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Randomized Controlled Trials Evaluating Patient-Reported Outcomes after Cholecystectomy: A Systematic Review

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There has been growing interest in patient-reported outcomes (PROs) in benign biliary disease. A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation by a clinician.[1] The PRO assessments are increasingly being measured in addition to traditional surgical outcomes.[2-8] Furthermore, PROs may be useful for shared decision-making. In order to effectively counsel patients about expected surgical outcomes, physicians need to be able to easily access information on PROs from high quality trials and be able to judge the methodologic quality of PRO assessment.

Standardized, evidence-based recommendations have been published to guide the reporting of multiple types of studies. For example, the Consolidated Standards of Reporting Trials, or CONSORT Statement, provides guidelines for reporting of randomized controlled trials (RCTs).[9] In 2013, a task force of the International Society of Quality of Life Research (ISOQOL) developed reporting standards for PROs, primarily health-related quality of life (HRQoL), in RCTs. The standards were based on a systematic review of the literature and a survey of the society's membership, who had, on average, 15 years of experience with PRO research.[10,11] The ISOQOL checklist contains 28 items for RCTs evaluating PROs' primary outcomes, such as inclusion of a summary of relevant PRO research in the introduction, and 17 items for RCTs evaluating PROs as secondary outcomes, such as statement of a PRO hypothesis. Previous work has suggested that trials meeting at least two-thirds of the criteria had higher potential to inform clinical practice, and are considered studies of high quality.[12] Building on these minimum standards, authors of the CONSORT statement obtained broader stakeholder input and expanded the scope of the guidelines to include all PROs.[11] The CONSORT-PRO extension was written using the methodologic standards of the Enhancing the QUAlity and Transparency of health Research (EQUATOR) Network.[13] The CONSORT-PRO includes all the same items as the ISOQOL checklist, while the ISOQOL checklist additionally defines tiered standards for reporting trials evaluating PROs as either secondary or primary outcomes.

Research on outcomes for benign biliary disease has traditionally focused on clinical outcomes such as bile duct injury, which is a devastating but rare complication. Laparoscopic cholecystectomy has a low rate of morbidity in terms of surgical site infections, bleeding, and mortality,[14] so using postoperative complications as the primary measure on which to compare therapies may not be useful in guiding patient decision-making.[15] For example, there are continually evolving modifications to cholecystectomy, ie use of mini-laparotomy vs full laparotomy or reduction in number of ports for laparoscopic cholecystectomy. Patient-reported outcomes such as pain, function, or cosmesis often drive adoption of these modifications, but are not always included or are listed as secondary outcomes in trials. Little is known about the quality of reporting of PROs in RCTs evaluating these variants of cholecystectomy.

The objectives of this study were to examine the quality of PRO reporting in RCTs of cholecystectomy for benign biliary disease and to investigate whether the quality of PRO reporting improved over time. We hypothesized that trials that included PROs as primary outcomes would have higher quality reporting.

METHODS

An expert librarian (AT) conducted searches in PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov.

CME questions for this article available at http://jacscme.facs.org

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Abbreviations and Acronyms

CONSORT = Consolidated Standards of Reporting Trials
HRQoL = health-related quality of life
ISOQOL = International Society of Quality of Life Research
PRO = patient-reported outcome
QOL = quality of life
RCT = randomized controlled trial

Preferred reporting items for systematic review (PRISMA) guidelines were followed. Controlled vocabulary (MeSH) and natural language (title, abstract, and other term) describing the concepts of cholecystectomy and PROs were tested for relevancy and used to retrieve articles. An additional sensitivity- and precision-maximizing version of Cochrane-validated search filter for randomized trials in PubMed was also applied. (Search strategy available in eDocument 1). Articles published from January 1, 2005, to July 6, 2017 were searched.

Two reviewers (KMM, LSK) evaluated all RCTs of benign biliary disease reporting PROs using the Rayyan systematic review application for blinding determination of inclusion. Exclusion criteria included trials evaluating analgesic medications, trials evaluating modes of insufflation, comparisons of specialized instruments, trials with less than 50 patients, and pediatric studies.

Two experienced and trained reviewers (KMM, LSK) reviewed all study abstracts for inclusion (Fig. 1). Data extracted included details of the study design, number of participants, demographics, intervention and control, primary and secondary outcomes including PROs, instruments used to assess PROs, and intervention effect on PROs; PRISMA guidelines were followed.

