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REVIEW ARTICLE

Systematic review on percutaneous aspiration and sclerotherapy versus surgery in symptomatic simple hepatic cysts

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Abstract

Background: Simple hepatic cysts (SHC) may cause pain and bloating and thus impair quality of life. Whereas current guidelines recommend laparoscopic cyst deroofing, percutaneous aspiration and sclerotherapy (PAS) may be used as a less invasive alternative. This review aimed to assess the efficacy of PAS and surgical management in patients with symptomatic SHC.

Methods: A systematic search in PubMed and Embase was performed according to PRISMA-guidelines. Studies reporting symptoms were included. Methodological quality was assessed by the MINORS-tool. Primary outcomes were symptom relief, symptomatic recurrence and quality of life, for which a meta-analysis of proportions was performed.

Results: In total, 736 patients from 34 studies were included of whom 265 (36%) underwent PAS, 348 (47%) laparoscopic cyst deroofing, and 123 (17%) open surgical management. During weighted mean follow-up of 26.1, 38.2 and 21.3 months, symptoms persisted in 3.5%, 2.1%, 4.2%, for PAS, laparoscopic and open surgical management, respectively. Major complication rates were 0.8%, 1.7%, and 2.4% and cyst recurrence rates were 0.0%, 5.6%, and 7.7%, respectively.

Conclusion: Outcomes of PAS for symptomatic SHC appear to be excellent. Studies including a step-up approach which reserves laparoscopic cyst deroofing for symptomatic recurrence after one or two PAS procedures are needed.

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Introduction

Simple hepatic cysts (SHC) are the most commonly diagnosed benign liver lesions and are found in 18% of the general population on abdominal CT imaging for unrelated pathology.[1–3] Simple SHC do not include parasitic and polycystic SHC, occur more frequently in women, and have an incidence which increases with age.[4] Formation of SHC is believed to arise congenitally from aberrant bile ducts, which are lined with epithelial cells secreting serous fluid.[5–7] Differentiation of SHC should be made from polycystic liver disease (PCLD),[8,9] mucinous cystic neoplasms and intraductal papillary neoplasms of the bile duct, especially since the latter two have a malignant potential. On imaging, the presence of septations (multilocularity) is the most indicative feature of mucinous cystic neoplasms.[10]

This paper is not based on a previous communication to a society or meeting.

[*] Shared first authorship.

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SHC are most often small (<3 cm) and asymptomatic.[3,6,11] About 15% of patients demonstrate severe epigastric discomfort or dyspeptic symptoms (abdominal distension, nausea and vomiting).[12–14] Various interventions are available for symptomatic SHC. Percutaneous aspiration and sclerotherapy (PAS) is a minimally invasive percutaneous procedure in which ultrasound-guided drainage is combined with administrating a sclerosing agent, often ethanol.[12,15] However, the rate of symptomatic recurrence after PAS is unclear. Open or laparoscopic cyst deroofing, sometimes supplemented by argon beam coagulation or filling of the former cavity with the greater omental flap, is the 'reference standard' treatment according to the American College of Gastroenterology (ACG) guidelines.[16–19] Therefore, hepato-pancreato-biliary surgeons are frequently faced with the decision to choose between surgical treatment and PAS.

Although various studies report on outcomes of symptoms and quality of life after treatment for symptomatic SHC, no recent systematic review has assessed the effect of different treatment modalities. This review aims to assess the outcome of PAS and (laparoscopic and open) surgical management as first-line treatment in patients with symptomatic SHC.

Methods

Study identification

A study protocol that defined the objectives, search strategy, outcome measures, and methodology of analysis was followed (see Supplemental Digital Content 1, standardised in- and exclusion form). Two independent reviewers performed a systematic literature search (A.F. and J.J.d.G.) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20] Identified articles were then screened on title, abstract and subsequently on full text. Disagreement during selection process was resolved by consensus. Reference lists of all included articles were screened for additional eligible articles.

Search strategy

The search was built with the aid of a clinical librarian (F.v.E.) and was executed in both PubMed and Embase (OVID interface). Free text words and MeSH-terms related to aspiration sclerotherapy, laparoscopic and open surgical management and hepatic cysts were used. The search strategies (displayed in Supplemental Digital Content 1) were executed on October 5, 2019. All studies until October 5, 2019 were included for screening by title and abstract.

Eligibility criteria

All cohort studies and case series reporting on the presence of symptoms or quality of life before and after PAS or elective surgery for SHC were included. When studies also included other types of cysts (such as PCLD or mucinous cystic neoplasms), only the patients with SHC were included. The study was only included of it reported symptoms before and after treatment separately for the patients with SHC. Patients who were preoperatively diagnosed with SHC, but in whom the diagnosis was adjusted to either "cystadenoma" (preferred term "mucinous cystic lesion", according to the 2010 WHO classification) or echinococcal cyst postoperatively, were also included according to the intention to treat principle. However, outcomes of these patients were reported separately (Table S1, Supplemental Digital Content 2), alongside the method of post-operative diagnosis.

Articles with overlapping data (the smaller study was excluded), studies concerning patients under the age of 18 years, studies containing fewer than five patients, studies concerning patients with posttraumatic or inflammatory cysts and studies on patients with concomitant malignancy in the liver or other organs or with severe comorbidity were excluded. Studies were included if at least five patients were treated with the same treatment method. Systematic reviews, conference abstracts, duplicates and articles not written in English, Dutch, French or German were excluded. Patients with cyst-related pathology resulting in a higher risk of post-operative morbidity and mortality (e.g. intracystic haemorrhage, infection and intraperitoneal cyst rupture) in which data of SHC were not reported separately were excluded.

