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Original Research

Evidence of nonsurgical treatment for polycystic liver disease

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Abstract

Background: Polycystic liver disease (PCLD) is the most common extrarenal manifestation of polycystic kidney disease. There is an urgent need to assess the efficacy and safety of nonsurgical modalities to relieve symptoms and decrease the severity of PCLD. Herein, we aimed to evaluate the efficacy of the nonsurgical treatment of PCLD and the quality of life of affected patients.

Methods: PubMed, Ovid, MEDLINE, EMBASE, and the Cochrane Library were searched for studies on the nonsurgical modalities, either medications or radiological intervention to manage PCLD. Treatment efficacy, adverse events (AEs), and patient quality of life were evaluated.

Results: In total, 27 studies involving 1037 patients were selected. After nonsurgical treatment, liver volume decreased by 259 ml/m [mean change (Δ) of 6.22%] and the effect was higher in the radiological intervention group [−1617 ml/m (−15.49%)] than in the medication group [−151 ml/m (−3.78%)]. The AEs and serious AEs rates after overall nonsurgical treatment were 0.50 [95% confidence interval (CI): 0.33–0.67] and 0.04 (95% CI: 0.01–0.07), respectively. The results of the SF-36 questionnaire showed that PCLD treatment improved physical function [physical component summary score of 4.18 (95% CI: 1.54–6.83)] but did not significantly improve mental function [mental component summary score of 0.91 (95% CI: −1.20 to 3.03)].

Conclusion: Nonsurgical treatment was effective and safe for PCLD, but did not improve the quality of life in terms of mental health. Radiological intervention directly reduces hepatic cysts, and thus they should be considered for immediate symptom relief in patients with severe symptoms, whereas medication might be considered for maintenance treatment.

Registration number: PROSPERO (International Prospective Register of Systematic Reviews) CRD42021279597

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Introduction

Polycystic liver disease (PCLD) is a rare hereditary disease characterized by the formation of multiple cysts in the liver.[1] PCLD is an extrarenal manifestation of autosomal dominant or recessive polycystic kidney disease.[2,3] Multiple mechanisms are involved in the development of hepatic cysts. Pathophysiological features include decreased intracellular calcium and subsequent increased intracellular cyclic adenosine monophosphate (cAMP) levels, promoting cholangiocyte proliferation and fluid secretion, and these characteristics are potential targets for pharmacological therapy. Patients with PCLD usually present progressive and massive liver enlargement but remain asymptomatic.[3,4] However, approximately 20% of patients eventually experience mechanical symptoms, such as abdominal pain, early satiety,

shortness of breath, poor nutritional status, and decreased quality of life (QoL), and life-threatening infectious complications, such as cholelithiasis, cyst infection, and cholangitis, necessitating the appropriate treatments such as surgical treatment, radiological intervention, and medication.[5–7]

Surgical treatments to treat patients with symptomatic PCLD include laparoscopic or open surgical cyst fenestration, liver resection, and orthotopic liver transplantation (OLT) in severe cases.[8,9] OLT is the most suitable option in cases of hepatic failure and clinical deterioration caused by large cysts; however, OLT is limited by organ donor shortage and high cost. In addition, cysts and symptoms tend to recur after other surgical treatment. However, radiological intervention procedures include percutaneous cyst aspiration with or without injection of sclerosing solution and transcatheter arterial embolization, whereas potentially effective pharmacological therapies for PCLD include somatostatin analogs, mammalian target of rapamycin inhibitors, ursodeoxycholic acid (UDCA), and vasopressin-2 receptor antagonists.[10] However, there is little consensus on the treatment of choice for PCLD.

Here, we assessed the efficacy and safety of overall nonsurgical treatment modalities including medication and radiological intervention for PCLD regarding cyst volume reduction and patients' QoL after nonsurgical treatment.

Materials and methods

The study protocol was registered at the International Prospective Register of Systematic Reviews (CRD42021279597). This systematic review and meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Inclusion and exclusion criteria and treatment outcomes

The inclusion criteria were randomized controlled trials (RCTs), cross-sectional studies, and prospective and retrospective cohort studies that evaluated patients older than 19 years of age with symptomatic PCLD who underwent nonsurgical treatment for PCLD. The exclusion criteria were meta-analyses, reviews, case reports, non-English studies, and studies on patients with infected cysts, biliary cystadenoma, Caroli disease, cystic fibrosis, hydatid cysts, and a single large cyst.

The primary outcome was the efficacy of overall nonsurgical treatment, evaluated as the reduction in total liver volume (TLV) or height-adjusted TLV (hTLV). The secondary outcomes were adverse events (AEs) and changes in the QoL in patients with PCLD.

Search strategy

PubMed (MEDLINE), EMBASE, and Cochrane Library were searched for English-language studies published until December 31, 2020. All searches were conducted by a professional librarian (E-A.J.).

The keywords were PCLD-related words (Liver diseases OR Polycyst* OR Multiple cyst* OR Polycystic liver disease OR PLD OR PCLD) and therapy-related words (Therapeutic use* OR Drug therap* OR Pharmacotherap* OR Molecular targeted therap* OR Immunosuppressive agent* OR Somatostatin OR Everolimus OR Sclerotherap* OR Percutaneous aspiration OR Ablation techniques). The keywords used in the Patient/Problem, Intervention, Comparison, and Outcome model and details of the search strategy are described in the Supplementary Material.

Study selection and data extraction

Two authors independently screened the titles and abstracts. Two researchers (H-I.C. and J-J.Y.) independently screened the full texts and assessed the risk of bias of the selected studies. Discrepancies were resolved by B.K.K. or J-S.L. H-I.C. and J-J.Y. extracted data on study characteristics and results to a standard form, and discrepancies were resolved by S.G.K. and Y.S.K.

