BJU Int 2021 doi:10.1111/bju.15522

BJUI
BJU International

Review

Natural history of small asymptomatic kidney and residual stones over a long-term follow-up: systematic review over 25 years

Catherine E. Lovegrove[1,2], Robert M. Geraghty[3,4], Bingyuan Yang[1], Eleanor Brain[5], Sarah Howles[1,2,6], Ben Turney[1,2] and Bhaskar Somani[7]

[1]*Department of Urology, Oxford University Hospitals NHS Trust,* [2]*Department of Surgical Sciences, University of Oxford Nuffield, Oxford,* [3]*Department of Urology, Freeman Hospital,* [4]*Translational and Clinical Research Institute, Faculty of Medical Sciences, International Centre for Life, Newcastle University,* [5]*Newcastle Medical School, Newcastle upon Tyne,* [6]*Academic Endocrine Unit, Radcliffe Department of Medicine, University of Oxford, Oxford, and* [7]*Department of Urology, University Hospital Southampton, Southampton, UK*

Objective

To systematically review the natural history of small asymptomatic kidney and residual stones, as the incidental identification of small, asymptomatic renal calculi has risen with increasing use of high-resolution imaging.

Materials and methods

We reviewed the natural history of small asymptomatic kidney and residual stones using the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. We searched MEDLINE, Scopus, EMBASE, EBSCO, Cochrane library and Clinicaltrials.gov using themes of ‘asymptomatic’, ‘nephrolithiasis’, ‘observation’, ‘symptoms’, ‘admission’, ‘intervention’ and similar allied terms for all English language articles from 1996 to 2020 (25 years). Inclusion criteria were studies with ≥50 patients, stones ≤10 mm, and a mean follow-up of ≥24 months. Primary outcomes were occurrence of symptoms, emergency admission, and interventions.

Results

Our literature search returned 2247 results of which 10 papers were included in the final review. Risk of symptomatic episodes ranged from 0% to 59.4%. Meta-analysis did not identify any significant difference in the likelihood of developing symptoms when comparing stones <5 mm to those >5 mm, nor those <10 mm to those >10 mm. Risk of admission varied from 14% to 19% and the risk of intervention from 12% to 35%. Meta-analysis showed a significantly decreased likelihood of intervention for stones <5 vs >5 mm and <10 vs >10 mm. Studies had variable risk of bias due to heterogeneous reporting of outcome measures with significant likelihood that observed differences in results were compatible with chance alone (Symptoms: I^2=0%, Cochran’s Q = 3.09, P = 0.69; Intervention: I^2=0%, Cochran’s Q = 1.76, P = 0.88).

Conclusions

The present systematic review indicates that stone size is not a reliable predictor of symptoms; however, risk of intervention is greater for stones >5mm vs <5 mm and >10 vs <10 mm. This review will inform urologists as they discuss management strategies with patients who have asymptomatic renal stones and offer insight to committees during the development of evidence-based guidelines.

Keywords

asymptomatic nephrolithiasis, surveillance, symptoms, intervention

Introduction

In recent years, the increased use of high-resolution imaging such as CT has led to a rise in the rates of incidental detection of asymptomatic renal calculi [1]. Studies estimate that the prevalence of asymptomatic kidney stone disease (KSD) is between 8% and 46% [1–5]. The natural history of asymptomatic stones remains uncertain, as does what treatment should be offered and when [6].

Existing treatment recommendations for renal stones ranging in size from 5 to 20 mm include observation, pharmacological therapy extracorporeal shockwave lithotripsy (ESWL), ureteroscopic (URS) surgery or percutaneous nephrolithotomy (PCNL) [7–12]. The cost of treatment in the UK varies with modality, e.g. one ESWL treatment cost ~£950 (pound sterling), whilst the tariff for PCNL was ~£4400 in the NHS in 2020 [13]. Many patients with renal stones ≤5 mm remain asymptomatic and no specific treatment is recommended [2,10,14]. Indeed, one study reported that ~80% of patients with incidentally detected kidney stones ranging from 1 to 20 mm remained symptom free at 10 years of follow-up. Furthermore, prophylactic ESWL for asymptomatic stones of <15 mm was not found to confer benefits in terms of stone-free rates (SFRs), requirement for any additional treatment (analgesia, antimicrobial therapy, ESWL, ureteric stent insertion or URS), symptoms, quality of life or renal function in a randomised controlled trial (RCT) of 228 patients [15]. Although overall rates of 'additional treatment' were not different, those in the control arm (observation) required more invasive interventions in the form of URS and stent placement compared to the patients who had prophylactic ESWL, of whom none needed invasive treatment and were manged with analgesia or antibiotics [15]. However, other reports indicate that 43% of individuals with residual fragments of <4 mm after ESWL experience stone-related symptoms or require intervention after 5 years of follow-up [16].

A study by members of the Endourology Disease Group for Excellence (the EDGE consortium) reported that a stone fragment of >4 mm after URS was associated with significantly higher rates of stone growth, complications, and need for re-intervention. The group therefore recommended that the aim of stone surgery should be complete stone-free status, regardless of whether stones were dusted or basketed for extraction [17]. Fragments of 2–4 mm were also described to have growth potential, but these were not associated with an increased risk of complications or need for interventions [17].

Considering the lack of clarity over the natural history of small asymptomatic renal stones, there is a need to appraise the literature to discern whether remnant fragments or small asymptomatic stones require intervention or follow-up [18]. The present systematic review interrogates the evidence related to small asymptomatic kidney stones and post-procedural fragments with relation to the primary outcomes of risk of symptoms, emergency admission, and need for intervention.

Materials and Methods

Search strategy and study selection

We performed a systematic search of the Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica dataBASE (EMBASE), Elton B. Stephens Co. (EBSCO), Scopus, Cochrane library and Clinicaltrials.gov following Cochrane's recommended methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19,20]. The following search terms were included (but were not limited to): 'asymptomatic', 'nephrolithiasis', 'observation', 'symptoms', 'admission', 'intervention', 'calculi', 'kidney', 'URS', 'ureteroscopy', 'RIRS', 'lithotripsy', 'SWL', 'ESWL', 'PCNL', 'PNL', 'percutaneous nephrolithotomy', 'residual' and 'fragments' (Appendix S1). The search was limited to English language publications between January 1996 and December 2020. Articles were identified using the full search strategy listed (Appendix S1). Additional studies were identified through manual review of the references of included articles. Titles and abstracts were reviewed independently by two authors (C.E.L., B.Y.). Disparities were discussed to reach consensus before full-text review. Only high-volume studies (≥50 patients) with a minimum follow-up of 2 years were included.

The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020179999).

Evidence acquisition: criteria for considering studies for the present review

Inclusion criteria:

1. Full-text, English language RCTs, case-control or cross-sectional studies and case-series.
2. Publication date within last 25 years or from inception of database to current (if <25 years old).
3. Adult patients (aged ≥18 years) with asymptomatic kidney stones or post-procedural fragments of ≤10 mm.
4. Studies with ≥50 patients and a minimum mean/median follow-up of 2 years.
5. Studies reporting risk of symptomatic event, emergency admission or intervention with URS or ESWL.

Exclusion criteria:

1. Animal studies, case reports, review articles, and editorials.
2. Studies of the same cohort that have subsequently been updated.
3. Studies of patients with anatomical abnormalities including renal transplantation, medullary sponge kidney, or horseshoe or pelvic kidney.

Data extraction

Two authors (C.E.L., R.M.G.) independently extracted the following data using an Excel spreadsheet: author, year, journal, study design, patient demographics, prior urological interventions, stone position, stone size, use of medical expulsive therapy (MET), occurrence of symptoms, emergency admission and treatment with URS, ESWL or any other intervention. Relative risk (RR), odds ratio (OR), hazard ratio (HR) and percentage rates were noted.

Meta-analysis (random effects model) was performed on studies with available data (complete 2×2 contingency table) to assess the relationship of stone size on symptom and intervention event rates using a 2×2 contingency table. Statistical analysis and Forest plots were generated with 'metafor' package in R (R foundation for statistical computing, Vienna, Austria) [21]. Statistical heterogeneity was tested for using I^2, Tau^2 and Cochran's Q. A $P < 0.05$ was considered statistically significant, I^2 values were interpreted according to chapter 9.5.2 of the Cochrane Handbook [22]. Publication bias was assessed with Egger's regression and 'trim-and-fill' analyses, where appropriate.

Risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool for randomised trials and Newcastle–Ottawa Scale risk of bias tool for observational studies, and the level of evidence was ascertained based on the Centre for Evidence-Based Medicine guidance [23–25].