Quality assessment

A quality assessment of included studies was performed using the MINORS (Methodological index for non-randomized studies) tool.[21]

Data collection and definitions

The data was extracted by two independent authors (A.F. and J.J.d.G.) using standardized forms (Supplemental Digital Content 1). Outcome measures were recorded per treatment method.

The primary outcomes were relief of symptoms, quality of life and symptomatic recurrence. Data on symptoms before treatment were compared with data after treatment. The group of symptomatic patients after treatment included patients whose complaints were unchanged, or patients whose symptoms were improved but did not disappear completely. Details on quality of life were tabulated if quality of life was recorded by any kind of validated or unvalidated quality of life questionnaire. If it was not explicitly stated whether a cyst recurrence was associated with symptoms, it was assumed symptoms had also developed. The number of patients undergoing further treatment was also recorded.

Secondary outcomes were related to the safety of the treatment. To this end, the following outcome parameters were assessed: the length of hospital stay, major complications, and cyst-related mortality. Major complications were recorded

according to the Society of Interventional Radiology (SIR) Classification System for Complications,[22] or a surgical classification system, i.e. Dindo-Clavien.[23] Major complications were defined as SIR C or higher, or Dindo-Clavien 3 or higher.

The following baseline data were collected: study design, number of patients included, number of cysts per patient, age, gender, symptoms before treatment, cyst size before treatment and length of follow-up.

Statistical analysis

Baseline characteristics and outcomes were reported according to treatment group, whereas the type of symptoms at baseline was reported per study. Data were displayed as they were in the original articles. In studies in which only certain patients fit the inclusion criteria of the current review, data were recalculated based on the available data. Dichotomous and categorical variables were reported as numerators and denominators with, if appropriate, percentages. Continuous data were reported as displayed in the original articles and when appropriate weighted means were calculated.

For the primary outcomes, pooled proportions with 95% confidence intervals were reported. Due to the frequent involvement of extreme proportions, raw proportions were transformed using the Freeman-Tukey (double arcsine) transformation.[24–26] Subsequently, these proportions were analysed by a random effects model using the DerSimonian-Laird method. Heterogeneity was assessed using the Cochrane Q statistic and the I^2 statistic. All meta-analyses were conducted in R using the metafor package.[27,28]

Sensitivity analyses excluded studies using other compounds than ethanol and studies published before the year 2000. No additional statistical analyses comparing the three treatment groups were performed due to substantial statistical heterogeneity between studies within the same treatment groups. Metaregression analysis took the size and left/right-ratios reported in the studies into account, irrespective of the type of treatment performed.

Results

Study identification

The search in Pubmed and Embase (OVID interface) identified 1063 and 1195 articles, respectively. After removal of duplicates, 1593 articles were screened on the basis of title and abstract. The remaining 102 were screened by full text, leading to inclusion of 34 articles (Fig. 1).[18,29–61]

Quality assessment

Quality assessment was done with the MINORS-tool (Table S2, Supplemental Digital Content 2). Overall quality of included articles was good, with comparative studies scoring a mean of 16.4/24 points and non-comparative studies scoring 10.7/16 points.

Baseline characteristics

Overall, 34 studies with 764 patients were included. There were eight prospective studies,[32,35,39,51–53,57,58] including two randomized controlled trials. Yan-Hong and Yu *et al.* compared PAS in a single session with repeated installation,[53] Yu *et al.* verified the ethanol concentration after repeated instillation by CT density values.[57,62] Baseline characteristics are reported in Table 1. Mean cyst sizes in the studies were 9.3, 12.7 and 11.9 cm before PAS, laparoscopic and open surgical treatment,