Assessment of methodological quality and risk of bias

The risk of bias was assessed independently by two researchers (B.K.K. and S.G.K.) using the Cochrane risk of bias tool for randomized trials and the risk of bias for nonrandomized studies tool version 2.0, and discrepancies were resolved by J-J.Y. or Y.S.K.

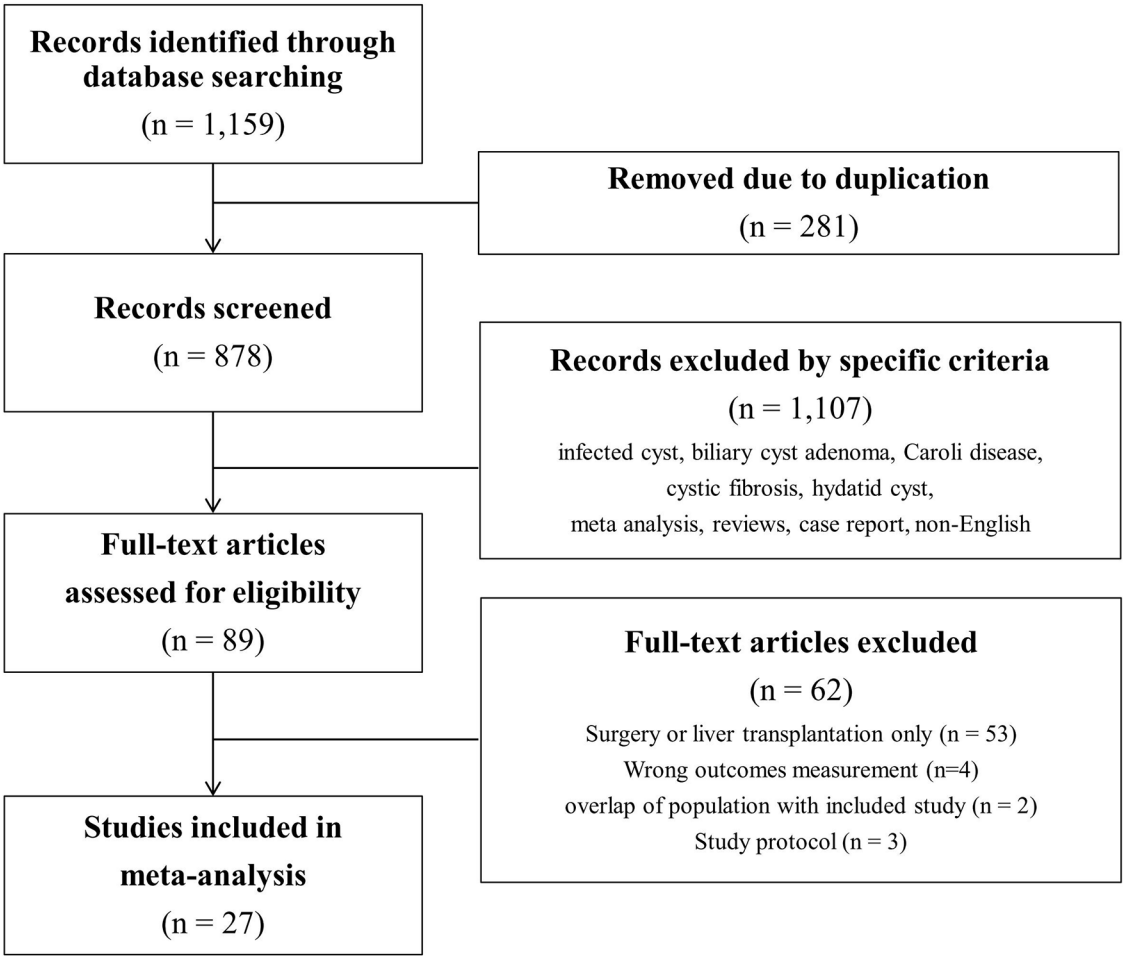

Figure 1. Flowchart displaying the selection process of studies eligible for the systematic review and meta-analysis.

Statistical analysis

Weighted mean differences and 95% confidence intervals were pooled using a random-effects model. Treatment efficacy was evaluated as the mean change in liver volume between before and after treatment using the Freeman–Tukey double arcsine transformation. Individual events rates were transformed using the Freeman–Tukey variant of the arcsine square-root transformed proportion, and overall rates were calculated as the back-transformation of the weighted mean of transformed rates using DerSimonian–Laird weights, assuming a random-effects model. In the analyses of more than 10 studies, publication bias was determined using a contour-enhanced funnel plot and Egger's test. Statistical analyses were performed using RevMan version 5.3 (Cochrane Library) or the meta package in R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the selected studies

A total of 1159 relevant studies were identified. Based on the title and abstract screening, we identified 89 potentially relevant studies. Among them, 62 studies were excluded for the following reasons: surgery or liver transplantation only ($n=53$), wrong outcome measurement ($n=4$), overlap of population ($n=2$), and study protocol ($n=3$). As a result, 27 studies were included in the meta-analysis (Figure 1).

The characteristics of the selected studies are shown in Table 1. Of 27 studies, 11 were prospective RCTs, 11 were prospective cohort studies, and 5 were retrospective cohort studies. The effectiveness of medications (i.e. somatostatin analogs, immunosuppressants, and UDCA) and

Table 1. Demographics and characteristics of studies included in the systematic review and meta-analysis.

