.69, $P = .14$) and uric acid 24-hour urine level (MD = –41.55 mg/day, 95% CI: –88.24 to 5.15, $P = .08$).

3.6. Risk factors of urolithiasis in patients with IBD

Pooled analysis of Inverse Generic variance showed that patients with IBD and a history of intestinal surgery were associated with a higher risk of developing urolithiasis (OR = 2.82, 95% CI: 2.122–3.525). A similar finding was observed for patients who never do physical activity (OR = 1.65, 95% CI: 1.62–1.68), male gender (OR = 1.65, 95% CI: 1.62–1.68), and history of glucocorticoid therapy (OR = 1.689, 95% CI: 1.300–2.026), ciprofloxacin (OR = 5.82, 95% CI: 2.60–9.04), and immunomodulatory (OR = 4.05, 95% CI: 2.23–5.87). On the other hand, we found a nonsignificant association between developing urolithiasis and age (OR = 1.056, 95% CI: 0.947–1.164), type of IBD (OR = 1.056, 95% CI: 0.467–1.645), and 5-aminosalicylic acid concurrent medication (OR = 0.996, 95% CI: 0.976–1.016). Individual studies[29,33,35,36,38,39] showed that there was a significant association between developing urolithiasis and the disease duration of IBD (OR = 1.03, 95% CI: 1.01–1.05), the presence of fistula, fissure, or abscess (OR = 2.01, 95% CI: 1.32–3.07), existence of stenosis (OR = 1.82, 95% CI: 1.18–2.8), NSAID intake (OR = 2.334, 95% CI: 1.415–3.851), activity index (OR = 1.032, 95% CI: 1.018–1.045), active UC (OR = 4.2, 95% CI: 1.1–15), white race (OR = 1.49, 95% CI: 1.087–2.048), number of bowel resections (OR = 1.415, 95% CI: 1.17–1.71), and CD treatment period (OR = 1.076, 95% CI: 1.04–1.113), Table 3.

3.7. Stone composition

Regarding stone composition, individual studies[16,31,33,42] demonstrated that calcium oxalate and uric acid stones were more common in IBD patients at 71.4% and 21.4% compared to non-IBD 56.25% and 18.8%, respectively. Calcium phosphate, cystine, and struvite stones were more common in non-IBD patients than in IBD patients, 12.5%, 6.2%, and 6.2% versus 7.1%, 0%, and 0%, respectively.

4. Discussion

In this systematic review and meta-analysis, our findings showed that the overall prevalence of renal stones in patients with IBD was 6.3%, 95% CI (4.8%–8.3%). The prevalence of renal stones in CD patients was higher than in patients with UC and un-specified IBD. CD patients may be more susceptible to urolithiasis because their digestive systems are more severely compromised.[44] A metabolic change that has been linked to an increased risk of oxalate stones in individuals with IBD is called hyperoxaluria, and it is more common in those who have ileal dysfunction as well as those who have a CD.[5,45,46]

Patients with IBD were associated with significantly lower urine volume, calcium 24-hour urine, citrate 24-hour urine, sodium 24-hour urine, and magnesium 24-hour urine, compared to non-IBD patients. Moreover, we found that the most common stones in IBD patients were calcium oxalate and uric acid stones. One of the possible explanations for the elevated risk of calcium oxalate stone formation is that bile salt malabsorption increases urine oxalate excretion. Oxalate binds to calcium in the intestinal lumen, limiting the quantity of oxalate absorbed in the intestines under normal circumstances.[47] Patients with a compromised or resected ileum are more likely to suffer from steatorrhea because bile salts are inadequately reabsorbed in the intestines. The increased amount of absorbed oxalate in the intestines is a result of the binding between the luminal-free calcium and the unabsorbed fats in the steatorrhea.[48] Increased endogenous production of oxalate, gastrointestinal hyperabsorption, and obesity all contribute to hyperoxaluria, which may be induced by high intake or hyperabsorption.[45,46] Enteric hyperoxaluria is a complication of severe chronic bowel disease, particularly when fat absorption is impaired, and intestinal oxalate absorption is subsequently elevated.[45,49] Besides the presence of hyperoxaluria, additional variables that may contribute to the development of kidney stones in these individuals include reduced excretion in the urine of inhibitors of crystallization (citrate, magnesium), dietary factors, medications, and a low volume of urine,[42] which was observed in our study, as we found that patients with IBD were associated with significantly lower urine volume, calcium 24-hour urine, citrate 24-hour urine, sodium 24-hour urine, and magnesium 24-hour urine, compared to non-IBD patients. Urate stones have been linked to both long-term diarrheal diseases and small intestinal ostomies.[7] Small intestinal ostomies are thought to cause urate stones because of metabolic acidosis and dehydration.[50] Urate