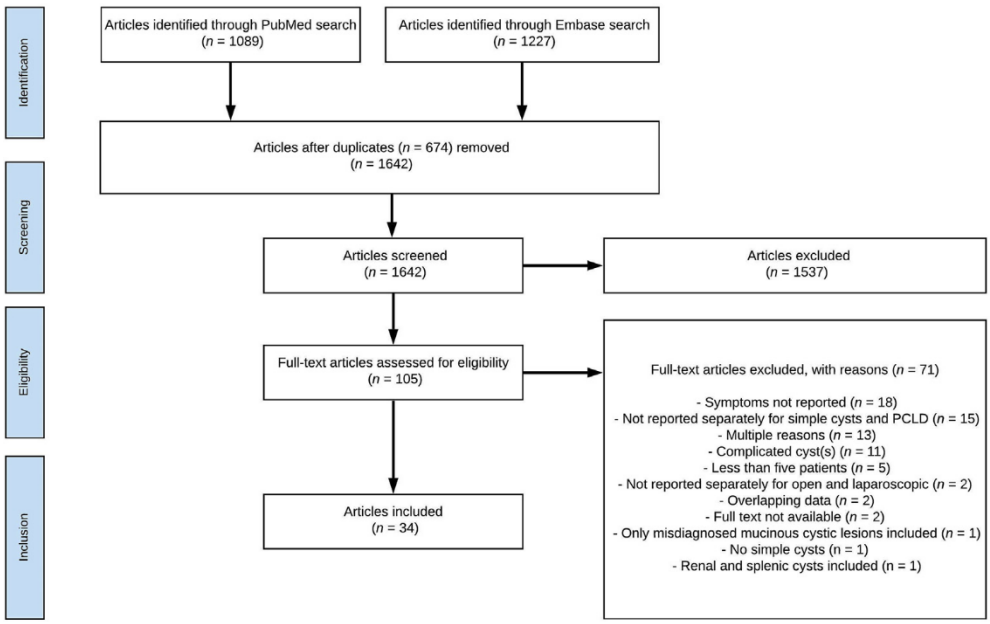

Figure 1 PRISMA flow diagram of the study selection process

Table 1 Baseline characteristics of 764 patients treated for SHC in 34 studies

Author (year)	No. of patients	Age (years)[a]	Female		Solitary	Multiple	Left	Right	Bilobar	Cyst size (cm)[a]
Percutaneous aspiration sclerotherapy (PAS)										
Bean (1985)[29]	6	62.0	3	(50)	3	3	2	1	1	9.2
Montorsi (1994)[31]	21	53.0	15	(71)	13	8	3	14	4	9.0
Yamada (1994)[32 c]	6	64.3	6	(100)	2	4	–	–	–	8.1
Cellier (1998)[36]	5	64.8	3	(60)	5	0	–	–	–	7.7
Okano (2000)[40]	8	71.1	7	(88)	8	0	–	–	–	13.8
Larssen (2003)[42]	5	57.2	4	(80)	5	0	–	–	–	–
Yoshida (2003)[43]	9	58.2	7	(78)	9	0	–	–	–	14.1
Poźniczek (2004)[44]	12	–	–	–	–	–	–	–	–	–
Jusufovic (2011)[52 c]	20	52.9	13	(65)	20	0	9	11	0	–
Yan-Hong (2012)[53 c]	67	61.8	40	(60)	–	–	–	–	–	9.2
Benzimra (2014)[55]	22	–	–	–	21	1	–	–	–	–
Lee (2014)[56]	17	66.0	15	(88)	15	2	14	5	0	8.9
Yu (2014)[57 c]	45	53.1	25	(56)	–	–	18	34	0	8.3
Souftas (2015)[58 c]	10	63.2	9	(90)	7	3	3	5	2	9.4
Akhan (2016)[59]	35	54.0	21	(60)	32	3	–	–	–	–
Total	**288**	**58.3**	**168**	**(66)**	**140**	**24**	**49**	**70**	**7**	**9.3**
Laparoscopic surgical treatment										
Emmermann (1997)[33]	18	57.0	18	(100)	18	0	4	14	0	12.2
Fabiani (1997)[34]	10	64.5	7	(70)	10	0	4	6	0	9.5
Hansen (1997)[35 c]	17	–	–	–	8	9	–	–	–	–
Martin (1998)[37]	13	–	–	–	–	–	–	–	–	–
Katkhouda (2000)[39 c]	16	35.0	12	(75)	16	0	–	–	–	–
Zacherl (2000)[41 b]	11	62.1	8	(73)	11	0	1	10	0	13.6
Poźniczek (2004)[44]	12		–	–	–	–	–	–	–	–
Fabiani (2005)[45]	40	68.8	35	(88)	37	3	21	19	0	11.0
Hsu (2005)[46 b]	6	59.5	6	(100)	2	4	3	3	0	16.8
Tan (2005)[47 b]	10	–	–	–	10	0	2	8	0	12.8
Neri (2006)[48]	12	–	–	–	7	5	–	–	–	9.4
Koea (2008)[49 b]	13	62.0	2	(15)	13	0	–	–	–	18.0
Gall (2009)[50]	48	–	–	–	–	–	–	–	–	–
Faulds (2010)[51 b,c]	6	62.2	6	(100)	0	6	2	4	0	11.3

Table 1 (*continued*)

Author (year)	No. of patients	Age (years)[a]	Female		Solitary	Multiple	Left	Right	Bilobar	Cyst size (cm)[a]
Wahba (2011)[18]	23	68.1	19	(83)	7	16	–	–	–	12.2
Brozzetti (2013)[54]	5	–	–	–	–	–	–	–	–	–
Kisiel (2017)[60]	48	69.0	39	(81)	35	13	–	–	–	–
Janssen (2019)[61]	48	58.8	45	(94)	11	37	20	24	2	14.2
Total	**356**	**62.4**	**197**	**(83)**	**185**	**93**	**37**	**64**	**2**	**12.7**
Open surgical treatment										
Madariaga (1993)[30]	18	55.1	15	(83)	–	–	–	–	–	–
Martin (1998)[37]	10	–	–	–	–	–	–	–	–	–
Payatakes (1999)[38]	9	62.1	–	–	1	8	–	–	–	–
Tan (2005)[47]	30	–	–	–	30	0	8	22	23	12.1
Gall (2009)[50]	19	–	–	–	–	–	–	–	–	–
Brozzetti (2013)[54]	10	–	–	–	–	–	–	–	–	–
Janssen (2019)[61]	24	59.0	21	(88)	7	13	13	8	3	11.7
Total	**120**	**58.2**	**36**	**(86)**	**38**	**21**	**11**	**23**	**26**	**11.9**

Values in parentheses are percentages. – Not reported.
[a] Totals are means.
[b] Includes a patient with a final diagnosis of a mucinous cystic lesion.
[c] Prospective research design.

respectively. Most studies on PAS used 95–99.9% ethanol as a sclerosing agent.[29,31,40,42,44,53,55–57,59] Occasionally, minocycline hydrochloride,[32,36,43] hypertonic saline with bleomycin,[58] or hypertonic saline alone was used.[52] Full PAS treatment protocols used are displayed elsewhere (Table S3, Supplemental Digital Content 2).

Prior treatment

Forty-seven of 476 surgically treated patients (10%) underwent treatment prior to their operation, one of 294 patients (0.3%) underwent treatment prior to PAS. Thirty-three patients underwent aspiration alone without sclerotherapy,[18,30,36,45–47,50,51,61] eleven underwent PAS,[34,39,44,46] four underwent laparoscopic surgical management.[45,61] In Figure S1 (Supplemental Digital Content 3), patients' prior and definitive treatments are represented.