Name	Country	Group	Treatment	Duration	Inclusion	Study type	Outcome	No. of patients
Qian *et al.*[11]	USA	Medication	Sirolimus *versus* tacrolimus	19.4 months	PCLD with kidney transplantation	Retrospective cohort study	TLV	16
Van Keimpema *et al.*[12]	Netherlands	Medication	Lanreotide	24 weeks	ADPKD with PCLD	Prospective RCT	TLV, TKV, QoL	54
Caroli *et al.*[13]	Italy	Medication	Octreotide LAR (Sandostatin)	28 days	ADPKD with PCLD	Prospective RCT	TLV	12
Hogan *et al.*[14]	USA	Medication	Octreotide LAR (Sandostatin)	1 year	Severe PCLD defined as a liver volume > 4000 ml or symptomatic disease	Prospective RCT	TLV, TKV, eGFR, QoL, safety	42
Chrispijn *et al.*[15]	Netherlands, Belgium	Medication	Lanreotide	12 months	Symptomatic PCLD patients	Prospective cohort study	TLV, QoL	31
Chrispijn *et al.*[16]	Netherlands	Medication	Octreotide LAR ± everolimus	48 weeks	Symptomatic PCLD patients (TLV > 2500)	Prospective RCT	Change of LV, KV, QoL	44
Gevers *et al.*[17]	Netherlands	Medication	Lanreotide	6 months	Symptomatic ADPKD patients with polycystic livers	Prospective cohort study	Change of LV, TKV	43
Higashihara *et al.*[18]	Japan	Medication	Octreotide LAR	24 weeks	eGFR (45 ml/min/1.73 m^2), TKV (1000 ml), and TLV (3000 ml)	Prospective cohort study	Safety of somatostatin analogue, TLV, TKV, QoL	4
Neijenhuis *et al.*[19]	Netherlands, Belgium	Medication	Lanreotide 120 mg	6–12 months	Liver volume of > 4000 ml (unadjusted for height) or with symptomatic PCLD	Prospective RCT	QoL, change of hTLV, QoL	87
Temmerman *et al.*[20]	Belgium	Medication	Lanreotide	18 months	Symptomatic PCLD patients	Prospective cohort study	Change of LV, QoL, and KV	53
D'Agnolo *et al.*[21]	Netherlands	Medication	UDCA	24 weeks	Symptomatic PCLD patients (TLV > 2500)	Prospective RCT	Proportional change in TLV, change of hTLV, hTKV, symptom, QoL	32
Iijima *et al.*[22]	Japan	Medication	UDCA	1 year	PCLD patients with elevated liver enzymes	Prospective cohort study	Change of liver enzymes, change of aTLV	7
Pisani *et al.*[23]	Italy	Medication	Octreotide LAR	3 years	Adults with polycystic kidney and liver disease (estimated glomerular filtration rate, 40 ml/min/1.73 m^2 or more)	Prospective RCT	Absolute and percent change in TLV	27
Van Aerts *et al.*[24]	Netherlands	Medication	Somatostatin analogue (lanreotide 120 mg or octreotide 40 mg)	44 weeks	IPLD registry (1) SA therapy-naïve PCLD patients treated with any type of SA for two separate cycles with a drug holiday in between; (2) each cycle (either treatment or drug holiday) lasted at least 3 months; (3) minimum interval between consecutive imaging was 3 months; and (4) hTLV was available	Retrospective cohort study	Change in hTLV	34

(Continued)

Table 1. (Continued)

Name	Country	Group	Treatment	Duration	Inclusion	Study type	Outcome	No. of patients
Wijnands *et al.*[25]	Netherlands	Radiological intervention	Pasireotide + sclerotherapy	4 weeks	Patients who underwent aspiration sclerotherapy of a large (>5 cm) symptomatic hepatic cyst	Prospective RCT	Mean proportional change (%) in cyst diameter, cyst volume reduction, QoL	34
Van Aerts *et al.*[26]	Netherlands	Medication	Lanreotide	120 weeks	(1)TLV ⩾ 2000 ml (2) Participants aged 18–60 years who had ADPKD	Prospective RCT	hTLV, absolute TLV, QOL, and AE	175
Hogan *et al.*[27]	USA	Medication	Pansomatostatin	48 weeks	Severe PCLD	Prospective RCT	hTLV, TKV, eGFR, QOL, and AE	48
Takei *et al.*[28]	Japan	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Retrospective cohort study	TLV, QOL	30
Van Keimpema *et al.*[29]	Netherlands	Radiological intervention	PCD and sclerotherapy	1 time	Symptomatic PCLD patients	Retrospective cohort study	TLV, QOL	11
Nakaoka *et al.*[30]	India	Radiological intervention	PCD and sclerotherapy	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	11
Park *et al.*[31]	Korea	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	3
Wang *et al.*[32]	China	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	21
Takita *et al.*[33]	Japan	Radiological intervention	PCD and sclerotherapy	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	14
Zhang *et al.*[34]	China	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	23
Sakuhara *et al.*[35]	Japan	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Prospective cohort study	TLV	5
Temmerman *et al.*[36]	Belgium	Medication	Lanreotide 90 mg	6 months	Symptomatic PCLD patients	Prospective RCT	Safety and efficacy of lanreotide, KV, eGFR, QOL	81
Temmerman *et al.*[36]	Belgium	Medication	Lanreotide 120 mg	6 months	Symptomatic PCLD patients	Prospective RCT	Safety and efficacy of lanreotide, KV, eGFR, QOL	77
Yang *et al.*[37]	Korea	Radiological intervention	TAE	1 time	Symptomatic PCLD patients	Retrospective cohort study	TLV	18

ADPKD, autosomal dominant polycystic kidney disease; AE, adverse events; eGFR, estimated glomerular filtration rate; hTLV, height-adjusted total liver volume; IPLD, International PLD Registry; KV, kidney volume; LAR, long-acting release; LV, liver volume; PCD, percutaneous catheter drainage; PCLD, polycystic liver disease; QoL, quality of life; RCT, randomized controlled trial; SA, somatostatin analogue; TAE, transcatheter arterial embolization; TKV, total kidney volume; TLV, total liver volume; UDCA, ursodeoxycholic acid.

radiological interventions [i.e. transarterial embolization (TAE), percutaneous catheter drainage (PCD), and sclerotherapy) was evaluated by 17 and 10 studies, respectively. Treatment outcomes included TLV, total kidney volume, estimated glomerular filtration rate, the safety of medication, AEs, and patient QoL. The selected studies were conducted in Europe (Belgium, Italy, and the Netherlands), Asia (China, India, Japan, and South Korea), and North America (United States). Risk of bias was summarized in Figure 2.