Results

Literature search

Our literature search identified 2247 articles of interest, of which 130 abstracts were reviewed and 47 manuscripts underwent full-text review. This process identified 10 studies for inclusion in the present systematic review (Figure 1) (Table 1) [26–35]. These studies comprised four cohort studies, one case-control study and five case series. Eight studies reported outcomes related to symptoms [26–33], two reported requirement for emergency admission [27,31], and nine reported occurrence of interventions including ESWL, URS, PCNL and decompression with retrograde stenting or nephrostomy insertion (Table 2) [26–35]. Additional identified outcomes were stone growth, spontaneous stone passage, stone migration, and adverse events. Inter-rater reliability was moderate after abstract screening (79.2%, Cohen's $\kappa = 0.54$) and substantial after full-text review (86.3%, Cohen's $\kappa = 0.65$).

Risk of symptoms

Eight studies ($N = 1527$ patients) evaluated risk of symptoms in patients who were asymptomatic at baseline with stones or residual fragments after ESWL/URS/PCNL of ≤10 mm (Figure 2) [26–33]. Parameters evaluated include pain, fever, haematuria, and UTI. Rates of symptoms varied widely from 0% in the Osman *et al.* [32] prospective analysis of patients with residual fragments of ≤5 mm after PCNL to 59.4% reporting pain in the Kanno *et al.* [30] case series observing and comparing patients with stones of ≤5 mm to those with stones >5 mm. Osman *et al.* [32] surveyed patients for symptoms, although what symptoms were considered is not described. Dropkin *et al.* [29] compared symptoms from stones of ≤10 mm to stones ≥10 mm and found no statistical difference in risk of symptoms over a mean (SD) 40.6 (18.6) months of follow-up (31% vs 39.1%, $P = 0.47$). Stone size >5 mm was identified as a risk factor for symptoms by Li *et al.* [31] when compared to smaller stones (HR 2.227, 95% CI 1.375–3.606; $P = 0.001$). Lower pole and right-sided locations were found to be protective for symptomatic episodes (HR 0.236, 95% CI 0.118–0.471, $P < 0.001$; and HR 0.493, 95% CI 0.307–0.790, $P = 0.003$, respectively).

Other than Kanno *et al.* [30], two other manuscripts assessed symptoms related to pain [26, 28]. Burgher *et al.* [26] found that 44–45% of patients with stones of <11 mm had pain and 45% of patients with stones of 11–15 mm reported pain. The Darrad *et al.* [28] case series of 238 patients with 301 stones and mean cumulative stone size of 10.8 mm reported that 15.3% had pain. There was no difference in symptomatic events between those with a stone size of <10 vs 10–19 mm (HR 1.03, 95% CI 0.55–1.93; $P = 0.913$) nor <10 vs >19 mm (HR 0.93, 95% CI 0.42–2.10; $P = 0.961$).

Meta-analysis of the included studies did not identify any significant difference in the likelihood of developing symptoms when comparing stones of <5 to those of >5 mm, nor those <10 to those of >10 mm (OR 0.05, 95% CI −0.32 to 0.43, $P = 0.79$; and OR 0.24, 95% CI −0.31 to 0.78; $P = 0.40$, respectively) (Figure 3). Heterogeneity analyses indicated that variability was due to sampling error within studies, rather than differences between studies; $I^2 = 0.00\%$, $H^2 = 1.00$, Tau^2=0 (SE 0.08), Cochran's Q = 0.46 ($P = 0.93$). Egger's regression did not demonstrate significant funnel plot asymmetry ($z = 0.68$, $p = 0.50$); however, trim-and-fill analysis did demonstrate two missing studies (Figure 4).

Risk of emergency admission

One case series and one prospective cohort study ascertained risk of emergency admission (Figure 5). Li *et al.* [31] followed 293 patients with a mean stone size of 4.7 mm for 50.4 months and reported 42 emergency admissions (14.3%). Similarly, D'Costa *et al.* [27] reported that 19% of 175 patients with a baseline stone size ranging from 1 to 9 mm observed for 58.8 months required emergency admission.

Risk of intervention

Nine studies ($N = 1583$) evaluated risk of intervention in patients with KSD or residual fragments of ≤10 mm after

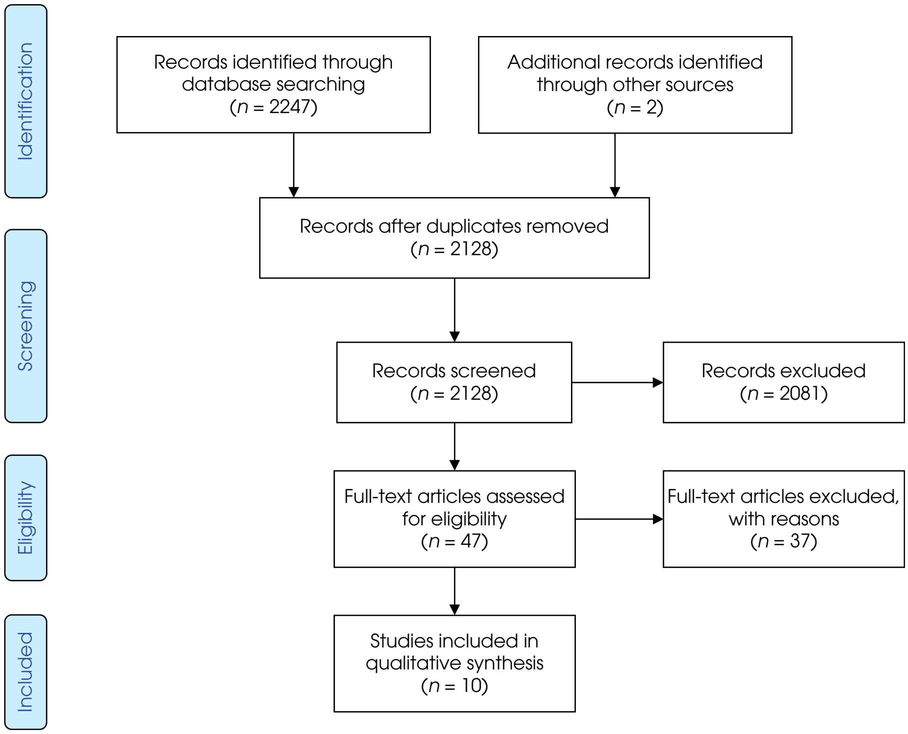


Fig. 1 PRISMA flow chart of study inclusion.

ESWL, URS or PCNL (Figure 6)[26,28–35]. In a case-control study of 169 patients with residual fragments after ESWL, 79 patients were managed conservatively rather than undergoing intervention [35]. Flexible URS and laser fragmentation of residual stones was booked immediately after ESWL in 51 patients. Of the cohort who initially were managed conservatively, 16 of the 79 patients (20%) required intervention (flexible or rigid URS) over a mean (range) follow-up of 27.6 (12–44.4) months [35]. Of note, there was an intervention rate of 87% (13/15) for upper pole stones but only 13% (two of 15) for mid-pole stones, and 2% (one of 49) for lower pole stones [35]. Darrad *et al.* [28] noted a similar intervention rate of 26.6% (80/301 renal units) for 238 patients with incidentally detected, asymptomatic calyceal stones on active surveillance, and surveillance of residual stone fragments of <5 mm after ESWL by Zanetti *et al.* [33] found that 14.7% (19/129) developed symptoms or required intervention. Larger stone size was noted to be a significant predictor of need for intervention by three studies. Thus, Burgher *et al.* [26] found that upper pole stones of <4 mm were less likely to require intervention than those of >4 mm (P = 0.027), Kanno *et al.* [30] identified that 20% of stones of ≤5 mm required intervention compared to 38% of stones of >5 mm (P = 0.0067), and Li *et al.* [31] reported that stones of >5 mm were associated with an adjusted HR of 8.635 (95% CI 3.253–22.925, P < 0.001). Similar, non-significant trends for the need for intervention in larger stones were observed by Dropkin *et al.* [29] (intervention in 16.4% of stones of <10 mm vs 34.8% in stones of >10 mm, P = 0.079) and Koh *et al.* [34] (intervention in 5% of stones of <5 mm, 9.5% in stones of 5–10 mm, and 14.3% in stones of >10 mm; P = 0.477).

Other factors reported to affect likelihood of intervention because of stone growth or patient choice include patient age <50 years (P = 0.01) and/or a history of treatment for KSD (P < 0.001) [30].