Symptoms before treatment

Before treatment almost all patients were symptomatic (Table 2). The most common complaints were those caused by digestive tract compression,[63–65] especially abdominal pain, which was present in 456/764 (60%) patients, but also nausea, bloating, dyspepsia, early satiety and weight loss. Dyspnoea caused by pulmonary compression, jaundice due to biliary compression and fatigue were occasionally reported. No portal hypertension or venous thrombosis caused by venous compression were reported, in one study vena cava compression was reported.[41]

Symptom relief and recurrence rates

Outcomes related to symptom relief and symptomatic recurrence are reported for 736 patients, as 28 patients were lost to follow-up. Of these 736 patients, 265 (36%) underwent PAS, 348 (47%) underwent laparoscopic and 123 (17%) underwent open surgical treatment. Weighted mean follow-up durations were 26.1, 38.2 and 21.3 months, respectively (Table S4, Supplemental Digital Content 2). Symptoms persisted in 3.5% (95% confidence interval (CI): 0.3–8.6%; heterogeneity: I^2 = 46%, p = 0.027), 2.1% (95% CI: 0.0–7.9%; I^2 = 73%, p < 0.001), 4.2% (95% CI: 0.0–2.1%; I^2 = 85%, p < 0.001), of patients treated with PAS, laparoscopic and open surgery, respectively (Fig. 2). Cyst recurrence rates were 0.0% (95% CI: 0.0–0.3%; I^2 = 0%, p = 0.994), 5.6% (95% CI: 1.6–11.2%; I^2 = 56%, p = 0.002) and 7.7% (95% CI: 1.1–17.9%; I^2 = 56%, p = 0.033) for PAS, laparoscopic, and open surgical treatment, respectively (Fig. 3).

Table 2 Symptoms prior to treatment per study

Author (year)	No. of patients	Pain	Bloating	Nausea	Palpable mass	Asymptomatic	Not specified	Other[a]
Bean (1985)[29]	6	3	3	2	2	0	0	0
Madariaga (1993)[30]	18	12	1	1	0	0	0	6
Montorsi (1994)[31]	21	20	0	0	0	0	0	1
Yamada (1994)[32] [b]	6	1	5	0	0	0	0	0
Emmermann (1997)[33]	18	11	5	0	0	0	2	1
Fabiani (1997)[34]	10	7	0	2	0	0	0	1
Hansen (1997)[35]	17	0	0	0	0	0	17	0
Cellier (1998)[36]	5	5	0	0	0	0	0	0
Martin (1998)[37]	23	22	0	0	0	0	14	0
Payatakes (1999)[38]	9	9	8	2	0	0	0	0
Katkhouda (2000)[39] [b]	16	10	0	0	0	0	0	6
Okano (2000)[40]	8	1	7	0	0	0	0	0
Zacherl (2000)[41] [c]	11	11	0	2	0	0	0	4
Larssen (2003)[42]	5	5	0	0	0	0	0	0
Yoshida (2003)[43]	9	9	0	0	0	0	0	0
Poźniczek (2004)[44]	24	0	0	0	0	0	24	0
Fabiani (2005)[45]	40	32	2	0	0	0	0	13
Hsu (2005)[46] [c]	6	3	6	0	0	0	0	1
Tan (2005)[47] [c]	40	31	23	4	0	0	0	18
Neri (2006)[48]	12	12	0	0	0	0	0	0
Koea (2008)[49] [c]	13	13	13	0	0	0	0	0
Gall (2009)[50]	67	55	16	15	22	3	0	31
Faulds (2010)[51] [b,c]	6	5	0	0	0	0	0	1
Jusufovic (2011)[52] [b]	20	20	11	0	6	0	0	4
Wahba (2011)[18]	23	0	0	0	0	0	23	0
Yan-Hong (2012)[53] [b]	67	26	18	0	0	0	18	5
Brozzetti (2012)[54]	15	10	5	2	0	0	0	6
Benzimra (2014)[55]	22	22	0	0	0	0	9	0
Lee (2014)[56]	17	6	2	0	0	0	4	7
Yu (2014)[57] [b]	45	18	17	0	0	0	0	0
Souftas (2015)[58] [b]	10	10	6	0	0	0	0	0
Akhan (2016)[59]	35	28	0	0	0	0	7	0
Kisiel (2017)[60]	48	0	0	0	0	0	48	0
Janssen (2019)[61]	72	39	0	0	0	1	32	0
Total	**764**	**456 (60)**	**148 (19)**	**30 (4)**	**30 (4)**	**4 (0.5)**	**198 (26)**	**105 (14)**

Values in parentheses are percentages.
[a] Dyspepsia, early satiety, weight loss, fatigue, dyspnoea, jaundice, vena cava compression, symptoms due to compression of other organs.
[b] Prospective research design.
[c] Includes a patient with a final diagnosis of a mucinous cystic lesion.