There were differences in the number of patients with autosomal dominant polycystic kidney disease and kidney transplantation between the studies. The proportion of patients with autosomal dominant polycystic kidney disease in addition to PCLD was reported in 13 studies and varied from 61.8% to 100%.

Treatment efficacy

Treatment efficacy was assessed by the mean reduction in cyst volume, TLV, and hTLV compared with baseline using a random-effects model (Table 2). The overall mean reduction in TLV was 259 ml/m (95% CI: 152–366 ml/m) in 21 studies and 6.22% (95% CI: 1.58–10.85%) in 13 studies. Forest plots are presented in Figure 3(a) and (b).

A subgroup analysis was conducted to explain the heterogeneity among the studies. The mean reduction in TLV in the medication group was 151 ml/m (95% CI: 47–253 ml/m) and 3.78% (95% CI: −9.39% to 1.82%). Among the medication group, the mean reduction in TLV in the somatostatin group was 158 ml/m (95% CI: 35–281 ml/m) and 3.27% (95% CI: 2.41–4.12%), whereas the mean reduction in TLV in the UDCA group was 102 ml/m (95% CI: 73–132 ml/m) and −4.60% (95% CI: −5.21% to −3.99%). There was one study related to mTOR inhibitor, showing that the TLV reduction rate was 11.85%, which was better than those of somatostatin and UDCA. Among the somatostatin group, the effect of lanreotide on TLV reduction (170 ml/m, 95% CI: 22–318) was better than that of octreotide (129 ml/m, 95% CI: 63–196). However, the TLV reduction rate compared with baseline was higher in the subgroup with octreotide (−4.99%, 95% CI: −6.95 to −3.04) than in the subgroup with lanreotide (−2.75%, 95% CI: −3.47 to −2.04). These data were summarized in the Supplementary Figures 2 and 3.

In the radiological intervention group [including TAE (six cases), and PCD plus sclerotherapy (one case)], the mean absolute and relative reduction in TLV was 1617 ml/m (95% CI: 1105–2129 ml/m) and 15.49% (95% CI: 4.90–26.07%), respectively, which were higher than those in the medication group. In the TAE group, the mean absolute and relative reduction in TLV was 1684 ml/m (95% CI: 1153–2216 ml/m) and 14.03% (95% CI: 0.72–27.34%), respectively. In the PCD and sclerotherapy group where the maximal cyst volume change (%) was the primary outcome in many cases, the largest cyst size change after procedure was −91.99% (95% CI: 87.03–96.95) from the baseline.

The overall mean reduction in TLV and hTLV between nonsurgical treatment and control (placebo or no treatment) groups from nine studies was 190 ml/m (95% CI: 100–279 ml/m) and 124 ml/m (95% CI: 18–229 ml/m), respectively. Of the nine studies, eight were in the somatostatin group and one study was in the UDCA group. The mean reduction in TLV in the somatostatin group compared with the controls from eight studies was 146 ml/m, which was lower than the UDCA group (190 ml/m, 95% CI: 279–350) (Supplementary Table 1). Among the somatostatin group, the mean reduction in TLV between lanreotide (four studies) and octreotide subgroups (four studies) compared with controls was 143 ml/m (95% CI: 113–173 ml/m) and 227 ml/m (95% CI: 67–388 ml/m), respectively.

Rate of AEs

The overall rate of AEs after overall nonsurgical treatment modalities in 15 studies was 50% (95% CI: 33–67%) (Table 3). The rate of diarrhea and abdominal pain/discomfort was 55% (95% CI: 38–71%) and 35% (95% CI: 19–53%), respectively. The rate of severe AEs (SAEs) after overall nonsurgical treatment modalities was 4% (95% CI: 1–7%). Forest plots are presented in Figure 3(c) and (d).

AEs were further analyzed in the medication and radiological intervention groups. The overall rate of AEs in the medication group was 46% (95% CI: 29–64%); 55% (95% CI: 36–72%) for the