Our meta-analysis of the results of these studies demonstrated significantly decreased likelihood of intervention for stones <5 vs >5 mm (OR 0.64, 95% CI 0.20–1.08; P = 0.004) and <10 vs >10 mm (OR 0.75, 95% CI 0.18–1.32; P = 0.01) (Figure 7). There was a substantial likelihood that observed differences in study effects are secondary to chance alone rather than heterogeneity (I^2 = 0.00%, H^2 = 1.00, Tau^2 = 0 (SE 0.11), Cochran's Q = 1.76; P = 0.88). Egger's regression did not demonstrate significant funnel plot asymmetry (z = 1.67, P = 0.10); however, trim-and-fill analysis did demonstrate two missing studies (Figure 8).

Additional outcomes

Spontaneous stone passage

Seven studies assessed spontaneous stone passage [27,28,30–34]. Kanno *et al.* [30] found no difference in spontaneous stone passage when comparing stones of ≤5 to >5 mm and

Table 1 Demographics of included studies.

Part A

Reference	Country	Year study conducted	Study design	LoE	Intervention considered	Sample size, *N*	Patient age, years, mean ± SD (range)
Burgher, *et al.*, 2004 [26]	USA	1996–2001	CS	4	observation	300	62.6 (23.1–89.0)
Darrad *et al.*, 2018 [28]	UK	2005–2016	CS	4	observation	238 301 stones	Median 56 (24–87)
D'Costa *et al.*, 2019 [27]	USA	2009–2013	PC	2	observation	175	49.6 ± 14
Dropkin *et al.*, 2015 [29]	USA	2008–2010	CS	4	observation	110 160 stones	55.8 ± 13.8 (19–82)
Kanno *et al.*, 2020 [30]	Japan	2010–2014	CS	4	observation	207 (71 with stones ≤5 mm, 136 with stones >5 mm)	Median 59 (IQR 45–68)
Koh *et al.*, 2012 [34]	Singapore	2005–2009	PRG	4	observation	50 85 stones	58 (32–90)
Li *et al.*, 2019 [31]	China	2007–2017	CS	4	observation	293	46.5 (15.2)
Osman *et al.*, 2013 [32]	Egypt	2000–2005	PC	2	observation of residual fragments (RFs) ≤5 mm after PCNL	75	47.3 ± 12.9 (13–72)
Pullar *et al.*, 2017 [35]	UK	2010–2013	CCS	3	FU after ESWL	313 ESWL treatment - 169 residual fragment - 79 managed conservatively	58 (19–93)
Zanetti *et al.*, 1997 [33]	Italy	1991–1994	PC	2	observation after ESWL	467 has ESWL at baseline - 299 (64%) stone free - 27 (6%) residual fragments >4mm and further treatment - 141 (30%) residual fragments/dust <5 mm (study cohort, 129 with 1 year FU, 95 with 2 year FU)	49.4 ±13.0 (19–80)

Part B

Reference	Male sex, *n* (%)	FU, months, mean ± SD (range)	Stone locations included	Stone size, mm, mean ± SD (range)	Outcomes reported
Burgher, *et al.*, 2004 [26]		39.12 (2.4–120.0)	Upper pole: 26% Mid pole: 28% Lower pole: 44% Pelvis: 2%	10.8 (1.0–74.0)	Symptoms Stone growth Intervention (ESWL, URS, PCNL)
Darrad *et al.*, 2018 [28]	196 (65)	Median 36 (12–132)	Lower pole only: 43% Mid pole only: 23% Upper pole only: 17% Multiple: 18%	Cumulative size 10.8 (3–63.8)	Spontaneous stone passage Surgical intervention Adverse events
D'Costa *et al.*, 2019 [27]	93 (53.1)	Median 58.8	Any pelvic/lower pole: 16.4% Vesico-ureteric junction stone: 40.0%	<3 mm/ no stone: 119 patients (72.1%) 3–6 mm: 29 patients (17.6%) >6 mm 17 patients (10.3%)	RR of new stone RR of stone growth RR of stone passage
Dropkin *et al.*, 2015 [29]	60 (54.5)	40.6 ± 18.6 (7–86)	Upper calyx: 82 (51%) Mid calyx: 35 (22%) Lower pole: 41 (25%) Pelvis: 3 (2%)	7.0 ± 4.2 (1–35)	Symptoms Spontaneous passage Surgical intervention Stone growth >50% initial size
Kanno *et al.*, 2020 [30]	129 (62.3)	Median 39.6 (IQR 13.2-67.2)	Lower pole only: 48 (23.2%) Others: 159 (76.8%)	Median 7.0 (4.0–10.0)	HR for all surgical interventions HR for surgical intervention with active indication (migration/pain/haematuria/fever)

Table 1 (continued)

Part B					
Reference	**Male sex, *n* (%)**	**FU, months, mean ± SD (range)**	**Stone locations included**	**Stone size, mm, mean ± SD (range)**	**Outcomes reported**
Koh *et al.*, 2012 [34]		46 (24-58)	Lower pole: 43% Mid pole: 26% Upper pole: 31%	5.7 (2-20)	Disease progression (increase >1mm on XR or >3 mm on CT/ US/combination) Intervention Spontaneous passage
Li *et al.*, 2019 [31]	180 (61.4)	50.4 (28.8)	Upper pole: 37.5% Mid pole: 32.1% Lower pole: 30.4%	4.7 ± 1.6 (2–10)	Elective stone removal Stone growth Spontaneous passage Renal colic - defined by clinician Silent obstruction Emergency attendance Surgical intervention for pain/ infection
Osman *et al.*, 2013 [32]	40 (53.34)	36.2 ± 20.1 (12–96)	Upper pole: 7 (9.34%) Mid pole: 22 (29.34%) Lower pole: 29 (38.67%) Renal pelvis: 17 (22.67%)	4.7 ± 0.7 (2–5)	OR of clinically significant (symptomatic/ growth/ migration to ureter with hydronephrosis) RFs vs clinically silent (stone-free/ asymptomatic/no RF growth) RFs
Pullar *et al.*, 2017 [35]	207 (66.13)	27.6 (12-44.4)	Baseline not described	Conservatively managed stones (*N* = 79): ≤4: *n* = 22 (28.12%) 5–7: *n* = 35 (18.21%) 8–9: *n* = 12 (27.85%) ≥10: *n* = 10 (12.66%)	
Zanetti *et al.*, 1997 [33]	60 (46.51)	129 patients 12 month FU 97 patients 24 month FU	Stone targeted by ESWL Upper pole: 16 (12.4%) Mid pole: 17 (13.2%) Lower pole: 62 (48%) Renal pelvis: 34 (26.4%) Fragments observed after ESWL: Upper pole: 10 (7.7%) Mid pole: 34 (26.3%) Lower pole: 85 (66.0%)	Mean size of stone treated by ESWL: 9.4 ± 3.2 (5–15) Fragments observed: <5	Fragment-free rate Fragment persistence Fragment growth (any increase)

CCS, case-control study; CS, case series; FU, follow up; LoE, Level of evidence; prospective cohort; PRG, prognosis (cohort)

D'Costa *et al.* [27] reported the same results comparing stones of <3, 3–6, and >6 mm. However, the remaining studies found that smaller stones were more likely to pass spontaneously [28,31–34]. Koh *et al.* [34] reported that stones of <5 mm passed spontaneously in 28% of cases, but only in 4.8% of cases where stones measured 5–10 mm, and no stones >10 mm passed spontaneously (P = 0.006). Darrad *et al.* [28] found that stones of <10 mm were more likely to pass than stones measuring 10–19 mm (HR 0.38, 95% CI 0.15–0.95; P = 0.037) and ≥20 mm (HR 0.10, 95% CI 0.01–0.77; P = 0.03), and Li *et al.* [31] reported that stones of <5 mm were less likely to pass than larger stones (HR 0.236, 95% CI 0.116–0.480; P < 0.001). Zanetti *et al.* [33] found that where there were residual fragments of <5 mm or dust after ESWL there was a SFR of 55.8% (53/95 patients) at 24 months of follow-up.

Stone growth

Five studies assessed stone growth. Stone growth was reported in 5.26–33.3% of stones [27,31–34]. Li *et al.* [31] found that stones grew over 5 mm in 16.7% participants as measured by ultrasonography, with a mean (range) onset time of 4.7 (2–9) years. Zanetti *et al.* [33] described that 9.5% (nine of 95) of patients observed for 2 years had stone regrowth or recurrence. On annual follow-up of 293 patients with a mean (SD) stone size of 4.7 (1.6) mm at baseline, of whom 16.7% (49/293) had significant stone growth, Li *et al.* [31] found no

Table 2 Results of primary outcome measures.