Evaluation of articles

All RCTs were further graded by 2 reviewers (KMM, DVC). Where there was disagreement, consensus was arbitrated by the principal investigating author (LSK). The ISOQOL checklist and the Cochrane Risk of Bias Tool were used to evaluate RCTs.[16] Studies that fulfilled at least 70% of the included elements for ISOQOL (12 of 17 for PRO as secondary outcome, and an additional 11 items for PRO as primary outcome, or a total of 20 of 28 for PRO as primary outcome) were considered high quality studies. Reporting was compared between trials evaluating PROs as a primary and secondary outcome. This cut-off was based on previous work suggesting that trials meeting at least two-thirds of the criteria had higher potential to inform clinical practice.[12] The risk of bias was

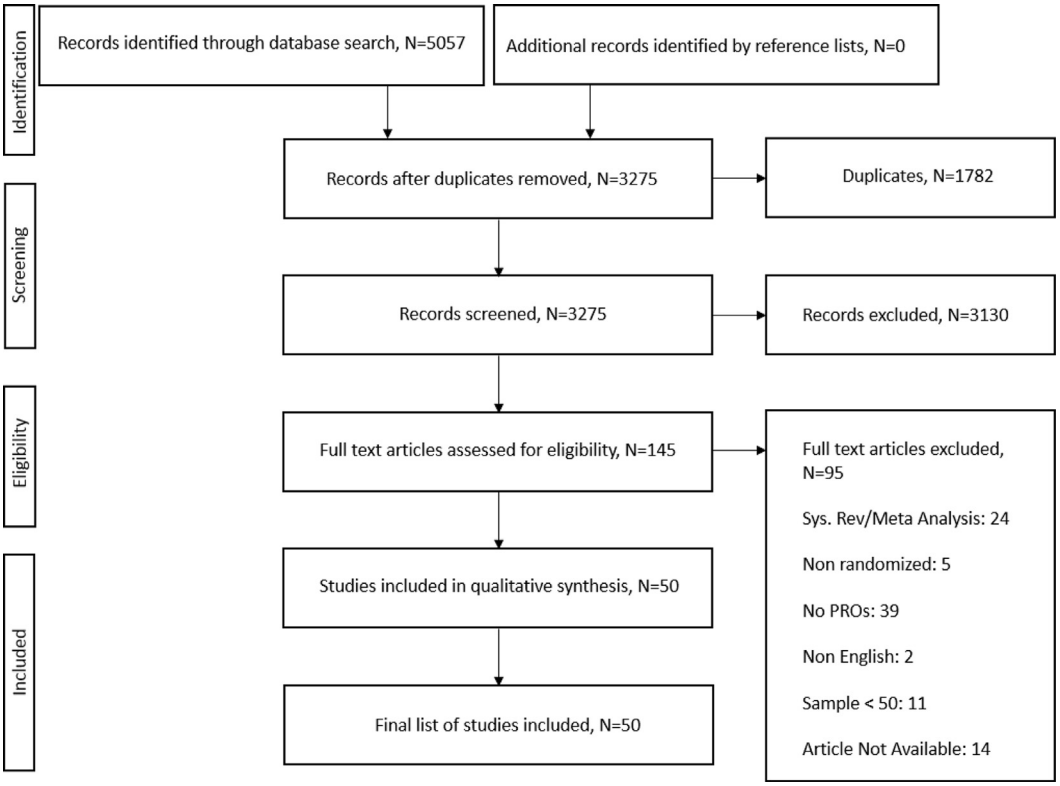

Figure 1. Article identification, screening, eligibility assessment, and inclusion. PRO, patient-reported outcomes.

Table 1. Characteristics of Included Trials (n = 50)

Characteristic	n	%
Publication year		
2005	1	2
2006	1	2
2007	2	4
2008	1	2
2009	0	0
2010	1	2
2011	4	8
2012	4	8
2013	12	24
2014	7	14
2015	5	10
2016	7	14
2017	5	10
Publication country		
North America	9	18
Europe	18	36
Asia	20	40
Intercontinental	3	6
Sample size		
50 to 100	25	50
101 to 150	12	24
151 to 200	6	12
201 to 250	1	2
251 to 300	3	6
>300	3	6
Industry supported	5	10
Diagnoses		
Symptomatic cholelithiasis	23	46
Symptomatic cholelithiasis and polyps	7	14
Symptomatic cholelithiasis and dyskinesia	1	2
Symptomatic cholelithiasis, polyps, and dyskinesia	3	6
Symptomatic cholelithiasis and choledocholithiasis	1	2
Acute or chronic cholecystitis	1	2
All gallstone disease	12	24
Not stated	2	4
PRO Measured, may be ≥1 PRO per trial		
Cosmesis	37	74
Body image	4	8
Health-related quality of life	21	42
Postoperative pain	42	84
Satisfaction	8	16
No. of PROs measured		
1	6	12
2	29	58
3	13	26
4	2	4
Instrument used, may be ≥1 instrument per PRO		
Cosmesis		
Likert scale	28	56
Patient Scar Assessment Questionnaire	4	8
Patient and Observer Scar Assessment Scale	2	4
Modified Hollander Cosmesis Scale	2	4
Body Image and Photo Series Questionnaire	2	4
Body image		
Body Image and Photo Series Questionnaire	4	8
HRQoL		
European Quality of Life Five Dimensions Questionnaire (EuroQoL EQ5D)	2	4
Gastrointestinal Quality of Life Index (GIQLI)	4	8
European Quality of Life Visual Analogue Scale (EQVAS)	1	2
Patient-Reported Outcomes Measurement Information System (PROMIS)	1	2
Linear Analogue Scale Assessment (LASA)	1	2
Surgical Outcomes Measurement System (SOMS) Instrument	2	4
Short Form 36	5	10
Short Form 24	1	2
Short Form12	3	6
Short Form 8	1	2
Likert scale	2	4
Postoperative pain		
Visual Analogue Scale (VAS)	39	78
Likert scale	3	6
Satisfaction		
Patient Satisfaction Score	1	2
Likert scale	7	14
PRO Outcome		
Primary	6	12
Secondary	24	48
Primary and secondary	20	40

PRO, patient-reported outcomes.

then compared between those studies reporting PROs as primary and secondary outcomes.