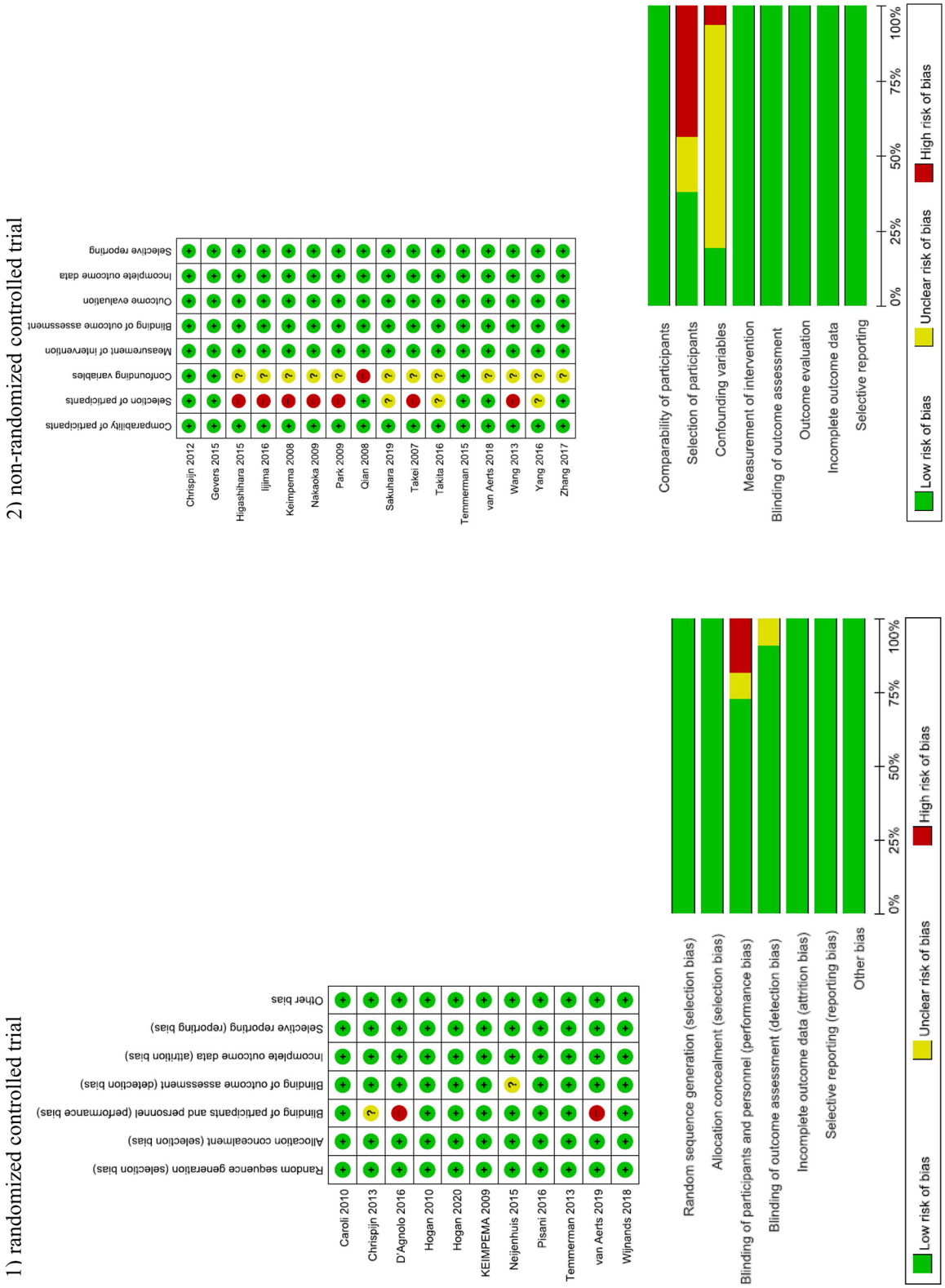

Figure 2. Risk of bias.

Table 2. Summary of the treatment efficacy in PCLD *versus* baseline.

Outcome/subgroup	No. of studies	MD (M-H, random)	95% CI	I^2 (%)	*p* for heterogeneity
All					
Maximal cyst volume change (ml/m)	4	−2152	−2762 to −1544	66	0.03
Maximal cyst volume change (%)	4	−74	−100 to −41	98	<0.01
TLV change (ml/m)	21	−259	−366 to −152	96	<0.01
TLV change (%)	13	−6.22	−10.85 to −1.58	100	<0.01
hTLV change (ml/m)	6	−57	−104 to −10	67	0.01
hTLV change (%)	3	−2.83	−4.19 to −1.46	66	0.05
Medication group					
TLV change (ml/m)	14	−151	−253 to −47	97	<0.01
TLV change (%)	10	−3.78	−9.39 to 1.82	100	<0.01
hTLV change (ml/m)	6	−57	−104 to −10	67	0.01
hTLVchange (%)	3	−2.83	−4.19 to −1.46	66	0.05
Somatostatin group					
TLV change (ml/m)	12	−158	−281 to −35	97	<0.01
TLV change (%)	8	−3.27	−4.12 to −2.41	55	0.03
hTLV change (ml/m)	5	−67	−109 to −25	62	0.03
hTLV change (%)	3	−2.83	−4.19 to −1.46	66	0.05
Radiological intervention group					
TLV change (ml/m)	7	−1617	−2129 to −1105	38	0.14
TLV change (%)	3	−15.49	−26.07 to −4.90	91	<0.01
TAE group					
Maximal cyst volume change (ml/m)	4	−2152	−2762 to −1544	66	0.03
TLV change (ml/m)	6	−1684	−2216 to −1153	40	0.14
TLV change (%)	2	−14.03	−27.34 to −0.72	94	<0.01

CI, confidence interval; MD, mean difference; M-H, Mantel–Haenszel; No.: number; PCLD, polycystic liver disease; TAE, transcatheter arterial embolization.

somatostatin group, and 3% (95% CI: 0–18%) for the UDCA group. There was no report about mTOR inhibitor. The overall rate of SAEs in the medication group was 4% (95% CI: 1–7%); 4% (95% CI: 1–8%) for the somatostatin group and 0% (95% CI: 0–0%) for the UDCA group. Data concerning other medications were summarized in the Supplementary Figure 2.

Although there were few studies reporting AEs (two studies) and SAEs (three studies) among the radiological intervention group, the rate of