Reference	Symptom outcomes	Admission outcomes	Intervention outcomes
Burgher *et al.*, 2004 [26]	Pain: <5 mm stones 45% 5–10 mm stones 44% 11–15 mm stones 45% >15 mm 56% Patients with solitary calculi <4 vs >4 mm by location: Upper pole: 34% vs 70% Mid pole: 56% vs 51% Lower pole: 51% vs 52% Renal pelvis: 98% vs 31%		Small upper pole stone <4 mm less likely to need intervention than larger, upper pole stones ($P = 0.027$) Small, upper pole stone less likely to need intervention compared to all asymptomatic stone formers (55% vs 78%, $P = 0.007$) Patients with solitary calculi <4 vs >4 mm by location: Upper pole: 0% vs 21% Mid pole: 15% vs 40% Lower pole: 28% vs 20% Renal pelvis: 98% vs 0%
Darrad *et al.*, 2018 [28]	Pain: 46/301 (15.3%), 38 interventions Infection: 29/301 (9.6%), 10 interventions Haematuria: 16/301 (5.3%) Median (range) time to onset 43 months (1–119) - 9% in first 12 months - 40% in 12–36 months - 30% in 36–60 months - 22% >60 months No effect of stone size on symptoms 0–9 mm stones vs: - 10–19mm: HR 1.03 (95% CI 0.55–1.93, $P = 0.913$) - ≥20mm: HR 0.93 (0.42–2.10, $P = 0.961$)		80/301 renal units (26.6%) - 57.5% ESWL - 25% URS - 12.5% PCNL - 5% stent/nephrostomy decompression Indications: - 30% pain - 25% stone migration - 16.3% stone growth - 12.5% UTI - 10% reducing renal function - 6.3% patient choice Median (IQR) time to intervention 48 (2–120) months, only 8% in the first 12 months No difference according to stone size: 0–9mm vs: - 10–19mm: HR 1.06 (95% CI 0.58-1.96; $P = 0.844$) - ≥20mm: HR 0.49 (95%CI 0.2-1.19; $P = 0.153$)
Dropkin *et al.*, 2015 [29]	36/116 (31%) stones <10 mm vs 9/23 (39.1%) stones ≥10 mm ($P = 0.47$) Stones ≥1 cm, OR 1.35 (95% CI 0.36–5.02, $P = 0.66$)		19/116 (16.4%) stones <10 mm vs 8/23 (34.8%) stones ≥10 mm ($P = 0.079$)
D'Costa *et al.*, 2019 [27]	Symptom recurrence: 30% Agreement between self-reported episode and clinical care episode: $k = 0.519$ (95% CI 0.37–0.67)	Clinical care for symptoms: 19%	
Kanno *et al.*, 2020 [30]	Fever: ≤5 mm 11.3% vs >5 mm 22.8% ($P = 0.044$) Haematuria: ≤5 mm 29.6% vs >5 mm 29.4% ($P = 0.98$) Pain: ≤5mm 59.4% vs >5mm 61.8% ($P = 0.34$) Stone growth: ≤5mm 8.5% vs >5mm 12.5% ($P = 0.38$) 5-year estimate for: Fever: ≤5mm less likely vs >5mm ($P = 0.041$) Spontaneous passage: no difference ($P = 0.33$) Haematuria: no difference ($P = 0.92$) Pain: no difference ($P = 0.92$) Stone growth >50%: no difference ($P = 0.317$)		66 (31.9%) - 57 SWL, 9 URS 14 (20%) patients with stone ≤5 mm vs 52 (38%) patients with stone >5 mm ($P = 0.007$) 5-year estimate for intervention in ≤5 vs >5mm = 23.7% vs 36.9% ($P = 0.024$) Active treatment indications (stones into ureter, symptoms): ≤5 mm ($n = 11$, 16%) vs >5 mm ($n = 27$, 20%) intervention ($P = 0.44$) (no difference between ≤5 vs >5mm groups ($P = 0.400$) Non-active treatment indications (stone growth/patient choice): ≤5mm ($n = 3$, 4.2%) vs >5mm ($n = 25$, 18.4%) ($P = 0.005$) Univariate analysis: stone size predictive for all surgical interventions (HR 1.96, 95% CI 1.09–3.55; $P = 0.026$), also bilateral vs unilateral stones (HR 1.89, 95% CI 1.12–3.18; $P = 0.017$) and past stone treatment (HR 2.45, 95% CI 1.41–4.26; $P = 0.0016$) Multivariate analysis: age >50 years (HR 1.96, 95% CI 1.17–3.26: $P = 0.0099$) and past stone treatment (HR 2.17, 95% CI 1.20–3.94; $P < 0.001$). Stone size not significant factor (HR 1.73, 95% CI 0.94–3.18 $P = 0.78$). Intervention for active treatment indication: Stone size >5 mm not significant on univariate/multivariate analysis. Multivariate analysis: age >50 years (HR 2.06, 95% CI 1.25–3.42; $P = 0.005$) and past stone treatment (HR 2.27, 95% CI 1.27–4.09; $P = 0.006$) 5-year intervention rate in patients with 1–2 adverse factors (age/ past stone treatment) = 35.0% vs 4.4% if 0 adverse factors ($P = 0.042$)

Table 2 (continued)

Reference	Symptom outcomes	Admission outcomes	Intervention outcomes
Koh *et al.*, 2012 [34]			<5 mm - 5% 5–10 mm - 9.5% >10 mm - 14.3% *P* = 0.477 No difference according to location but that not controlled for size
Li *et al.*, 2019 [31]	83/293 (28.3) - mean (range) time to onset 4.37 (1–9) years - 3-year probability 14.8%, 5-year probability 23.4% Multivariate analysis: More likely in stones >5 mm (HR 2.227, 95% CI 1.375–3.606; *P* = 0.001) Less likely if lower pole stone (HR 0.236, 95% CI 0.118– 0.471, *P* < 0.001) Less likely if right-sided stone (HR 0.493, 95% CI 0.307–0.790, *P* = 0.003)	42/293 (14.3%)	36/293 (12.3%) - 33/36 (91.7%) SWL - 3/36 (8.3%) URS - mean (range) time to onset 6.9 (3–9) years - 3-year probability 1.3%, 5-year 4.4% Multivariate Cox analysis: • Stones >5 mm increased risk (HR 8.635, 95% CI 3.253–22.925; *P* < 0.001) • Age>60 years increased risk (HR 3.158, 95% CI 1.230–8.109; *P* = 0.017)
Osman *et al.*, 2013 [32]	100% asymptomatic		18.7% (*n* = 14) ESWL, 12% (*n* = 9) PCNL, 2.67 (*n* = 2) declined intervention 4% (*n* = 3) stone migration to ureter; 100% URS
Pullar *et al.*, 2017 [35]			144 patients with complete stone clearance after ESWL 20% intervention 9.47% (*n* = 16) URS; 8 flexible, 8 rigid Comparison of baseline stone size needing intervention: ≤4 mm: *n* = 20 (91%) managed conservatively, *n* = 2 (9%) URS 5–7 mm: *n* = 27 (77%) managed conservatively, *n* = 8 (23%) URS 8–9 mm: *n* = 8 (67%) managed conservatively, *n* = 4 (33%) URS ≥10 mm: *n* = 8 (80%) managed conservatively, *n* = 2 (20%) URS Comparison of baseline stone position needing intervention: Upper pole: *n*= 2 (13%) managed conservatively, *n* = 13 (87%) URS Mid pole: *n* = 13 (87%) managed conservatively, *n* = 2 (13%) URS Lower pole: *n* = 48 (98%) managed conservatively, *n* = 1 (2%) URS 169 patients with residual fragments after ESWL 51/169 intervention (30.2%) 37/169 (73% of *n* = 51) treatment for pain 6/169 (12%) treated for concern re: stone size 4/169 (8%) patient choice 1/169 (0.59%) solitary kidney 1/169 (0.59%) profession (pilot) 1/169 (0.59%) young age 1/169 (0.59%) infections
Zanetti *et al.*, 1997 [33]	15/129 (11.6%) symptoms in 12 months of follow-up 7/95 (7.3%) symptoms in second year of follow-up		19/129 (14.7%) symptoms or needed treatment in 12 months follow up

difference in risk of stone growth when stratifying by stone size ≤5 vs >5 mm (adjusted HR 0.886, 95% CI 0.45–1.721; P = 0.721).