Statistical analysis

All statistical analyses were completed using Stata 14.0 (Statacorp). Reporting was compared between trials evaluating PROs as a primary outcome and as a primary or secondary outcome using the chi-square test. The ISOQOL checklist score was used in multivariable linear regression analyses to assess for factors associated with higher scores and to compare trials published before and after publication of the ISOQOL reporting standards in 2013. Univariate linear regression analyses were

performed to assess for variables associated with higher normalized ISOQOL checklist scores. Variables assessed on univariate analysis included year of publication, continent of publication, sample size, industry sponsorship, PRO as a primary or secondary outcome, and whether the trial was conducted before or after the ISOQOL checklist publication. Variables chosen for inclusion in the final multivariable linear regression model were those with a value of $p < 0.2$ on univariate linear regression, and included continent of publication, industry sponsorship, PRO outcome as primary or secondary, and risk of bias. All tests of significance were set at a p value of 0.05 and were 2-sided.

RESULTS

Search results

Overall, there were 5,057 studies on initial search (Fig. 1). A total of 1,782 articles were excluded as duplicates, and 3,275 studies were available for abstract review. Of those, 3,130 articles were excluded, leaving 145 full text articles to be assessed for eligibility. Ninety-five of these were excluded as systematic reviews or meta-analyses, nonrandomized studies, not having PROs, sample size less than 50 patients, and lack of article availability. This left 50 trials to be included in the final review and analysis (a complete list of included articles can be found in eTable 1).

Trial characteristics

A majority of included trials were conducted after publication of the ISOQOL standards in 2013 (Table 1). Patient-reported outcomes were most often secondary outcomes. Only 12% of studies included PROs as the sole primary outcome. Most trials were conducted in Asian countries, followed by Europe and North America. Most had sample sizes less than 200 participants, and included patients with nonurgent diagnoses such as symptomatic cholelithiasis, polyps, or biliary dyskinesia. A minority of trials reported industry support.

Across the studies, a variety of PROs were measured, including postoperative pain, cosmesis, body image, patient satisfaction, and HRQoL. Postoperative pain and cosmesis were the most commonly included PROs. Similarly, instruments used in PRO assessments varied widely. The Visual Analogue Scale (VAS) was the most commonly used pain assessment, and a standard Likert scale was often used for cosmetic and satisfaction assessments. Broader instruments were used to measure HRQoL, including the short forms (SF) 8, 12, and 36, and organ system-specific items like the Gastrointestinal Quality of Life Index (GIQLI).

International Society of Quality of Life Research item assessment

A minority of RCTs were considered to include high-quality reporting of PRO assessment as measured by ISOQOL—22% of trials overall and 31% of trials with PROs as primary outcome. Less than half of the 26 trials with PROs as a primary outcome reported on additional details regarding the hypothesis, such as rationale for domain and expected direction of PRO change stated, and the manner in which multiple comparisons had been addressed as explicitly stated (Table 2). In the 24 trials including PROs as secondary outcomes, less than half reported on the PRO hypothesis, rationale for choice of PRO instrument, evidence of PRO validity and reliability cited, identification of post hoc analysis where appropriate, analysis of missing data, limitations of PRO components, and discussion of generalizability issues unique to PROs.

Risk of bias assessment

Using the Cochrane Risk of Bias Tool, a majority of included studies had either a high or unclear risk of bias in all items except for incomplete outcomes data (Table 3). When comparing trials that included PROs as a primary or a secondary outcome, there were no differences in frequency of random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, or incomplete outcomes data, while the trials evaluating PROs as a primary outcome were more likely to include blinding of outcome assessments (Table 4). Comparison of study quality of PRO reporting as judged by the completeness of the ISOQOL checklist with risk of bias revealed a majority of high quality reporting studies to have a low risk of bias, while low quality reporting studies were more likely to have a high or unclear risk of bias (Table 5).

Regression analyses

There was no significant difference between normalized ISOQOL scores in the pre- and post-ISOQOL groups. Linear regression analyses for factors associated with higher normalized ISOQOL scores demonstrated no difference between quality of reporting in trials before and after publication of the ISOQOL guidelines (Table 6). There were likewise no differences in quality of reporting based on publication continent or industry sponsorship. However, those trials reporting on PROs as both primary and secondary outcomes, as well as those trials with a low risk of bias, were associated with higher normalized ISOQOL checklist scores.