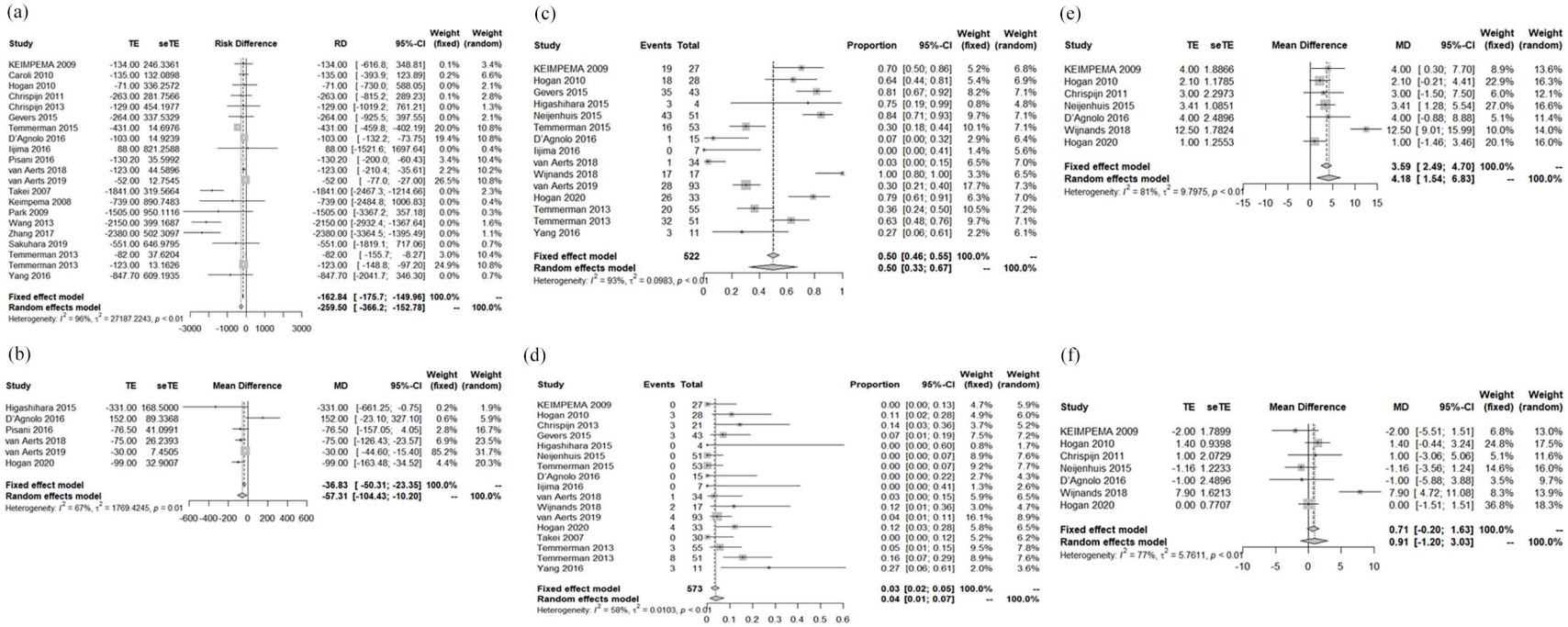

Figure 3. Forest plots for effects of overall nonsurgical treatment on (a) TLV change (ml/m), (b) hTLV change (ml/m), (c) any type of AEs, (d) serious AEs, (e) physical component summary, and (f) mental component summary.

Table 3. AE of treatment in PCLD.

Outcome/subgroup	No. of studies	No. of patients, AE/total	Event rate (M-H, random)	95% CI	I^2 (%)	*p* for heterogeneity
All						
Any type of AE, overall	15	262/522	0.50	0.33–0.67	93	<0.01
SAE, overall	17	34/573	0.04	0.01–0.07	58	<0.01
Diarrhea	11	209/369	0.55	0.38–0.71	89	<0.01
Abdominal pain/discomfort	12	156/424	0.35	0.19–0.53	91	<0.01
Medication group						
Any type of AE, overall	13	242/494	0.46	0.29–0.64	93	<0.01
SAE, overall	14	29/515	0.03	0.01–0.07	55	<0.01
Somatostatin group						
Any type of AE, overall	11	241/472	0.55	0.36–0.72	93	<0.01
SAE, overall	12	29/493	0.04	0.01–0.08	61	<0.01
Discontinuation of drug	7	27/330	0.04	0.00–0.14	87	<0.01
Dose reduction of drug	5	15/246	0.01	0.00–0.09	86	<0.01
Liver cyst infection	3	10/170	0.06	0.02–0.10	0	0.77
Diarrhea	9	196/345	0.58	0.41–0.74	89	<0.01
Abdominal pain/discomfort	9	143/385	0.40	0.23–0.59	91	<0.01
Radiological intervention group						
Any type of AE, overall	2	20/28	0.74	0.00–1.00	95	<0.01
SAE, overall	3	5/58	0.08	0.00–0.32	78	0.01
TAE group						
SAE, overall	2	3/41	0.07	0.00–0.50	87	<0.01

AE, adverse events; CI, confidence interval; MD, mean difference; M-H, Mantel–Haenszel; No.: number; PCLD, polycystic liver disease; SAE, severe adverse events; TAE, transcatheter arterial embolization.

AE in the radiological intervention group was 74% (95% CI: 0–100%), which was higher than that in the medication group. In detail, the AE rate of the TAE group was 27% (95% CI: 4–58%), whereas that of the PCD and sclerotherapy group was 100% (95% CI: 90–100%). The SAE rates in the radiological intervention were 8% (95% CI: 0–32%); in detail, those of the TAE and PCD and sclerotherapy group were 7% (95% CI: 0–50%) and 12% (95% CI: 0–32%), respectively.

For the sensitivity analysis, nine articles that reported AEs in the nonsurgical treatment and control (placebo or no treatment) groups were analyzed (nine studies, Supplementary Table 2); the somatostatin (seven studies), UDCA (one study), or PCD and sclerotherapy (one study)

Table 4. Summary of the QoL according to treatment in PCLD.