Quality assessment and risk of bias

All studies were assessed using the Newcastle–Ottawa Tool for observational studies as no randomised trials were identified [24] (Table 3) [26–35]. Only two studies reported the inclusion or exclusion criteria of patients on alpha receptor antagonist medication [26,31]. Of note, one study changed the imaging modality used for annual follow-up from ultrasonography to CT during the study period [26].

Discussion

The present systematic review has identified that rates of symptoms, emergency admission and intervention for asymptomatic stones or residual fragments of <10 mm are highly variable across the literature. Stone size was consistently assessed by studies to define whether this affected our three primary outcomes of symptoms, emergency admission or intervention.

Risk of developing symptoms over at least 24 months of follow-up in patients who were asymptomatic at baseline with stones or residual fragments of ≤10 mm was described by eight of the included studies [26,28–33,35]. Rates of symptoms were reported between 0% and 59.4% [30,32]. The 5-year case series from Burgher *et al.* [26] observed 300 asymptomatic patients with stones with a mean (range) size of 10.8 (1–74) mm and a mean follow-up of 39.12 months. In this cohort, 28% of patients received 'targeted medical therapy' based on their metabolic evaluation. Overall, reported rates of pain were 45% in stones of <5 mm, 44% in stones of 5–10 mm, 45% in stones of 11–15 mm, and 57% in stones of >15 mm. Both Burger et al. [26] and Darrad *et al.* [28] found no association between stone position (upper pole, mid-pole, lower pole, or renal pelvis) and symptoms. Dropkin *et al.* [29] also compared patients with stones of <10 mm and those ≥10 mm in their case series of 110 patients with a mean (SD, range) stone size of 7.0 (4.2, 1–35) mm and reported rates of symptoms to be comparable (31% [36/116] in stones <10 mm vs 39.1% [nine of 23] in stones of ≥10 mm, $P = 0.47$). Unlike Darrad *et al.* [28] and Burgher *et al.* [26], this study did describe stone location as a factor predisposing to symptoms with 28/69 upper and mid-pole stones resulting in symptoms compared with 17/70 lower pole stones (40.6% vs 24.3%, $P = 0.047$). Our meta-analysis of results from the identified studies confirms that stone size is not a significant predictor of symptoms.

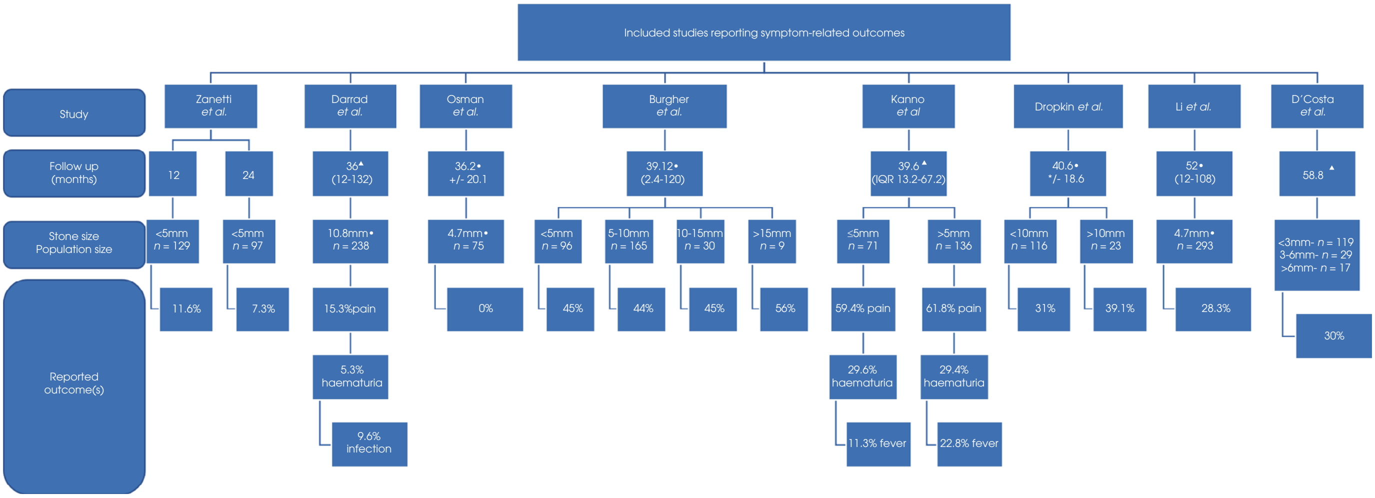
Risk of emergency admission was only reported by Li *et al.* [31] and D'Costa *et al.* [27], with similar rates of 14.3% and 19%, respectively. The D'Costa *et al.* [27] prospective cohort study of 175 patients reported moderate agreement between occurrence of symptoms and a clinical care episode ($k = 0.519$, 95% CI 0.37–0.67). The study by Li *et al.* [31] reported an emergency admission rate and intervention rate of 14.3% (42/293) and 12.3% (36/293), respectively, in their series with a mean (SD, range) stone size of 4.7 (1.6, 2–10) mm.

Nine of the included studies ($N = 1583$) analysed whether patients with small stones or residual fragments required intervention within at least 24 months of follow-up, with overall rates of intervention ranging from 12% to 35% in stones of ≤10 mm [11,26,28–30,32–35]. On multivariate Cox analysis, risk of intervention was greater if the stone size was >5 mm (HR 8.635, 95% CI 3.253–22.925; $P < 0.001$) and in patients aged >60 years (HR 3.158, 95% CI 1.230–8.109; $P = 0.017$) [31]. A stone size of >5 mm was also recorded as a significant predictor of need for intervention by Kanno *et al.* [30], whereas Dropkin *et al.* [29] compared patients with stones of <10 mm and those ≥10 mm. The intervention rate was 16.4% for stones of <10 mm and 34.8% for stones of >10 mm, although not significant, perhaps in part due to the smaller sample size of the latter group (116 vs 23 patients) [29]. Koh *et al.* [34] also failed to find a significant difference between rates of intervention according to stone size, with rates of 5%, 9.5% and 14.3% for stones of <5, 5–10 and >10 mm, respectively ($P = 0.477$). One study suggested that intervention is frequently triggered by pain symptoms and reported this to be the case in 73% (27/51) of interventions in a total of 169 patients [35]. The Kang *et al.* [18] retrospective analysis of 347 patients with asymptomatic kidney stones is a relevant study but outside our search criteria, as there was no subgroup analysis of patients with stones of ≤10 mm. They too described a significant difference in stone size in patients requiring intervention (4.9 vs 2.2 mm, $P = 0.016$)), adding to our observation that the size boundary for risk of failure of conservative management lies nearer to 5- than the 10-mm territory. Our meta-analysis demonstrates the importance of stone size as a factor linked to rates of intervention, revealing a significantly decreased likelihood of intervention for stones of <5 vs >5 mm (OR 0.64, 95% CI 0.20–1.08; $P = 0.004$) and <10 vs >10 mm (OR 0.75, 95% CI 0.18–1.32; $P = 0.01$) (Figure 4).

There is a paucity of RCTs concerning observation for small, asymptomatic renal stones, thus reducing the quality of literature available from which to draw recommendations. On heterogeneity analysis, literature concerning the conservative management of asymptomatic stones or post-procedural fragments of ≤10 mm was found to be homogenous, although there was a moderate risk of bias, given amongst other factors, the lack of high-quality evidence. In addition, many studies lack description of whether patients received concurrent MET or metabolic therapy; this may introduce bias. There is level 1 evidence for no benefit from MET in reducing requirement for intervention for stone clearance after 4 weeks for ureteric calculi; however, several studies report that α-blockers can improve stone clearance and reduce post-procedural pain after ESWL [36–39]. Given that two included studies used surveillance after ESWL and multiple other studies intervened with ESWL, this is an important variable to be considered.

Several studies highlight the European Association of Urology (EAU) guidance regarding indications for treatment (stone growth, *de novo* obstruction, associated infection, and acute or chronic pain). However, only Kanno *et al.* [30] discern between 'active indications' (i.e. those suggested by the EAU) and 'all' indications for intervention in their study [11,30,31,35]. It is recognised that these aforementioned objective measures are not the sole reason patients have active management of KSD and that patient-reported outcome measures (PROMs) also contribute to patient

Fig. 2 Included studies and their timing of reported symptom-related outcomes (•mean, ▲median) [26–33].