DISCUSSION

Despite the increasing number of RCTs on PROs in benign biliary disease over time (Fig. 2), the majority of trials did not

Table 2. International Society of Quality of Life Research Checklist Items and Number of Trials Reporting Each Item

PRO as secondary outcome	n (%), (Total n = 50)	PRO as primary outcome	n (%), (Total n = 26)
Title and abstract			
The PRO should be identified as an outcome in the abstract.	50 (100)	The title of the paper should be explicit as to the RCT including a PRO.	13 (50)
Introduction, background, and objectives			
The PRO hypothesis should be stated and should specify the relevant PRO domains.	15 (30)	The introduction should contain a summary of PRO research relevant to the RCT.	19 (73)
		Additional details regarding the hypothesis should be provided, including rationale for selected domains, expected direction of change, and timepoints for assessment.	10 (38)
Methods, outcomes			
The mode of administration of the PRO tool and methods of collecting data should be described.	43 (86)	A citation for the original development of the PRO instrument should be provided.	13 (50)
The rationale for choice of the PRO instrument used should be provided.	21 (42)	Windows for valid PRO responses should be specified and justified.	26 (100)
Evidence of PRO instrument validity and reliability should be provided or cited.	17 (34)		
The intended data collection schedule should be provided.	48 (96)		
PROs should be identified in the trial protocol and any post hoc analyses should be identified.	13 (26)		
The status of PRO as either a primary or secondary outcome should be stated.	50 (100)		
Methods, sample size		There should be a power/ sample size calculation relevant to the PRO based on clinical rationale.	16 (62)
Methods, statistical analysis			
There should be evidence of appropriate statistical analysis for each PRO hypothesis tested.	47 (94)	The manner in which multiple comparisons have been addressed should be provided.	0 (0)
Statistical methods for dealing with missing data should be explicitly stated, and the extent of the missing data should be stated.	5 (10)		

(Continued)

Table 2. Continued

PRO as secondary outcome	n (%), (Total n = 50)	PRO as primary outcome	n (%), (Total n = 26)
Results, participant flow			
A flow diagram or allocation description and loss to follow-up should be provided for PROs.	44 (88)		
The reasons for missing data should be explained.	28 (56)		
Results, baseline data			
The study patients' characteristics should be described including baseline PRO scores.	44 (88)		
Results, outcomes and estimation		Analysis of PRO data should account for survival differences between groups if relevant.	26 (100)
		Results should be reported for all PRO domains and items in the reference instrument.	23 (88)
		The proportion of patients achieving pre-defined responder definitions should be provided where relevant.	26 (100)
Discussion, limitations			
Limitations of the PRO components of the trial should be explicitly discussed.	18 (36)		
Discussion, generalizability			
Generalizability issues unique to PRO results should be discussed.	20 (40)		
Discussion, interpretation			
The clinical significance of the PRO findings should be discussed.	44 (88)		
The PRO results should be discussed in the context of clinical outcomes.	47 (94)		
Protocol		A copy of the instrument should be included if it has not been published previously.	20 (77)

PRO, patient-reported outcomes; RCT, randomized controlled trial.

adhere to ISOQOL reporting guidelines. Contrary to our hypothesis, trials that included PROs as a primary outcome performed poorly, similar to those with PROs as secondary outcomes. Although a lack of reporting does not necessarily indicate a lack of performance, previous studies have suggested a correlation between poor reporting or RCTs and poor methodologic rigor.[17] The implication of poor reporting is that those studies that report less than two-thirds of ISOQOL items are less likely to influence clinical practice.[12]

Although RCTs are considered the gold standard for comparing health-related interventions, they can be subject to methodologic biases.[17] To ensure that results are valid and reliable, reporting guidelines such as CONSORT and ISOQOL have been disseminated and aid authors in producing rigorous studies that offer credible estimates of treatment effect. The CONSORT-PRO extension is one of several elaborations of the CONSORT statement, and establishes reporting standards for RCTs

Table 3. Trial Assessment Using the Cochrane Risk of Bias Tool

Variable	n	%
Selection bias, random sequence generation		
Low	23	46
High	10	20
Unclear	17	34
Selection bias, allocation concealment		
Low	7	14
High	13	26
Unclear	30	60
Reporting bias, selective reporting		
Low	14	28
High	3	6
Unclear	33	66
Performance bias, blinding of participants and personnel		
Low	19	38
High	24	48
Unclear	7	14
Detection bias, blinding of outcome assessment		
Low	23	46
High	15	30
Unclear	12	24
Attrition bias, incomplete outcome data		
Low	29	58
High	5	10
Unclear	16	32

that include PROs.[18] The ISOQOL checklist is similar to the CONSORT-PRO extension in that it includes elements essential to the adequate reporting of trials incorporating PROs. Although the ISOQOL checklist uses all of the items included in the CONSORT-PRO, it additionally defines tiered standards for reporting in trials evaluating PROs as either secondary or primary outcomes. It includes additional items such as rationale for instrument, citation for original instrument development, and inclusion of PROs in the title if the PRO outcome is primary. Unfortunately, adherence of published literature to these guidelines has minimally improved over time in a wide variety of specialties.[17,19]