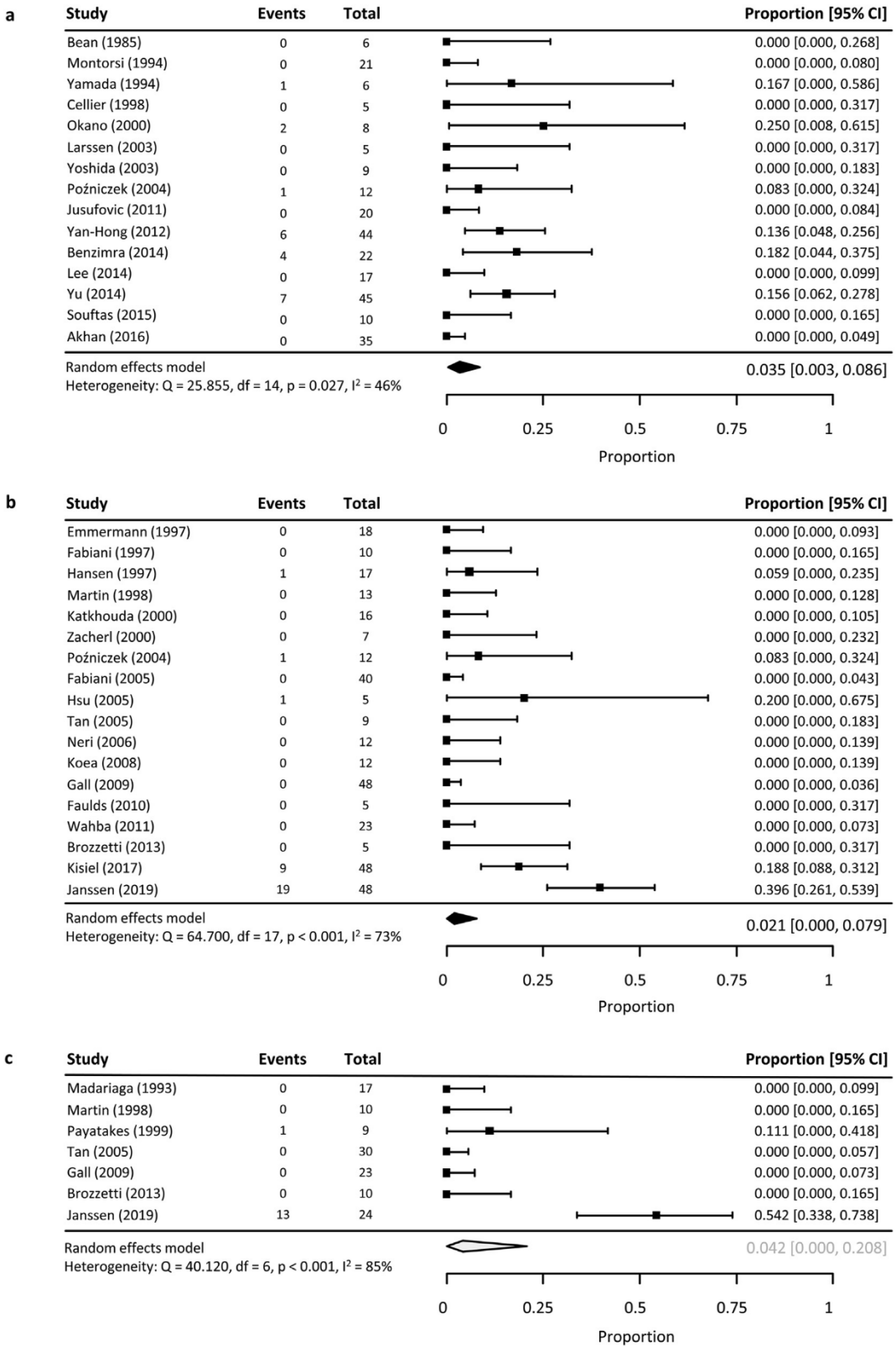

Figure 2 Meta-analysis of proportions of patients symptomatic after treatment. **a**. Percutaneous aspiration and sclerotherapy. **b**. Laparoscopic surgical treatment. **c**. Open surgical treatment (diamond displayed in light grey to indicate that due to substantial heterogeneity pooling might not be appropriate)