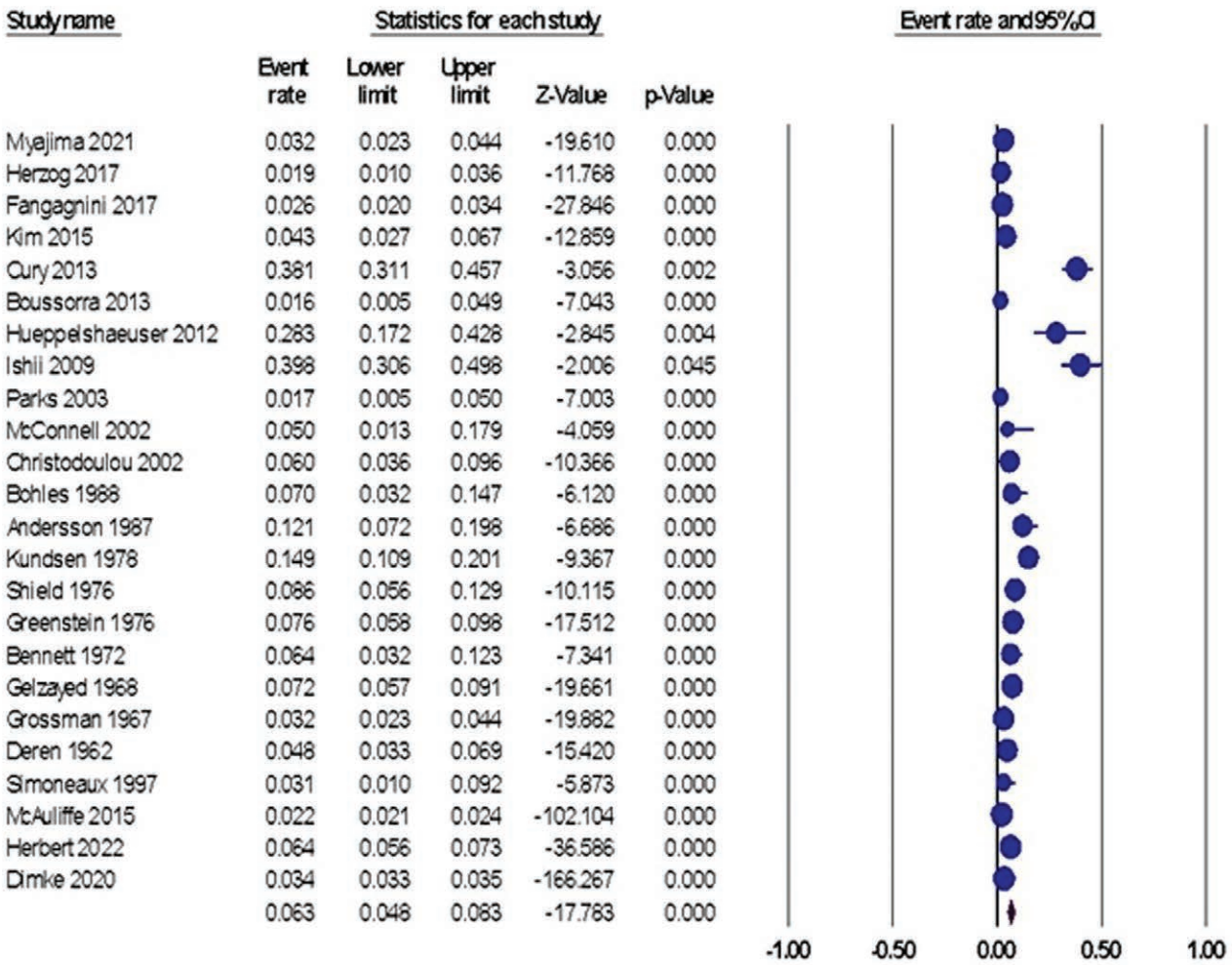

Figure 2. The random-effect forest plot of the pooled prevalence of urolithiasis in patients with IBD. IBD = inflammatory bowel disease.