The low prevalence of high quality PRO reporting in trials of cholecystectomy identified in this study is consistent with findings in other systematic reviews. Efficace and colleagues[12,20,21] conducted reviews of trials in prostate, gynecologic, and other cancers, and found that few trials meet criteria for high quality PRO reporting, and therefore, studies incorporating PROs often fail to inform clinical practice. Rees and associates[22] had similar findings in a systematic review of PROs in RCTs in colorectal cancer. More recently, a systematic review looking at PROs in the context of postoperative recovery after abdominal surgery found that none of the 35 included studies met the ISOQOL's minimum reporting standards.[23]

However, unlike the results in this study, Efficace and coworkers[12,20,21] found that the quality of PRO reporting has improved over time. This difference in results may be related to the times being compared, as in the Efficace review reporting in trials between 1980 and 2001 was compared to reporting between 2004 and 2012. The CONSORT standards for reporting in RCTs were initially developed in 1996, and clinical interest in PROs and reporting standards for their inclusion in trials has been an even more recent development in the literature. It is, therefore, not surprising to find reporting to be poor in the first time period, and to subsequently improve in the second time period. In this review, dates for included trials are much more recent and span a shorter time, so may not reflect the time required for dissemination and implementation of these reporting standards in RCTs reporting on PROs.

There are multiple reasons for studying PROs in patients undergoing cholecystectomy. First, in a recent prospective cohort study, McLean and coauthors[24] found that PROs were more frequently associated with higher patient satisfaction than traditional clinical outcomes. Several studies have demonstrated that preoperative symptoms and patient characteristics such as preoperative duration of symptoms were associated with postoperative PROs, and concluded that these factors should be used to guide patient selection for cholecystectomy.[25,26] Second, PROs are often more important to patients than traditional outcomes. Parkin and colleagues[27] found that rather than factors such as duration of hospital stay, patients rated long-term QOL and postoperative pain control as

Table 4. Risk of Bias in Randomized Controlled Trials Evaluating Patient-Reported Outcomes as a Primary vs Secondary Outcome

	PRO as primary outcome (n = 26)		PRO as secondary outcome (n = 24)		
Variable	n	%	n	%	p Value
Random sequence generation	13	50	10	42	0.58
Allocation concealment	4	15	3	13	1.00
Selective reporting	9	35	5	21	0.35
Blinding of participants and personnel	13	50	6	25	0.09
Blinding of outcome assessment	16	62	7	29	0.03
Incomplete outcome data	17	65	12	50	0.39

PRO, patient-reported outcomes.

Table 5. Quality of Reporting vs Risk of Bias

Quality of PRO reporting	Low risk of bias (n = 17)	Uncertain risk of bias (n = 20)	High risk of bias (n = 13)	p Value
High quality PRO reporting, n (%) (n = 11)	10 (59)	1 (5)	0 (0)	<0.01
Low quality PRO reporting, n (%) (n = 39)	7 (41)	19 (95)	13 (100)	

PRO, patient-reported outcomes.

most important. Last, given the rapid rise of innovations in cholecystectomy such as single vs multiple port, robotic, and transvaginal cholecystectomy, there is an even greater need to assess PROs. Chow and associates[28] found that the patient perspective on emerging surgical techniques was positive, and represented potential benefits including better cosmesis and improved patient satisfaction. Patient-reported outcomes are clearly emerging as important to both patients and clinicians, both in preoperative assessments and postoperative care, and it is necessary to ensure that future trials work to improve reporting to reinforce confidence in their methodologic rigor, but also to influence clinical practice.

Deficiencies in reporting may be related to challenges unique to PRO research. There is significant heterogeneity in types of PROs and instruments to measure them; this heterogeneity was apparent in the trials included in this review. There may be variability in administration and interpretation by both patients and practitioners. The ideal properties of a PRO instrument include specificity for the disease, conceptual equivalence across languages or cultures, basis on a conceptual framework with supporting evidence, easy for the target population to understand, short, and reproducible.[1] With this in mind, suggestions for future PRO research in cholecystectomy patients might include use of disease-specific PRO instruments and development of such an instrument if one does not currently exist. The only instrument used in the included trials that was specific to gastrointestinal pathology was the Gastrointestinal Quality of Life Index (GIQLI). Furthermore, future studies may wish to limit use of instruments with poor reproducibility such as the Visual Analogue Scale (VAS) or Likert scale, as these scales may not be refined enough to capture subtle differences in outcomes.[29,30]