Outcome/subgroup	No. of studies	MD (M-H, random)	95% CI	I^2 (%)	*p* for heterogeneity
All					
PCS (*versus* baseline)	7	4.18	1.54 to 6.83	81	<0.01
PCS (*versus* control)	6	2.09	−0.67 to 4.85	50	0.08
MCS (*versus* baseline)	7	0.91	−1.20 to 3.03	77	<0.01
MCS (*versus* control)	6	−0.34	−2.52 to 1.84	31	0.20
Medication group					
PCS (*versus* baseline)	6	2.60	1.44 to 3.77	0	0.66
PCS (*versus* control)	5	1.56	−1.34 to 4.45	50	0.09
MCS (*versus* baseline)	6	0.06	−0.90 to 1.03	0	0.45
MCS (*versus* control)	5	−1.41	−3.32 to 0.51	0	0.95
Somatostatin group					
PCS (*versus* baseline)	5	2.52	1.32 to 3.72	0	0.57
PCS (*versus* control)	4	1.05	−2.08 to 4.18	55	0.09
MCS (*versus* baseline)	5	0.07	−1.00 to 1.15	12	0.34
MCS (*versus* control)	4	−1.60	−3.60 to 0.39	0	0.97

CI, confidence interval; MCS, mental component summary; MD, mean difference; M-H, Mantel–Haenszel; No.: number; PCLD, polycystic liver disease; PCS, physical component summary.
QoL indicators were reported in a total of seven papers; the somatostatin ($n=5$), UDCA ($n=1$), and PCD and sclerotherapy ($n=1$) groups.

groups *versus* controls. The risk of AEs was higher in the nonsurgical group than in the control group from nine studies (RR = 2.65, 95% CI: 1.68–4.18). The overall risk of SAEs was similar between the nonsurgical and control groups (RR = 1.82, 95% CI: 0.83–4.00). In detail, the risk of AE in the somatostatin, UDCA, and PCD and sclerotherapy groups compared with controls was RR = 3.31 (95% CI: 2.01–5.46), RR = 0.38 (95% CI: 0.04–3.26), and RR = 1.52 (95% CI: 1.08–2.13), respectively. In addition, the risk of SAE in the somatostatin, UDCA, and PCD and sclerotherapy groups compared with controls was RR = 2.08 (95% CI: 0.87–4.96), RR = 0 (95% CI: 0–0), and RR = 1.0 (95% CI: 0.16–6.30), respectively.

QoL

Changes in the QoL after overall nonsurgical treatment are shown in Table 4. QoL indicators were reported in a total of seven papers; the somatostatin ($n=5$), UDCA ($n=1$), PCD and sclerotherapy ($n=1$) groups. The mean change in physical component summary (PCS) in the nonsurgical treatment groups was 4.18 (95% CI: 1.54–6.83) higher than at baseline and 2.09 (95% CI: 0.67–4.85) higher than in the control groups. In contrast, the mean change in mental component summary (MCS) in the treated groups *versus* baseline and control groups was 0.91 (95% CI: −1.20 to 3.03) and −0.34 (95% CI: −2.52 to 1.84), indicating no significant intergroup differences in this parameter. Forest plots are shown in Figure 3(e) and (f).

The mean change in PCS in the medication groups *versus* baseline and respective control groups was 2.60 (95% CI: 1.44–3.77) and 1.56 (95% CI: −1.34 to 4.45), respectively. In contrast, the mean change in MCS in the medication groups *versus* baseline and respective control groups was 0.06 (95% CI: −0.90 to 1.03) and −1.41 (95% CI: −3.32 to 0.51), respectively.

Table 5. Meta-regression for the TLV change during treatment in patients with PCLD.

Variable	Coefficient (95% CI)	*p*
Age (year)	−14.83 (−31.35 to 1.68)	0.078
Female (%)	−4.28 (−10.75 to 2.17)	0.193
BMI (kg/m^2)	5.67 (−21.49 to 32.84)	0.682
ADPKD (%)	−2.85 (−11.02 to 5.30)	0.492
Baseline TLV (ml/m)	−0.11 (−0.17 to −0.05)	<0.001
Baseline hTLV (ml/m)	−0.06 (−0.04 to 0.03)	0.758

ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CI, confidence interval; PCLD, polycystic liver disease; TLV, total liver volume.

The mean change in PCS in the somatostatin group *versus* baseline and control group was 2.52 (95% CI: 1.32–3.72) and 1.05 (95% CI: −2.08 to 4.18), respectively. In turn, the mean change in MCS in the somatostatin group *versus* baseline and control group was 0.07 (95% CI: −1.00 to 1.15) and −1.60 (95% CI: −3.60 to 0.39), respectively. In the UDCA group, mean change of PCS compared with baseline or control group was 4.0 (95% CI: −0.88 to 8.88) or 54.0 (95% CI: −1.64 to 11.64), respectively. The mean change of MCS in the UDCA group *versus* baseline or control group was −1 (95% CI: −5.88 to 3.88), or 1.0 (95% CI: −6.0 to 8.0), respectively. In the PCD and sclerotherapy group, the mean change of PCS compared with baseline or control group was 12.5 (95% CI: 9.01–15.99) or 5.8 (95% CI: −0.52 to 12.12), respectively. The mean change of MCS in the PCD and sclerotherapy group *versus* baseline or control was 7.9 (95% CI: 4.72–11.08), or 5.0 (95% CI: 0.48–9.52), respectively.

Meta-regression analysis

Along with the subgroup analysis, we performed the meta-regression analysis because heterogeneity among studies was high. Meta-regression analyses were performed considering patient age, female proportion, body mass index, proportion of polycystic kidney disease, and baseline TLV prior to treatment (Table 5). Only baseline TLV (ml/m) was significantly associated with total volume change after treatment (coefficient −0.11, 95% CI: −0.17 to −0.05, $p < 0.001$).

Discussion

This meta-analysis found that treatment efficacy was significantly higher in the radiological intervention group than in the medication group, reflected in ΔTLV of −15.49% and −3.78%, respectively. However, the rates of AEs and SAEs were higher in the radiological intervention group (74% and 8%, respectively) than in the medication group (46% and 3%, respectively). Nonsurgical treatment did not improve the QoL in terms of mental health.