stones may occur even if the patient's urate level is not increased because of the acidic urine that arises from bicarbonate loss and intestinal fluid.[51]

Poor socioeconomic level, gout, DM, high BMI, and male gender are all common risk factors for kidney stones in the general population [34]. IBD patients, on the other hand, had a somewhat distinct set of risk variables. A previous history of intestinal surgery, no physical activity, male gender, history of glucocorticoid therapy, ciprofloxacin, and immunomodulatory were associated with a higher risk of developing urolithiasis. Anatomical changes to the gastrointestinal system as a consequence of bowel surgery may either reduce food intake or result in nutritional malabsorption. Urolithiasis risk may be increased by bariatric surgery, even though obesity is an independent risk factor for developing stones. Stone formation is more likely to occur with restrictive operations than malabsorptive ones, which seem to provide the lowest risk.[52] Physical exercise reduces the risk of urinary stone development, but the exact mechanism by which this occurs is still a mystery. Bone resorption, hypercalciuria, and the risk of urolithiasis are all exacerbated by prolonged bed rest.[53] A recent observational study reported that among postmenopausal women, increased levels of physical activity and lower energy intake were associated with a significant reduction in the risk of kidney stones, even after taking into account animal protein, dietary sodium, calcium, intake of fluid, history of diabetes, and BMI.[54] However, a large cohort study (n = 215,133 patients) showed that there was no significant independent association between physical activity and urolithiasis [hazard ratio = 1.00, 95% CI: 0.87–1.14, $P = .94$].[55] A meta-analysis of 13 cohorts demonstrated that both high and low physical activity were comparable in terms of the risk of urolithiasis (RR = 0.93, 95% CI: 0.78–1.10).[56] A more recent systematic review also supports the hypothesis of no significant association between physical activity and the risk of urolithiasis.[57] The difference between our study and these studies is that they investigate the association in the general population, but in this study, we investigate it in the selected group of patients (IBD patients). Regarding the male gender, many studies have confirmed that males have a higher risk of urolithiasis than females. Wang et al showed that men contributed more calcium oxalate stones than women at age 30 to 49 years ($P < .01$) and more uric acid stones at 30 to 59 years ($P < .05$). Moreover, they reported that the prevalence peak was 50 to 59 years in men and 60 to 69 years in women, and both genders had the lowest prevalence in adolescence.[58] However, a recent systematic review highlighted that in recent years, a significant change had been observed. They claimed that the rise in prevalence of urolithiasis is higher in females compared to males, even though males are more likely to have metabolic and nutritional disorders than females. Furthermore, they showed that uric acid supersaturation in males is more common, men excrete more calcium and oxalate than women, and their urine pH is lower.[59]

Medication may also cause urinary calculi when the drugs crystallize and become the main component of the stones. In this