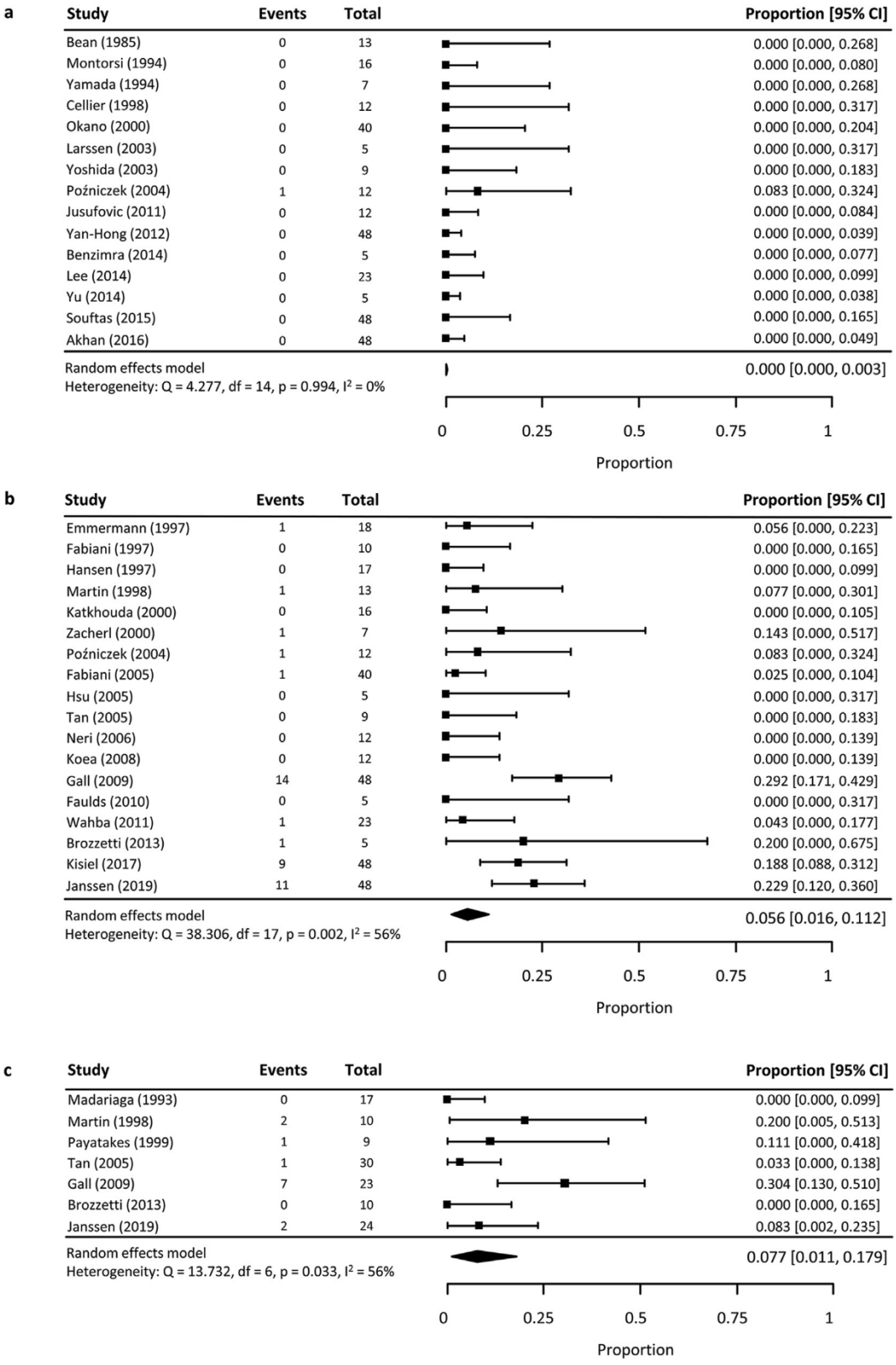

Figure 3 Meta-analysis of proportions of patients with symptomatic recurrences after treatment. **a**. Percutaneous aspiration and sclerotherapy. **b**. Laparoscopic surgical treatment. **c**. Open surgical treatment

No patients in any of the treatment groups experienced an increase of symptoms after treatment.

Five patients were at final pathology diagnosed with mucinous cystic neoplasm and one patient with a hydatid cyst (Table S1, Supplemental Digital Content 2).[41,46,47,49,51] This diagnosis was not suspected preoperatively. The most common surgical procedure for SHC was deroofing, however occasionally segmental resection rather than cyst deroofing was performed. All patients with laparoscopic surgical treatment underwent cyst deroofing. Outcomes of patients divided according to open deroofing and open resection are displayed in Table 3.

Further treatment

Three of 265 (1.0%) patients underwent laparoscopic cyst deroofing after PAS.[44,55] Twelve other patients (4.5%) underwent multiple PAS procedures, but it was often unclear whether this was a part of the treatment protocol or these were unplanned treatments due to recurrent or persistent symptoms (Table S3, Supplemental Digital Content 2). Nine of these patients underwent two procedures, two patients underwent three procedures, and one patient underwent four procedures.

Further treatment after laparoscopic surgical treatment was performed in 16/348 patients (4.6%). Two of these sixteen patients underwent additional laparoscopic surgical treatment,[18,41] one underwent PAS.[44] All other patients underwent open surgical treatment,[18,33,37,50,60,61] including a patient who underwent liver transplantation.[60] Overall, further treatment was performed in 7/123 patients (5.7%) after open surgical treatment, all by additional open surgical treatment.[37,47,50,61]

Quality of life assessment

Three of the 34 included articles (8.8%) used a quality of life or symptom questionnaire. All of these studies were on surgical management of cysts and none involved PAS. Response rates in these studies were 64/102 (63%),[50] 48/92 (52%),[60] and 88/132 (67%).[61] The study by Gall *et al.* used the SF-36 questionnaire and showed no statistical differences in the quality of life after laparoscopic cyst deroofing, open deroofing and resection.[50] However, no preoperative quality of life assessment was performed in this study. Therefore, variations in baseline quality of life may have influenced these outcomes. The structured telephone interview performed by Kisiel *et al.* only provided data on the number of asymptomatic patients, therefore these data are displayed along with the other data in Figs. 2 and 3.[60] Data of Janssen *et al.*, excluding patients with PCLD and an infected cyst, are reported separately (Table S4, Supplemental Digital Content 2). These authors are part of the Dutch collaborative network (Dutch Benign Liver Tumor Group, DBLTG) who supplied their data. Results of the EORTC QLQ-C30 questionnaire indicated an increased summary score (SumSc) and thereby an increased quality of life after laparoscopic and open surgical fenestration (68.3 before vs. 88.9 after fenestration [95% CI 14.9–27.4, $p < 0.001$]). Nonetheless, quality of life data were obtained in a retrospective manner and may thereby be flawed by recall bias.

Complications

Major complications were reported in 2/265 (0.8%), 6/348 (1.7%) and 3/123 (2.4%) after PAS, laparoscopic surgery, and open surgery, respectively (Table S5, Supplemental Digital Content 2). The

Table 3 Outcomes of patients undergoing open deroofing and open resection

Author (year)	Patients (n)	Follow up (months)	Symptomatic after (n, %)	Symptomatic recurrence (n, %)
Open surgical treatment - Deroofing				
Martin (1998)[37]	7	56	0 (0)	2 (29)
Payatakes (1999)[38]	9	36	1 (11)	1 (11)
Tan (2005)[47]	17	20	0 (0)	1 (6)
Gall (2009)[50]	11	–	0 (0)	4 (36)
Brozzetti (2013)[54]	9	–	0 (0)	0 (0)
Janssen (2019)[61]	20	36	10 (50)	2 (10)
Total	**73**	**34**	**11 (15)**	**10 (14)**
Open surgical treatment – Resection				
Madariaga (1993)[30]	17	12	0 (0)	0 (0)
Martin (1998)[37]	3	19	0 (0)	0 (0)
Tan (2005)[47]	13	29	0 (0)	0 (0)
Gall (2009)[50]	12	–	0 (0)	3 (25)
Brozzetti (2013)[54]	1	–	0 (0)	0 (0)
Janssen (2019)[61]	4	5	3 (75)	0 (0)
Total	**50**	**13**	**3 (6)**	**3 (6)**

patients with complications after PAS both underwent ethanol sclerotherapy, with a longer exposure time (40 min),[56] and higher relative volume of ethanol (30–50% of cyst volume) compared to other studies using ethanol sclerotherapy. No mortality related to the cyst or treatment of the cyst was reported.