Improving the reporting of PROs will require multiple strategies. First, patients need to be engaged as stakeholders in clinical research including in selection of outcomes important to them.[31] In order to conduct patient-centered research, PROs need to be incorporated into clinical trial design.[32] Entities such as the Patient Centered Outcomes Research Institute promote the use of PROs in comparative effectiveness research.[33] Therefore, PROs need to be able to be easily collected and incorporated into electronic health records[34,35] and to be integrated into clinical care (ie for shared decision-making).[36] As PROs become a part of routine clinical care, they will become increasingly familiar to clinicians and surgical trainees. Second, engaging clinician and researcher stakeholders can also improve PRO measure implementation.[37] These stakeholders can champion the use of PROs and educate peers about their importance in clinical care, research, and quality improvement.[38] Lastly, journal reviewers and editors need to reinforce the importance of standardized reporting of PRO research. Just as many journals require following guidelines for randomized trials and systematic reviews, journals should require adherence to guidelines or checklists specific to PROs such as ISOQOL. In order to make this a reality, experts in PRO research should be encouraged to be involved in the peer-review process, and make themselves available to journals as reviewers for such publications.

There needs to be harmonization of PROs and patient-reported outcome measures (PROMs) across societies and regulatory bodies to ensure valid comparisons.

Measurement of PROs is of increasing interest to many surgical groups, such the American College of Surgeons, which may lead the way in ensuring their meaningful use.[31] Incorporation of PROs into the National Surgical

Table 6. Multivariable Linear Regression Analysis, Variables Associated with Higher Normalized International Society of Quality of Life Research Checklist Scores

Variable	Coefficient	p Value	95% CI
Publication continent			
North America	—	—	—
Europe	10.42	0.085	−1.49–22.33
Asia	10.76	0.063	−0.60–22.13
Multiple	8.63	0.317	−8.60–25.86
Industry sponsorship	8.82	0.197	−4.77–22.42
PRO Outcome			
Secondary	—	—	—
Primary	9.64	0.090	−1.58–20.87
Both	8.64	0.035	0.62–16.66
Risk of bias			
Low	—	—	—
Unclear	−12.55	0.019	−22.90 to −2.19
High	−12.75	0.006	−21.55 to −3.95

PRO, patient-reported outcomes.

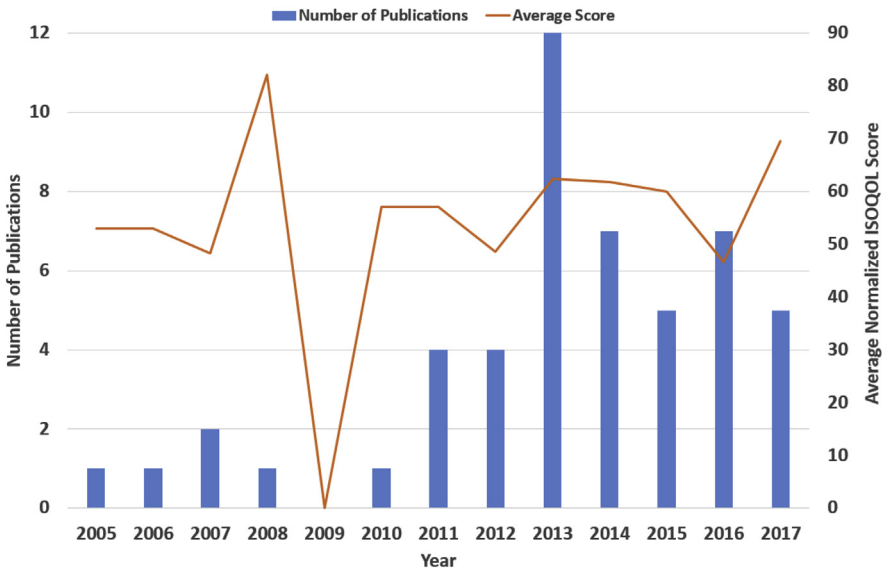

Figure 2. Annual publication of randomized controlled trials evaluating patient-reported outcomes in gallstone disease and average International Society of Quality of Life Research (ISOQOL) checklist scores.

Quality Improvement Program may provide insights into how PROs can complement clinical outcomes to provide actionable data on which to improve the quality of surgical care. Patient-reported outcomes have also been of interest to regulatory bodies such as the Food and Drug Administration for research involving new drugs and devices.[39] The International Society for Pharmacoeconomics and Outcomes Research has published good research practice recommendations for electronic PRO capture.[40] Additionally, PROs are already being used to compare provider performance, with significant implications related to the choice of measure.[41] Ultimately, it is important for physician advocacy groups and health services researchers to work together to develop and validate patient-reported outcome measures for specific disease states and to standardize the methodology for their development and reporting.

There are several limitations to this study. First, there is subjectivity in grading trials using ISOQOL checklists. However, all articles were scored by 2 trained reviewers, and disagreements were settled by a third reviewer to ensure accuracy. Second, dates of publication of the ISOQOL standards and CONSORT PRO extension are not equivalent to dates of effective dissemination and implementation, and there is no set time frame for reporting guidelines to make it into widespread practice. Finally, in this study we have used date of publication of the included studies, as opposed to study inception or acceptance for publication date. We chose this date because in some trials, not all of these 3 dates are given or are readily accessible; however, we recognize that this may inflate the measurement of time elapsed between ISOQOL checklist publication and that of included trials.