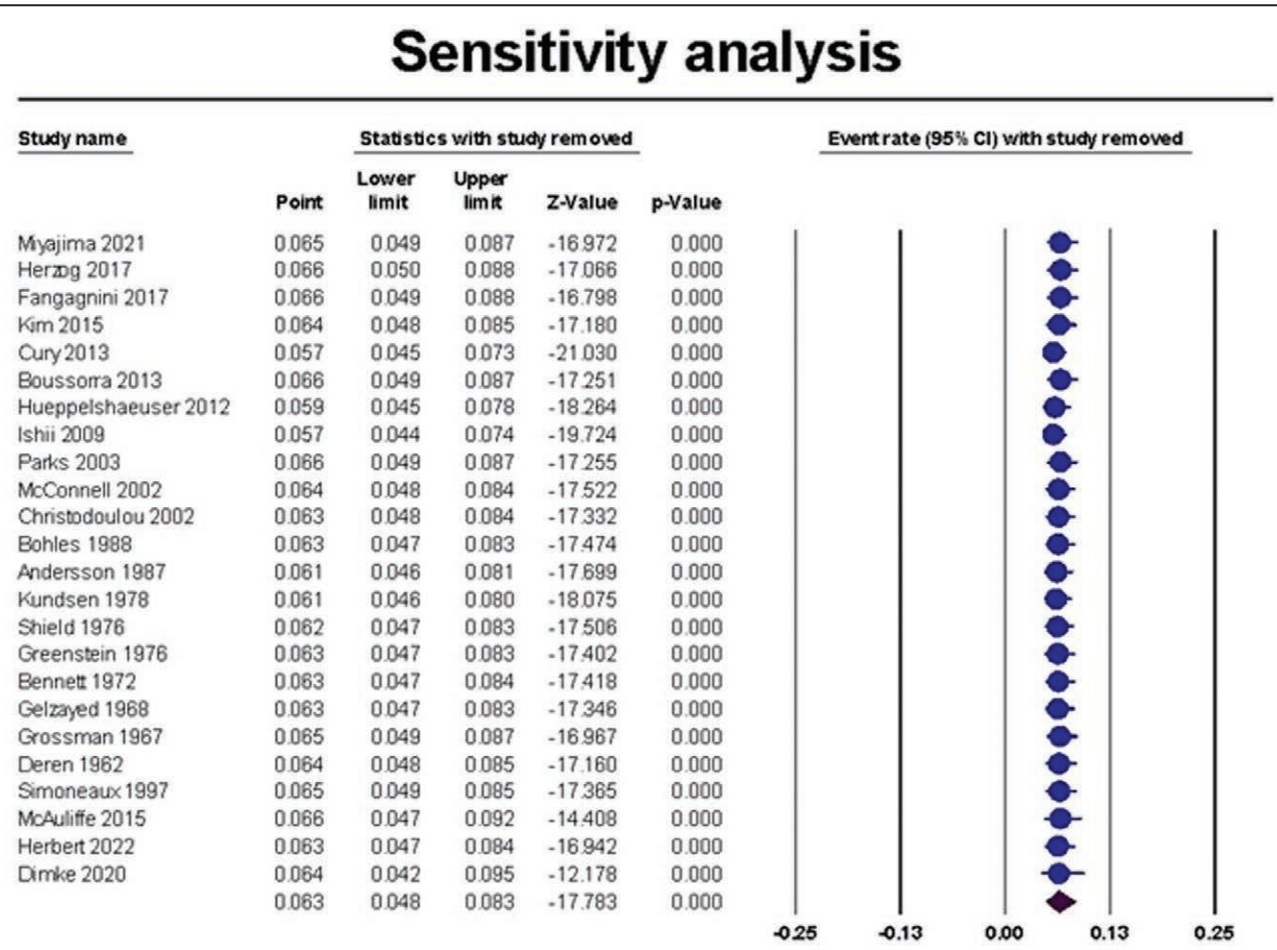

Figure 3. The sensitivity analysis of the prevalence of urolithiasis in patients with IBD. IBD = inflammatory bowel disease.