Sensitivity analyses

Exclusion of studies published before 2000 led to increased proportions of patients with persistent symptoms after PAS (4.3% [95% CI: 0.6–10.1%]) and after open surgical treatment (6.4% [95% CI 0.0–38.1%]). Cyst recurrence increased after laparoscopic surgical treatment (11.7% [95% CI: 5.4%–19.5%]) and open surgical treatment (11.4% [95% CI: 1.8%–25.9%]). Excluding studies using other sclerosing agents than ethanol led to an increase of the proportion of patients with persistent symptoms after PAS (4.9% [95% CI: 0.7–11.4%]). Nonetheless, these data showed wide confidence intervals largely overlapping aforementioned data (Table S7, Supplemental Digital Content 2).

In metaregression analysis, the left/right ratio reported in the studies was correlated neither to recurrence rates ($p = 0.877$) nor to symptom relief ($p = 0.494$). Cyst size appeared to influence the recurrence rates ($p = 0.007$), but not the rate of symptom relief ($p = 0.538$, Figure S2 and S3, Supplemental Digital Content 3).

Discussion

This systematic review demonstrated that outcome of PAS for symptomatic SHC appears to be excellent with symptoms persisting is less than 4% of patients and complication and recurrence rates each <1%. Although the rate of persistent symptoms was slightly higher after PAS as compared to laparoscopic cyst deroofing, this difference (3.5% vs 2.1%) is clinically not relevant, especially given the lower recurrence rate with PAS, as compared to laparoscopic surgical cyst deroofing. Open surgery showed the least favourable outcomes. Nonetheless, no statistical analysis was performed to compare the three groups as there was substantial statistical heterogeneity within the treatment groups themselves, in particular regarding the analysis of symptom relief. Quality of life questionnaires were used in only a very limited number of studies, and only to compare laparoscopic with open surgical treatment. It therefore seems that, despite current guideline advice,[19] a step-up approach could be advised wherein laparoscopic cyst deroofing is reserved for patients with a symptomatic recurrence of SHC after one or two PAS procedures. Studies describing the outcome with such an approach are, however, scarce.

The findings of the current study are in line with previous systematic reviews. The review by Moorthy *et al.*, published in 2001, already suggested that PAS may be associated with a lower incidence of complications than laparoscopic or open surgical treatment.[66] Laparoscopic and open surgical treatment were compared by Antonacci *et al.*, suggesting that the laparoscopic approach might be the treatment of choice.[67] In the ACG guideline, it is noted that high level evidence by means of randomized clinical trials and long-term cohort studies comparing treatment methods are lacking. Nonetheless, surgical deroofing is advised as primary treatment with PAS as an alternative for patients who are either unfit for or unwilling to undergo surgery, due to high recurrence rates attributed to PAS.[19] Only the study by Tocchi *et al.*, however, reported high recurrence rates.[68] Despite the poor outcomes of PAS in their study, of which the cause remains unknown, prior PAS was actually found to ease subsequent cyst excision. The current review might provide means to close the literature gap regarding the efficacy of PAS and laparoscopic cyst deroofing.

(Pre)malignant cysts, such as IPNB and mucinous cystic neoplasms, are an important differential diagnosis to SHC. If no atypical features are seen, PAS or laparoscopic cyst deroofing may be safely performed in order to resolve cyst-related symptoms. In this respect, both laparoscopic deroofing and PAS yielded excellent outcomes in the current review, However, it should be emphasized that this may be (partly) attributable to a placebo effect. Moreover, excluding other causes of abdominal symptoms is necessary before undertaking treatment with associated risks. Although imaging techniques have greatly evolved, if atypical features are found in imaging differentiation of atypical SHC and (pre)malignant cysts on the basis of CT and MRI characteristics remains notoriously difficult.[69–71] Five patients in the current review had a mucinous cystic lesion which was not suspected before treatment, highlighting this difficulty. Thus, in patients with atypical simple cysts, and no differentiation with IPNB and mucinous cystic neoplasms can be made, total excision is still advised.[72]

The number of PAS procedures that should be performed remains a matter of debate. A single session PAS, planned repeated instillation, and repeated installation in case of persistent or recurrent symptoms are all described in the currently included studies. In a randomized controlled trial, planned repeated installation within one session was superior to single session PAS regarding cyst size, although no statistical differences were seen regarding symptom relief.[53] To date, no studies have been performed evaluating the success of PAS after an initial procedure associated with persistent symptoms or symptom recurrence. Repeated installation may not be advisable if post-procedural increase of cyst volume occurs shortly after the procedure (for example within three months), as this increase might arise from an inflammatory reaction of remnant vital cyst wall and may subside after time.[42,73] In the current review, patients with multiple procedures usually underwent two PAS procedures. The number of repeats of PAS may be primarily guided by patients' preference.

Some limitations of this review should be taken into account. First, selection bias may be present. Centres may apply different protocols regarding patient and treatment selection. For example, in most centres open surgery is considered obsolete, reflected by the low number of patients in this treatment group.