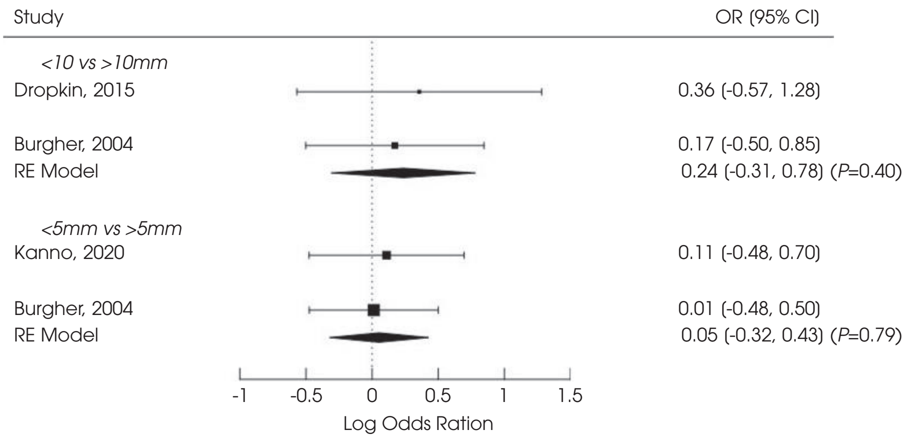


Fig. 3 Comparison of symptom development.

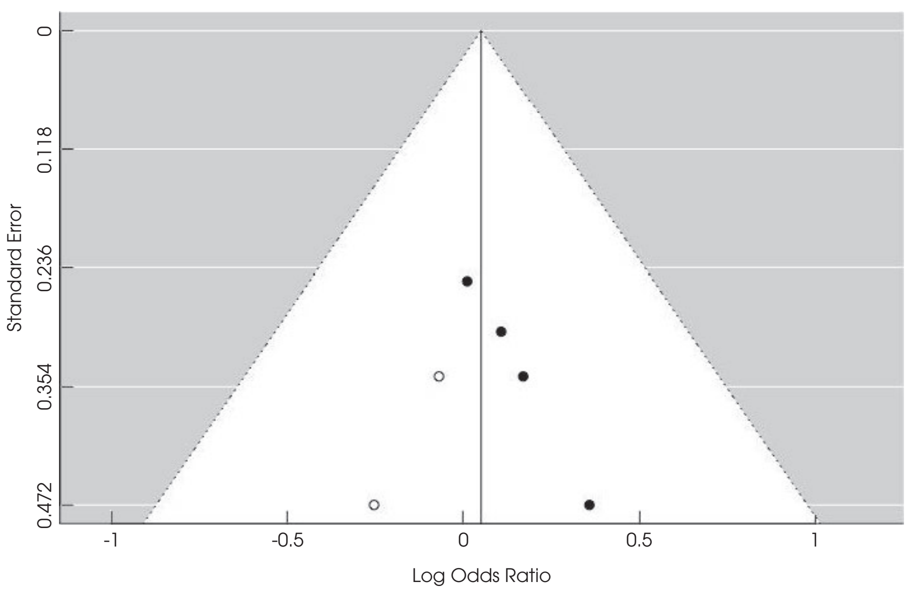


Fig. 4 Trim & fill analysis for studies reporting symptom occurrence.

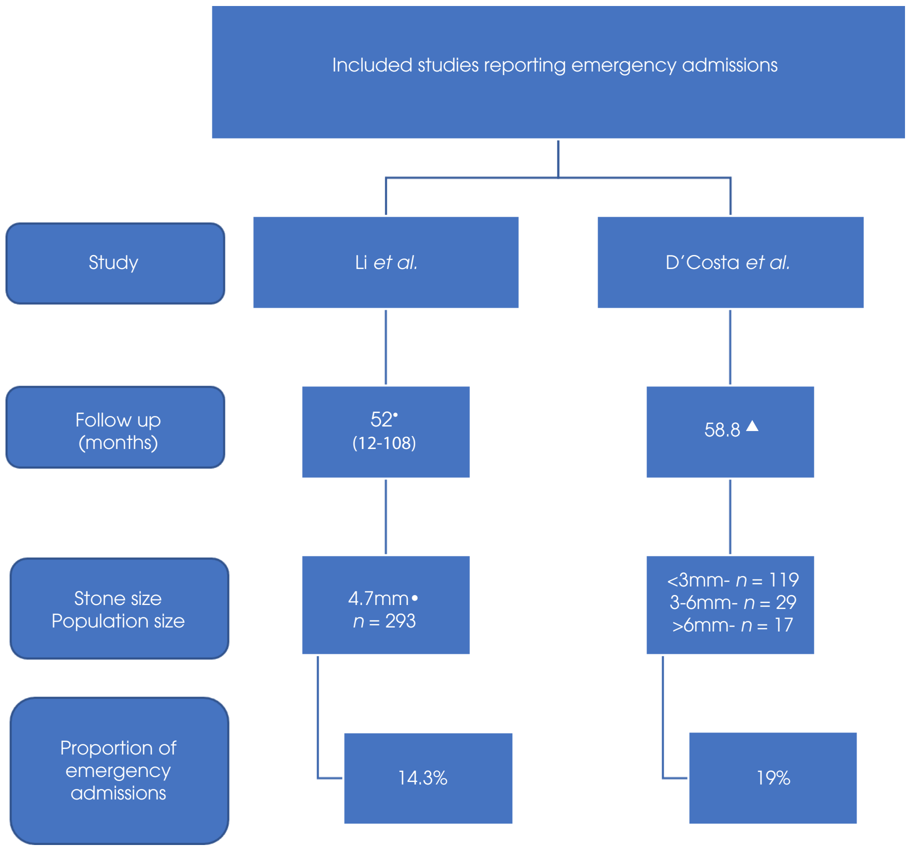
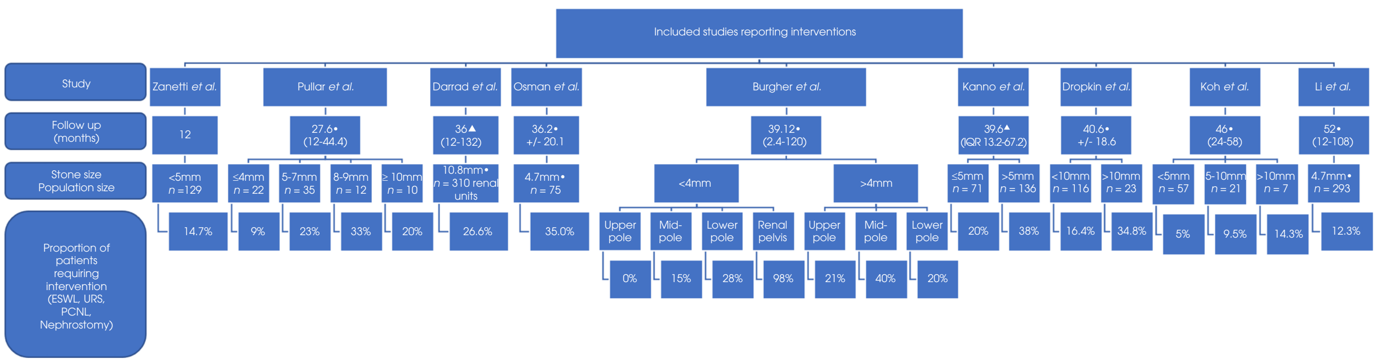


Fig. 5 Included studies and their timing of reported emergency admissions (•mean, ▲median) [27,31].

Fig. 6 Included studies and their timing of reported interventions (•mean, ▲median) [26,28–35].



management, as well as patient preference [40]. The Cambridge Renal Stone PROM (CReSP) has been developed and validated for use in KSD with six domains pertaining to quality of life [41].

The present systematic review highlights that greater stone size is associated with higher rates of intervention but not with increased risk of symptoms. However, firm conclusions cannot be drawn due to incomplete reporting of patient and surgeon variables in the existing literature. Future studies should detail use of concurrent MET, reason for intervention, PROMs and surgeon preferences to ascertain the relative importance of each in patient outcomes.