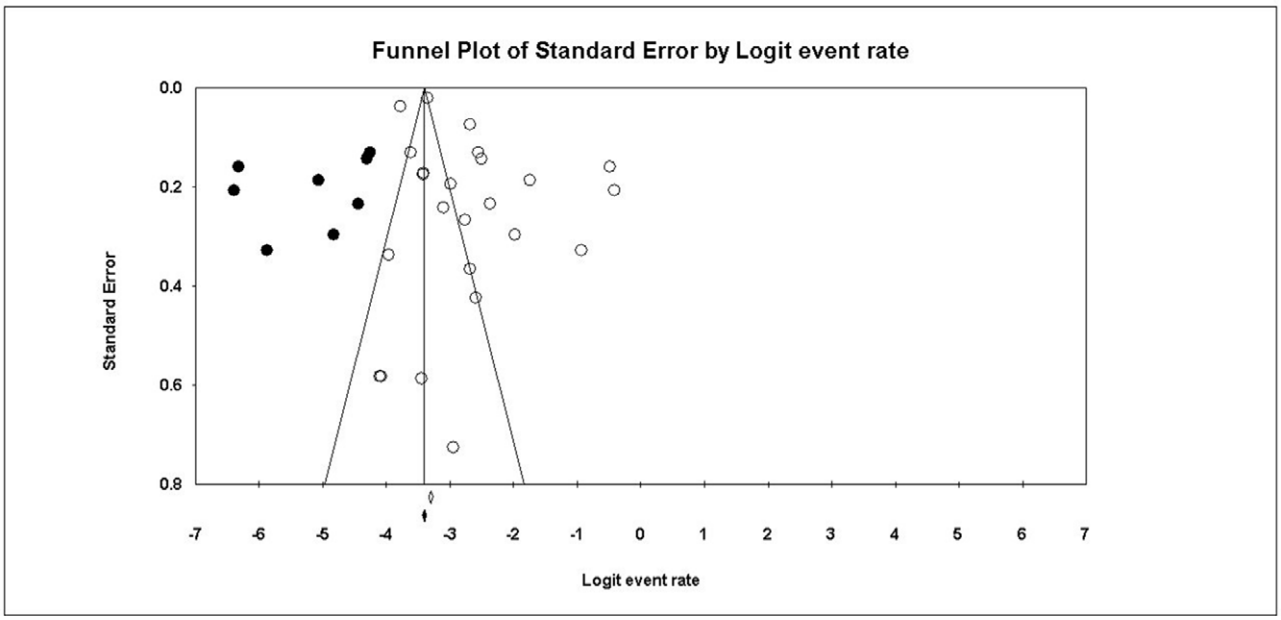

Figure 4. shows the funnel plot of the pooled studies.

situation, the agent's urinary supersaturation may encourage the production of calculi. The agent's urinary supersaturation may encourage the development of calculi in this situation. In the literature, the most common drugs that induce urolithiasis were ephedrine, indinavir, triamterene, sulfa medications, ciprofloxacin, magnesium trisilicate, and corticosteroids.[60] In this study, we could not find any significant association between urolithiasis and receiving 5-aminosalicylic acid, Azathioprine

Table 2

Prevalence of renal calculi in patients with IBD.

Subgroup analysis		Studies	Prevalence (95% CI)	Heterogeneity
IBD	CD	8	7.9% (3.1% to 18.7%)	$I^2 = 95.83\%$, $P < .001$
	UC	5	5.6% (3.9%–7.8%)	$I^2 = 81.62\%$, $P < .001$
	Un-specified	11	5.6% (3.8%–8.1%)	$I^2 = 98.45\%$, $P < .001$
Stone location-IBD	Urolithiasis	5	7.1% (3.2–15.2)	$I^2 = 99.57\%$, $P < .001$
	Nephrolithiasis	3	2.1% (0.3–12.8)	$I^2 = 99.65\%$, $P < .001$
	Both	3	11.0% (6.5–18.1)	$I^2 = 50.52\%$, $P = .132$
Stone location-UC	Urolithiasis	6	6.8% (3.3–13.4)	$I^2 = 98.86\%$, $P < .001$
	Nephrolithiasis	2	4.2% (2.1–8.1)	$I^2 = 77.72\%$, $P = .034$
	Both	3	9% (2.1–31.0)	$I^2 = 45.82\%$, $P = .158$
Stone location-CD	Urolithiasis	6	7.1% (3.6–13.6)	$I^2 = 99.17\%$, $P < .001$
	Nephrolithiasis	2	4.6% (3.6–5.8)	$I^2 = 0.00\%$, $P = .812$
	Both	3	11.9% (8.4–16.6)	$I^2 = 0.00\%$, $P = .774$
Study design	Cohort	19	6.9% (5.0%–9.4%)	$I^2 = 98.19\%$, $P < .001$
	Case-control	5	4.1% (3.0%–5.6%)	$I^2 = 49.02\%$, $P = .097$
Year of publication	From inception to the end of 2009	14	7.3% (4.8%–11.0%)	$I^2 = 92.23\%$, $P < .001$
	From 2010–2022	10	5.2% (3.5%–7.5%)	$I^2 = 98.51\%$, $P < .001$

CD = Chron's disease, CI = Confidence interval, IBD = inflammatory bowel disease, UC = Ulcerative colitis.