Potential selection bias is reflected in the current data by a smaller mean cyst size before PAS (9.3 cm) than those treated through laparoscopic and open surgery (12.7 and 11.9 cm), and the higher rate of patients who underwent any treatment prior to surgical treatment (47/476, 9.9 percent), compared to prior to PAS (1/294, 0.3%). Moreover, patients undergoing laparoscopic surgical treatment were older (62 years) than patients undergoing open surgery or PAS (58 years). These factors could have negatively influenced treatment outcomes, in particular recurrence and cyst size were correlated in this study. Second, validated quality of life questionnaires were rarely used. Comparison of the extent of symptom relief between studies may therefore be influenced by a varying interpretation of subjective signs. An example of a study using a strict interpretation of subjective signs is the study by Janssen *et al.* They found relatively low rates of symptom relief.[61] Using a validated quality of life questionnaire in all studies would make results more reliable and more comparable. Third, recurrence necessitating further surgical treatment was only reported once after PAS in the dedicated studies. In the surgical series though, there were eleven patients who had undergone previous PAS, which may suggest recurrence after PAS is underreported. The mean follow-up of the studies included in this review was approximately two years. Whether this is a suitable amount of time to monitor recurrence is unknown, as prospective studies on time to recurrence are lacking. The same mechanism may also apply to surgical management, although the follow-up period after laparoscopic treatment was longer, 38 months. Fourth, results

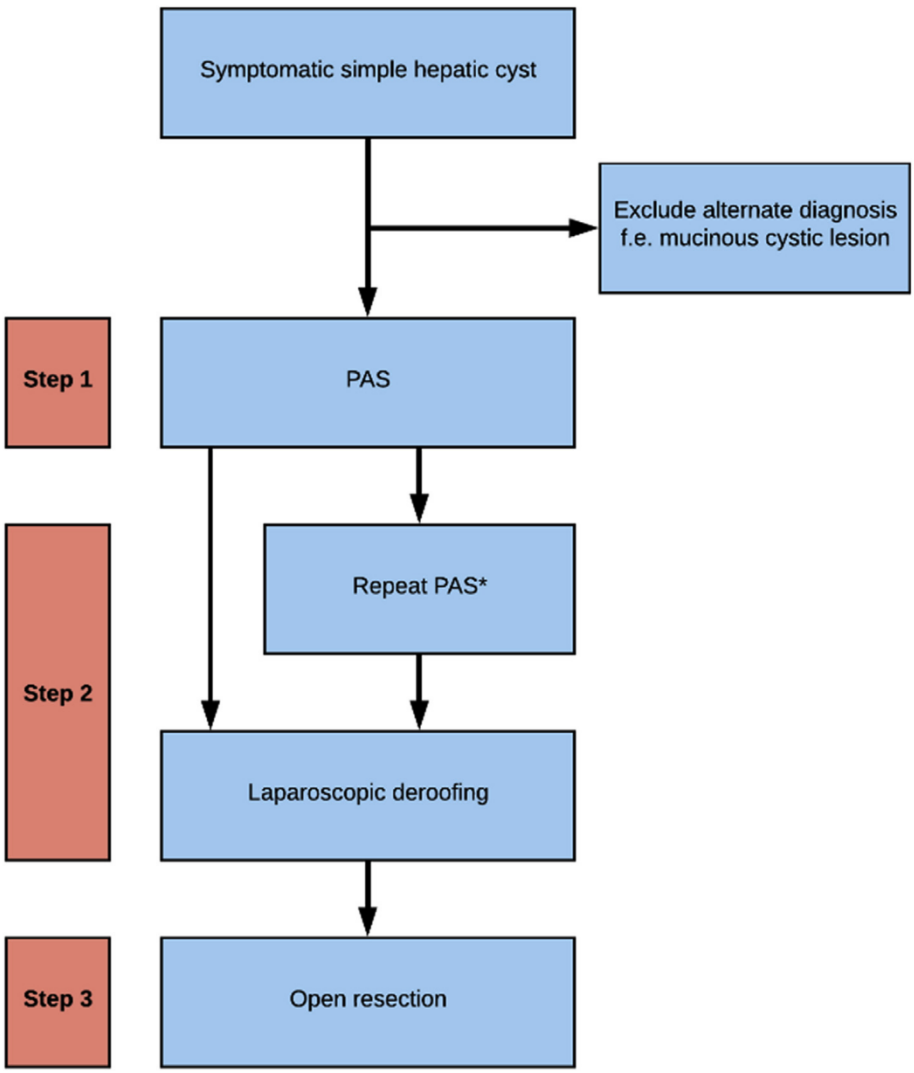

Figure 4 Suggested step-up approach for future studies on symptomatic simple hepatic cysts PAS as primary treatment, escalation to laparoscopic cyst deroofing if PAS fails. Open hepatic resection as a final resort for recurrent cysts or if PAS and/or laparoscopic cyst deroofing are not possible. It is yet to be determined how often PAS should be attempted before escalating to (laparoscopic) cyst deroofing

of the current review may not be extrapolated to patients with polycystic liver disease, as these patients were excluded. Some evidence suggests that these patients are less likely to experience symptom relief.[74,75] As a consequence, a number of studies using mixed cohorts of polycystic liver disease and SHC patients were also excluded.

In conclusion, outcomes of PAS and laparoscopic cyst deroofing for symptomatic SHC appear to be excellent. Ideally, future studies would include a randomized study on the short- and long-term outcomes of PAS, laparoscopic deroofing and a control group of conservatively treated patients. Alternatively, although ethically debatable, the ideal control group would be a sham-operated group given the large placebo effect. However, this design will be difficult given the good outcomes of both techniques and potential drop-out of conservatively treated patients. Thus, future prospective studies may focus on describing the outcomes of a step-up approach for cysts smaller than 10 cm in diameter such as illustrated in Fig. 4, which reserves laparoscopic cyst deroofing for patients with a symptomatic recurrence of SHC after one or two PAS procedures. This review provides an overview of the currently available literature on the topic and may provide an outline for the conceptualization of such studies.

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Conflict of Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.07.005.