Previous evidence has shown that stone-related factors amenable to annual observation include non-uric acid stones of <4 mm, lower pole stones of <10 mm, and asymptomatic fragments of <4 mm after ESWL or <2 mm after PCNL [42]. Similarly, our meta-analysis demonstrates that individuals with stones of <5 mm are 36% less likely to require

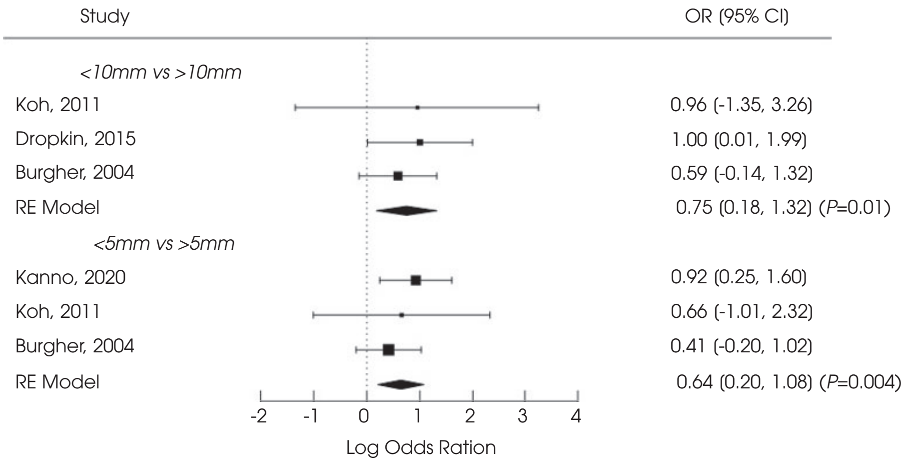


Fig. 7 Comparison of Intervention.

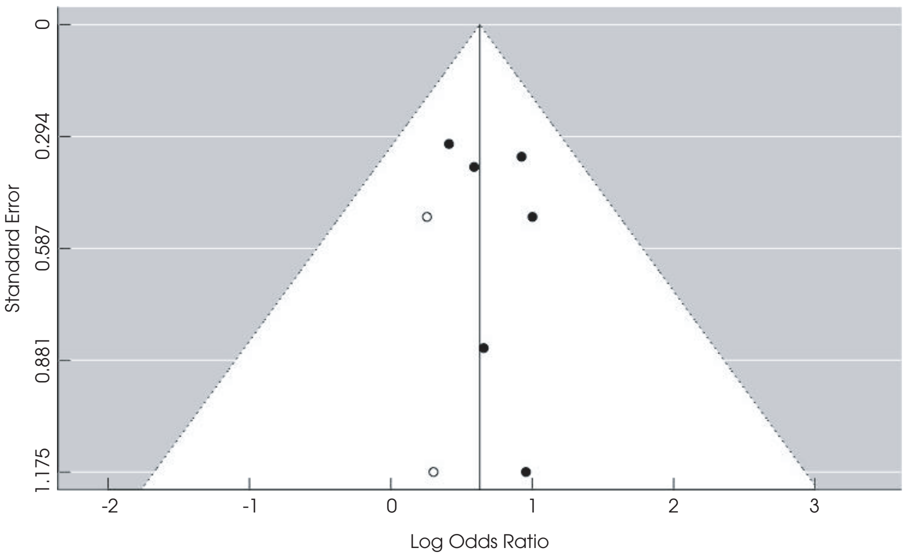


Fig. 8 Trim & fill analysis for studies reporting interventions.

intervention compared to those with larger stones and therefore can be managed with a programme of active surveillance whilst they remain asymptomatic. However, stone size is not a reliable indicator of likelihood of symptoms in patients with stones or fragments of ≤10 mm; rate of symptoms varies from 0% to 59% and this is important for patient counselling [30]. Improving the quality of reporting in future longitudinal studies will supplement results of the present review to help generate evidence-based active surveillance protocols for KSD.

The present systematic review adds to the previous review, which did not have strict inclusion criteria based on size but did report wide variation in rates of symptoms and intervention, as we have also highlighted [43]. The present review was prospectively registered with PROSPERO for transparency of data collection and reporting of outcome measures, which was based on large studies with a long-term follow-up of small stones, an area that poses the greatest uncertainty in KSD management [44]. The PRISMA guidelines were followed, and a validated risk of bias tool utilised to critically appraise the existing literature [19,24]. A thorough search was conducted with two independent assessors screening papers for inclusion. It is possible that relevant studies have been overlooked, e.g. from the grey literature, unfinished work, or unreported outcomes secondary to publication bias, a probability given the 'missing studies' identified on trim-and-fill analysis, although Egger's regression was non-significant. Given that only a few studies were included in the meta-analysis, it reduces the overall power of the study. The small number of relevant studies available both to review and meta-analyse also prohibits sub-group analysis to discern whether there is a systematic difference in outcomes between patients with incidentally identified, asymptomatic small stones and post-procedural ones. We are unable to draw conclusions on any potential role of trauma from instrumentation of the renal tract resulting in oedema, inflammation or scarring [45]. Future work ought to include prospective, RCTs to evaluate the

Table 3 Newcastle–Ottawa Scale risk of bias tool for observational studies (● = low risk, ▲= medium risk, ■= high risk)

Reference	Selection				Comparability	Outcome		
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study (no pain/ admission/ emergency intervention for that stone)	Comparability of cohorts based on design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
	●-truly/somewhat representative of average patient cohort ▲-no description of the derivation of the cohort ■-selected group of users e.g. nurses, volunteers	●-same community as exposed cohort. ▲-no description of derivation of non-exposed cohort ■-drawn from different cohort	●-secure records/ structured interview ▲-no description ■-written self-report	●-not present at start of study. ■-present at start of study	●-study controls for use of alpha blocker ▲-no description ■-no control made	●-independent, blind assessment/ record reviews no description ■-self-reported outcomes	●-yes ■-no	●-all subjects accounted for/ >25 patients accounted for ▲-no statement ■-follow up <1 year or <25 patients
Burgher *et al.*, 2004 [26]	●		●	●	▲	●	●	●
Dropkin *et al.*, 2015 [29]	■		●	●	▲	●	●	●
Kanno *et al.*, 2020 [30]	●		●	●	▲	●	●	●
Koh *et al.*, 2012 [34]	●		●	●	▲	●	●	●
Li *et al.*, 2019 [31]	●		●	●	●	●	●	●
Darrad *et al.*, 2018 [28]	●		●	●	▲	●	●	●
D'Costa *et al.*, 2019 [27]	●		●	●	▲	■	●	●
Osman *et al.*, 2013 [32]	●		●	●	▲	●	●	●
Pullar *et al.*, 2017 [35]	●	●	●	●	●	●	●	●
Zanetti *et al.*, 1997 [33]	●		●	●	▲	●	●	●

absolute risk of conservative management in patients with stones of ≤10 mm identified incidentally or in individuals with residual fragments after interventions, with defined outcome measures for ease of comparison.

In conclusion, available evidence suggests that stone size is not a reliable predictor of symptoms; symptoms are reported from 0% to 59.4% in stones measuring ≤10 mm [30,32]. For stones of ≤10 mm, risk of emergency admission lies between 15% and 20% over 50 months of follow-up [5,31]. For stones measuring ≤10 mm over 36 months, intervention rates varied from 12% to 35% [31,32]. We have found that the need for intervention is linked to stone size, thus stones of >5 mm have a 36% greater risk of intervention compared with stones of <5 mm and stones of >10 mm have a 25% greater risk than those of <10 mm over at least 24 months. Future long-term studies must specifically report symptoms, stone growth and indications for intervention. These findings will provide vital information for urologists as they discuss management strategies with patients who have asymptomatic renal stones and offer insight to committees during the development of evidence-based guidelines.

Acknowledgements

We acknowledge the help of Eli Harriss, a librarian at the Bodleian Health Care Libraries, University of Oxford who helped design the search strategy and perform the systematic literature search. Catherine E. Lovegrove and Robert M. Geraghty are Academic Clinical Fellows supported by the National Institute for Health Research (NIHR). Sarah Howles was an NIHR Academic Clinical Lecturer at the time of the review. Ben Turney is supported by the NIHR Oxford Biomedical Research Centre (BRC).