Table 3

Risk factors of urolithiasis in patients with IBD.

Risk factors	Studies	OR (95% CI)	Heterogeneity
Age (old vs young)	3	1.056 (0.947–1.164)	$I^2 = 99.60\%$, $P < .001$
Intestinal surgery (Yes)	2	2.824 (2.122–3.525)	$I^2 = 0.00\%$, $P = .733$
Physical activity (Never)	2	1.650 (1.620–1.680)	$I^2 = 49.53\%$, $P = .159$
Gender (Male)	3	1.650 (1.620–1.680)	$I^2 = 0.00\%$, $P = .371$
Type of IBD (UC vs CD)	3	1.056 (0.467–1.645)	$I^2 = 92.86\%$, $P < .001$
History of glucocorticoid therapy (Yes)	3	1.689 (1.300–2.026)	$I^2 = 35.37\%$, $P = .213$
Concurrent medication (5-ASA)	2	0.996 (0.976–1.016)	$I^2 = 0.73\%$, $P = .316$
Ciprofloxacin	2	5.821 (2.602–9.040)	$I^2 = 0.00\%$, $P = .327$
Immunomodulatory	2	4.047 (2.227–5.868)	$I^2 = 0.00\%$, $P = .872$

5-ASA = 5-aminosalicylic acid, CD = Chron's disease, CI = Confidence interval, IBD = Inflammatory bowel disease, OR = Odds ratio, UC = Ulcerative colitis.

and 6-mercaptopurine, and anti-Tumor necrosis factor agents. However, a significant association between urolithiasis and corticosteroids, ciprofloxacin, and immunomodulatory was highlighted.

This is the first systematic review and meta-analysis that investigate the prevalence and associations of urolithiasis in patients with IBD. We included a large number of studies with a huge number of patients, which may support the generalizability of our findings. We acknowledge that our study has some limitations, including the high heterogeneity observed in the prevalence analysis; however, this heterogeneity is expected in this type of analysis due to the significant variation in the year of publication and the country of population. Another limitation is the significant publication bias, which was handled by trim and fill analysis.

5. Conclusion

The overall prevalence of renal stones in patients with IBD was comparable to the general population. Patients with CD were associated with a higher prevalence of urolithiasis compared to UC. A previous history of intestinal surgery, no physical activity, male gender, history of glucocorticoid therapy, ciprofloxacin, and immunomodulatory were associated with a higher risk of developing urolithiasis. Patients with IBD were associated with significantly lower urine volume, calcium 24-hour urine, citrate 24-hour urine, sodium 24-hour urine, and magnesium 24-hour urine, compared to non-IBD patients.

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Author contributions

Conceptualization: Abdulrhman Aldukhayel, Nurah Ibrahem Alhmed.
Data curation: Adil Alsweed, May Rashed Alotaibi, Shahad Fahad Alahmadi.
Formal analysis: Abdulrhman Aldukhayel, Adil Alsweed, May Rashed Alotaibi, Abdullah Yousef Aldakhil, Shahad Fahad Alahmadi, Saud Musallum Albishri, Nurah Ibrahem Alhmed.
Investigation: Abdulrhman Aldukhayel, Adil Alsweed.
Methodology: Abdulrhman Aldukhayel, Adil Alsweed.
Software: Abdulrhman Aldukhayel, May Rashed Alotaibi.
Supervision: Abdulrhman Aldukhayel.
Validation: Abdulrhman Aldukhayel.
Visualization: Adil Alsweed.
Writing – original draft: Abdulrhman Aldukhayel, Adil Alsweed, May Rashed Alotaibi, Abdullah Yousef Aldakhil, Shahad Fahad Alahmadi, Saud Musallum Albishri, Nurah Ibrahem Alhmed.
Writing – review & editing: Abdulrhman Aldukhayel, Adil Alsweed, May Rashed Alotaibi, Abdullah Yousef Aldakhil, Shahad Fahad Alahmadi, Saud Musallum Albishri, Nurah Ibrahem Alhmed.

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