CONCLUSIONS

Despite an increase in RCTs in the last decade, the quality of the evidence base for PROs after surgical management of benign biliary disease remains poor. Trials that include PROs in benign biliary disease frequently deviate from established reporting guidelines, and a majority had either an unclear or high risk of bias. Incorporation of PROs into physician practice is necessary for the delivery of high quality, patient-centered care in our evolving health care system. In order for practitioners to effectively use literature on PROs, better quality publications are needed, with transparent reporting, adherence to reporting standards, and low risk of bias. A concerted effort is needed to improve the quality of reporting in these publications. This should include education of researchers in rigorous research methodology, guidelines for reporting results of different types of studies, and resources available for guidance in PRO research. Furthermore, journals and editors should strictly enforce standards for study conduct, reporting, and quality before granting publication, particularly in newer fields such as trials evaluating PROs.

Author Contributions

Study conception and design: Mueck, Cherla, Taylor, Ko, Liang, Kao

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Analysis and interpretation of data: Mueck, Cherla, Taylor, Ko, Liang, Kao
Drafting of manuscript: Mueck, Cherla, Taylor, Ko, Liang, Kao
Critical revision: Mueck, Cherla, Taylor, Ko, Liang, Kao

REFERENCES

1. Deshpande PR, Rajan S, Sudeepthi BL, Nazir A. Patient-reported outcomes: a new era in clinical research. Perspect Clin Res 2011;2:137–144.
2. Carraro A, El Mazloum D, Bihl F. Health-related quality of life outcomes after cholecystectomy. World J Gastroenterol 2011;17:4945–4951.
3. Wybourn CA, Kitsis RM, Baker TA, et al. Laparoscopic cholecystectomy for biliary dyskinesia: which patients have long term benefit? Surgery 2013;154:761–767.
4. Weinert CR, Arnett D, Jacobs D, Kane RL. Relationship between persistence of abdominal symptoms and successful outcome after cholecystectomy. Arch Intern Med 2000;160:989–995.
5. Wanjura V, Lundström P, Österberg J, et al. Gastrointestinal quality-of-life after cholecystectomy: indication predicts gastrointestinal symptoms and abdominal pain. World J Surg 2014;38:3075–3081.
6. Russo MW, Wei JT, Thiny MT, et al. Digestive and liver diseases statistics, 2004. Gastroenterology 2004;126:1448–1453.
7. Brazzelli M, Cruickshank M, Kilonzo M, et al. Systematic review of the clinical and cost effectiveness of cholecystectomy versus observation/conservative management for uncomplicated symptomatic gallstones or cholecystitis. Health Technol Assess 2014;18:637–647.
8. Berger MY, Olde Hartman TC, Bohnen AM. Abdominal symptoms: do they disappear after cholecystectomy? A systematic literature review. Surg Endosc Other Interv Tech 2003;17:1723–1728.
9. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT Statement. JAMA 1996;276:637–639.
10. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res 2013;22:1889–1905.
11. Brundage M, Blazeby J, Revicki D, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res 2013;22:1161–1175.
12. Efficace F, Feuerstein M, Fayers P, et al. Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. Eur Urol 2014;66:416–427.
13. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7[2]:e1000217.
14. Burney RE, Jones KR. Ambulatory and admitted laparoscopic cholecystectomy patients have comparable outcomes but different functional health status. Surg Endosc 2002;16:921–926.
15. Wanjura V, Sandblom G. How do quality-of-life and gastrointestinal symptoms differ between post-cholecystectomy patients and the background population? World J Surg 2016;40:81–88.
16. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
17. Huwiler-Muntener K, Juni P, Junker C, Egger M. Quality of reporting of randomized trials as a measure of methodologic quality. JAMA 2002;287:2801–2804.
18. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO Extension. JAMA 2013;309:814–822.
19. Hopewell S, Dutton S, Yu LM, et al. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 2010;340:c723.
20. Efficace F, Fayers P, Pusic A, et al. Quality of Patient-Reported Outcome (PRO) reporting across cancer randomized controlled trials according to the CONSORT PRO Extension: a pooled analysis of 557 trials. Cancer 2015;121:3335–3342.
21. Efficace F, Jacobs M, Pusic A, et al. Patient-reported outcomes in randomised controlled trials of gynaecological cancers: investigating methodological quality and impact on clinical decision-making. Eur J Cancer 2014;50:1925–1941.
22. Rees JR, Whale K, Fish D, et al. Patient-reported outcomes in randomised controlled trials of colorectal cancer: an analysis determining the availability of robust data to inform clinical decision-making. J Cancer Res Clin Oncol 2015;141:2181–2192.
23. Fiore JF, Figueiredo S, Balvardi S, et al. How do we value postoperative recovery? A systematic review of the measurement properties of patient-reported outcomes after abdominal surgery. Ann Surg 2017 Aug 1 [Epub ahead of print].
24. McLean KA, Sheng Z, O'Neill S, et al. The influence of clinical and patient-reported outcomes on post-surgery satisfaction in cholecystectomy patients. World J Surg 2017;41:1752–1761.
25. Lamberts MP, Oudsten BLD, Gerritsen JJGM, et al. Prospective multicentre cohort study of patient-reported outcomes after cholecystectomy for uncomplicated symptomatic cholecystolithiasis. Br J Surg 2015;102:1402–1409.
26. Wennmacker S, Lamberts M, Gerritsen J, et al. Consistency of patient-reported outcomes after cholecystectomy and their implications on current surgical practice: a prospective multicenter cohort study. Surg Endosc 2017;31:215–224.
27. Parkin E, Stott M, Brockbank J, et al. Patient-reported outcomes for acute gallstone pathology. World J Surg 2017;41:1234–1238.
28. Chow A, Purkayastha S, Dosanjh D, et al. Patient reported outcomes and their importance in the development of novel surgical techniques. Surg Innov 2012;19:327–334.
29. Bijur PE, Silver W, Gallagher J. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med 2001;8:1153–1157.
30. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth 2008;101:17–24.
31. Concannon TW, Fuster M, Saunders T, et al. A systematic review of stakeholder engagement in comparative effectiveness and patient-centered outcomes research. J Gen Intern Med 2014;29:1692–1701.
32. Snyder CF, Jensen RE, Segal JB, Wu AW. Patient-reported outcomes (PROs): putting the patient perspective in patient-centered outcomes research. Med Care 2013;51:S73–S79.