References

1 **Edvardsson VO, Indridason OS, Haraldsson G, Kjartansson O, Palsson R.** Temporal trends in the incidence of kidney stone disease. *Kidney Int* 2013; 83: 146–52

2 **Boyce CJ, Pickhardt PJ, Lawrence EM, Kim DH, Bruce RJ.** Prevalence of urolithiasis in asymptomatic adults: objective determination using low dose noncontrast computerized tomography. *J Urol* 2010; 183: 1017–21

3 **Bansal AD, Hui J, Goldfarb DS.** Asymptomatic nephrolithiasis detected by ultrasound. *Clin J Am Soc Nephrol* 2009; 4(3): 680–4

4 **Kittanamongkolchai W, Vaughan LE, Enders FT et al.** The changing incidence and presentation of urinary stones over 3 decades. *Mayo Clin Proc* 2018; 93: 291–9

5 **D'Costa MR, Pais VM, Rule AD.** Leave no stone unturned: defining recurrence in kidney stone formers. *Curr Opin Nephrol Hypertens* 2019; 28: 148–53

6 **Daga S, Wagaskar VG, Tanwar H, Shelke U, Patil B, Patwardhan S.** Efficacy of medical expulsive therapy in renal calculi less than or equal to 5 millimetres in size. *Urol J.* 2016; 13: 2893–8

7 **Pearle MS, Goldfarb DS, Assimos DG et al.** Medical management of kidney stones: AUA guideline. *J Urol* 2014; 192: 316–24

8 **Assimos D, Krambeck A, Miller NL et al.** Surgical management of stones: American urological association/Endourological society guideline. PART I. *J Urol* 2016; 196: 1153–60
9 **Assimos D, Krambeck A, Miller NL et al.** Surgical management of stones: American urological association/Endourological society guideline. PART II. *J Urol* 2016; 196: 1161–9
10 **NICE.** NICE Guideline - Renal and ureteric stones: assessment and management: NICE (2019) Renal and ureteric stones: assessment and management. *BJU Int*. 2019; 123(2): 220-32.
11 **Türk C, Petřík A, Sarica K et al.** EAU Guidelines on Interventional Treatment for Urolithiasis. *Eur Urol* 2016; 69: 475–82
12 **Türk C, Petřík A, Sarica K et al.** EAU guidelines on diagnosis and conservative management of urolithiasis. *Eur Urol* 2016; 69: 468–74
13 **National institute for Health and Care Excellence (NICE).** Minimally invasive percutaneous nephrolitholapaxy medium (MIP-M) for removing kidney stones: National Institute for Health and Care Excellence (NICE), 2018. Available from: https://www.nice.org.uk/advice/mib138. [Accessed 06/04/2020]
14 **Glowacki LS, Beecroft ML, Cook RJ, Pahl D, Churchill DN.** The natural history of asymptomatic urolithiasis. *J Urol* 1992; 147: 319–21
15 **Keeley FX Jr, Tilling K, Elves A et al.** Preliminary results of a randomized controlled trial of prophylactic shock wave lithotripsy for small asymptomatic renal calyceal stones. *BJU Int* 2001; 87: 1–8
16 **Streem SB, Yost A, Mascha E.** Clinical implications of clinically insignificant store fragments after extracorporeal shock wave lithotripsy. *J Urol* 1996; 155: 1186–90
17 **Chew BH, Brotherhood HL, Sur RL et al.** Natural history, complications and re-intervention rates of asymptomatic residual stone fragments after ureteroscopy: a report from the EDGE Research Consortium. *J Urol* 2016; 195: 982–6
18 **Kang HW, Lee SK, Kim WT et al.** Natural history of asymptomatic renal stones and prediction of stone related events. *J Urol* 2013; 189: 1740–6
19 **Liberati A, Altman DG, Tetzlaff J et al.** The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research ed).* 2009; 339: b2700
20 **Higgins JP, Green S.** Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0. *The Cochrane Collaboration* 2011. Available from: www.cochrane-handbook.org
21 **Viechtbauer W.** Conducting meta-analyses in R with the metafor Package. *J.Stat Softw* 2010; 36: 48
22 **Higgins JP, Thomas J, Chandler J et al.** *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: John Wiley & Sons, 2019.
23 **Sterne JA, Savovic J, Page MJ et al.** RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
24 **Wells GA, Shea B, O'Connell D et al.** *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. The Ottawa Hospital Research Institute; 2009. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. [Accessed 6/7/2020]
25 **OCEBM Levels of Evidence Working Group.** The Oxford 2011 Levels of Evidence: Oxford Centre for Evidence-Based Medicine; 2011. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence. [Accessed 18/01/2021]
26 **Burgher A, Beman M, Holtzman JL, Monga M.** Progression of nephrolithiasis: long-term outcomes with observation of asymptomatic calculi. *J Endourol* 2004; 18: 534–9
27 **D'Costa MR, Haley WE, Mara KC et al.** Symptomatic and radiographic manifestations of kidney stone recurrence and their prediction by risk factors: A prospective cohort study. *J Am Soc Nephrol* 2019; 30: 1251–60
28 **Darrad MP, Yallappa S, Metcalfe J, Subramonian K.** The natural history of asymptomatic calyceal stones. *BJU Int* 2018; 122: 263–9
29 **Dropkin BM, Moses RA, Sharma D, Pais VM Jr.** The natural history of nonobstructing asymptomatic renal stones managed with active surveillance. *J Urol* 2015; 193: 1265–9
30 **Kanno T, Takahashi T, Ito K, Okada T, Higashi Y, Yamada H.** The natural history of asymptomatic renal stones <= 5 mm: comparison with > 5 mm. *J Endourol* 2020; 23: 23
31 **Li X, Zhu W, Lam W, Yue Y, Duan H, Zeng G.** Outcomes of long-term follow-up of asymptomatic renal stones and prediction of stone-related events. *BJU Int* 2019; 123: 485–92
32 **Osman Y, Harraz AM, El-Nahas AR et al.** Clinically insignificant residual fragments: an acceptable term in the computed tomography era? *Urology* 2013; 81: 723–6
33 **Zanetti G, Seveso M, Montanari E et al.** Renal stone fragments following shock wave lithotripsy. *J Urol* 1997; 158: 352–5
34 **Koh LT, Ng FC, Ng KK.** Outcomes of long-term follow-up of patients with conservative management of asymptomatic renal calculi. *BJU Int* 2012; 109: 622–5
35 **Pullar B, Lunter C, Collie J et al.** Do renal stones that fail lithotripsy require treatment? *Urolithiasis.* 2017; 45: 597–601
36 **Naja V, Agarwal MM, Mandal AK et al.** Tamsulosin facilitates earlier clearance of stone fragments and reduces pain after shockwave lithotripsy for renal calculi: results from an open-label randomized study. *Urology* 2008; 72: 1006–11
37 **Vicentini FC, Mazzucchi E, Brito AH, Chedid Neto EA, Danilovic A, Srougi M.** Adjuvant tamsulosin or nifedipine after extracorporeal shock wave lithotripsy for renal stones: a double blind, randomized, placebo-controlled trial . *Urology.* 2011; 78: 1016–21
38 **Gravina GL, Costa AM, Ronchi P et al.** Tamsulosin treatment increases clinical success rate of single extracorporeal shock wave lithotripsy of renal stones. *Urology* 2005; 66: 24–8
39 **Pickard R, Starr K, MacLennan G et al.** Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet* 2015; 386: 341–9
40 **Mehmi A, Jones P, Somani BK.** Current status and role of patient-reported outcome measures (PROMs) in Endourology. *Urology* 2021; 148: 26–31
41 **Ragab M, Baldin N, Collie J et al.** Qualitative exploration of the renal stone patients' experience and development of the renal stone-specific patient-reported outcome measure. *BJU Int* 2020; 125: 123–32
42 **Skolarikos A, Laguna MP, Alivizatos G, Kural AR, de la Rosette JJ.** The role for active monitoring in urinary stones: A systematic review. *J Endourol* 2010; 24: 923–30
43 **Han DS, Cher BA, Lee D, Rajendran S, Riblet NB, Pais VM Jr.** The durability of active surveillance in patients with asymptomatic kidney stones: a systematic review. *J Endourol* 2019; 33: 598–605
44 **International prospective register of systematic reviews.** Natural history of incidental or post-procedural, asymptomatic renal stones: a systematic review of the literature: National Institute for Health Research; 2020. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=179999. [Accessed 20/01/2021]
45 **Eisenberger F, Schmidt A.** ESWL and the future of stone management. *World J Urol* 1993; 11: 2–6

Correspondence: Catherine E. Lovegrove, Department of Urology, Churchill Hospital, Old Road, Headington, Oxford OX3 7LE, UK.

e-mail: Catherine.lovegrove@nds.ox.ac.uk

Abbreviations: EAU, European Association of Urology; ESWL, extracorporeal shockwave lithotripsy; HR, hazard ratio; KSD, kidney stone disease; MET, medical expulsive therapy; OR, odds ratio; PCNL, percutaneous nephrolithotomy; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROM, patient-reported outcome measure; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomised controlled trial; RR, relative risk; SFR, stone-free rate; URS, ureteroscopy/ureteroscopic.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search Results.