Radiological intervention was more effective than medication in reducing liver volume in PCLD patients, which is because the former reduces cyst volume, whereas the latter acts more slowly. In accordance with such a difference, the response evaluation of the radiological intervention group was performed on average 4 weeks after the procedure, whereas that of the medication group was performed between 6 and 12 months. Signaling pathways involving adenosine 3,5-cyclic monophosphate (cAMP) and mammalian target of rapamycin (mTOR) are dysfunctional in PCLD and stimulate cyst formation in the liver.[38] Somatostatin analogs reduce intracellular cAMP levels, which might prevent fluid accumulation in hepatic cysts.[39] Several studies assessed the beneficial effects of somatostatin analogs on reduction of TLV.[40–42] Nevertheless, considering patients' large TLV at baseline, but the reduction by at most < 200 ml and the relatively long duration of medication, the actual symptom relief might be marginal. Radiological intervention directly reduces hepatic cysts, and thus they

should be considered for immediate symptom relief in patients with severe symptoms, such as abdominal pain, early satiety, shortness of breath, poor nutritional status, and decreased QoL, whereas medication might be considered for maintenance treatment. In the radiological intervention group, TAE was more effective in decreasing TLV than the medication group. Although three studies assessed PCD combined with sclerotherapy, only one study reported TLV values and two studies reported cyst volume reduction as the primary outcome. PCD combined with sclerotherapy is highly effective in reducing cyst volume. However, the efficacy of this treatment should be assessed in a given cyst eligible to undergo such procedures regarding size and location and not for the remaining cysts. Only a few studies evaluated the efficacy of PCD combined with sclerotherapy to reduce TLV in PCLD patients because up to 90% of these patients have more than 20 hepatic cysts limiting the comparison of treatment efficacy data among the selected studies.[43,44]

The rate of AEs after overall nonsurgical treatment of PCLD was 40–50%. The rate of AEs and SAEs in the somatostatin group was 55% and 4%, respectively. Their main AEs were diarrhea and abdominal pain/discomfort, with a rate of 58% and 40%, respectively, in line with the literature. Somatostatin analogs are currently used to treat acromegaly, gastroenteropancreatic neuroendocrine tumors, upper gastrointestinal hemorrhage, and PCLD.[45] Gastrointestinal side effects occur within hours after the first subcutaneous injection of these medications. In addition, these side effects tend to be dose-dependent and usually subside spontaneously within the first few weeks of treatment.[46] In terms of AEs by other medication, the AE and SAE rates in the somatostatin group were higher than those of the UDCA group (AE 55% *versus* 3%; SAE 4% *versus* 0%, respectively). The rate of AEs and SAEs in the radiological intervention group (74% and 8%, respectively) was higher than that in the medication group. Such AEs included pain or fever immediately after the intervention procedure. Other side effects were not assessed because they were not reported in the selected studies. There were no deaths in the treated groups.

This study systematically analyzed the effect of treatment on the QoL of patients with PCLD. Recently, the QoL has been emphasized as a treatment outcome, and this result is clinically relevant. We observed that nonsurgical treatment, mostly reported in somatostatin group, improved physical function but not mental function, which might be explained by a higher rate of AEs and lower TLV reduction than expected. Therefore, surgical treatments such as hepatic resection and liver transplantation may be useful to improve the QoL of affected patients.

To the best of our knowledge, this study is the first meta-analysis that assessed the efficacy and AEs of overall nonsurgical treatment for PCLD. There are no treatment guidelines for PCLD because the efficacy and safety of current treatment options are limited. Nevertheless, radiological intervention is recommended in cases involving a dominant cyst, and medication should be used in cases involving multiple cysts. Furthermore, developing integrated QoL tools optimized for patients with PCLD is essential. Although pharmacological treatments with UDCA, sirolimus, and sorafenib are being developed, further evidence is required to apply them in clinical practice.

This study has limitations. First, the study did not evaluate surgical treatments, such as hepatic resection and liver transplantation. Combining studies concerning radiological intervention and surgical treatment may be inappropriate from a methodological viewpoint because of the high between-study heterogeneity in pathophysiological characteristics and treatment outcomes. Furthermore, the surgical treatment of PCLD may be contraindicated because of the high rates (20–80%) of perioperative complications (ascites, pleural effusion, bile spillage, and hemorrhage), high rate of recurrence (~30%) after hepatic resection,[47,48] and shortage of donor organs. Therefore, our meta-analysis may be more practical for physicians. Second, the selected studies evaluated different treatment outcomes, including TLV and hTLV, limiting the interpretation of clinical data. Moreover, since most of the individual AEs were reported only in the somatostatin group, it was difficult to conduct a sub-analysis based on AEs of other medication types. Likewise, there were limited data about the efficacy of mTOR inhibitor or UDCA. Further studies are required to resolve such issues. Third, differences in health questionnaires limited the

accurate evaluation of patient QoL. SF-36, the most commonly used and validated questionnaire, was used by seven studies. Therefore, the results should be interpreted with caution.

Conclusion

Nonsurgical treatment was effective and safe for PCLD, but did not improve the QoL in terms of mental health. Radiological intervention directly reduces hepatic cysts, and thus they should be considered for immediate symptom relief in patients with severe symptoms, such as abdominal pain, early satiety, shortness of breath, poor nutritional status, or decreased QoL, whereas medication might be considered for maintenance treatment.

Declarations

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval of Ethical committee and informed consents were waived from the Institutional Review Board (IRB) due to the study design, meta-analysis.

Consent for publication

Not applicable.

Author contributions

Jeong-Ju Yoo: Conceptualization; Formal analysis; Software; Writing – original draft.
Hye In Jo: Conceptualization; Writing – original draft.
Eun-Ae Jung: Methodology; Writing – original draft.
Jae Seung Lee: Methodology; Writing – original draft.
Sang Gyune Kim: Methodology; Writing – original draft.
Young Seok Kim: Methodology; Writing – original draft.
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Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Reporting checklist

The authors have completed the PRISMA reporting checklist.

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Supplemental material

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