33. Jensen RE, Snyder CF, Basch E, et al. All together now: findings from a PCORI workshop to align patient-reported outcomes in the electronic health record. J Comp Eff Res 2016; 5:561−567.

34. Ahmed S, Ware P, Gardner W, et al. Montreal Accord on patient-reported outcomes use series- Paper 8: patient-reported outcomes in electronic health records can inform clinical and policy decisions. J Clin Epidemiol 2017;89:160−167.

35. Jensen RE, Rothrock NE, DeWitt EM, et al. The role of technical advances in the adoption and integration of patient-reported outcomes in clinical care. Med Care 2015;53:153−159.

36. Noonan VK, Lyddiatt A, Ware P, et al. Montreal Accord on patient-reported outcomes use series-paper 3: patient-reported outcomes can facilitate shared-decision making and guide self-management. J Clin Epidemiol 2017;89:125−135.

37. Kwan BM, Sills MR, Graham D, et al. Stakeholder engagement in a Patient-Reported Outcomes (PRO) Measure Implementation: a report from the SAFTINet Practice Based Research Network (PBRN). J Am Board Fam Med 2016;29:102−115.

38. Ovretveit J, Zubkoff L, Nelson EC, et al. Using patient-reported outcome measurement to improve patient care. Int J Qual Health Care 2017:1−6.

39. Acquadro C, Berzon R, Dubois D, et al. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003;6: 522−531.

40. Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. Value Health 2009;12: 419−429.

41. Neuburger J, Hutchings A, Van der Meulen J, Black N. Using patient-reported outcomes (PROs) to compare the providers of surgery: does the choice of measure matter? Med Care 2013; 51:517−523.

eDocument 1.

Search Strategy, July 6, 2017

(((((((((("Cholecystectomy, Laparoscopic"[Mesh] OR "Cholecystectomy"[Mesh] OR "Postcholecystectomy Syndrome"[Mesh] OR "Cholecystectomy, Laparoscopic/adverse effects"[Mesh] OR "Cholecystectomy, Laparoscopic/rehabilitation"[Mesh] OR "Gallbladder Diseases/surgery"[Mesh]) OR ("needlescopic cholecystectomy"[tiab] OR "transvaginal cholecystectomy"[tiab] OR natch[tiab] OR "SPLC"[tiab] OR "CLC"[tiab] OR Postcholecystectomy[tiab] OR "gallstone surgery"[tiab] OR Cholecystectom* [tiab] OR "CHE"[tiab] OR "NC"[tiab] OR "TVC"[tiab] OR "needlescopic cholecystectomy"[tiab] OR "transvaginal cholecystectomy"[tiab] OR "lap chole"[tiab]) OR (Cholecystectom*[ot] OR Postcholecystectomy[ot] OR "lap chole"[ot] OR "transvaginal cholecystectomy"[ot]))))) OR (((((("Surgical Procedures, Operative"[Mesh] OR "Specialties, Surgical"[Mesh] OR "surgery" [Subheading] OR "Minimally Invasive Surgical Procedures"[Mesh] OR "Natural Orifice Endoscopic Surgery"[Mesh]) OR (surgery[tiab] OR surgeries[tiab] OR NOTES[tiab] OR surgical[tiab] OR "Natural Orifice Endoscopic Surgery"[tiab]) OR (surgery[ot] OR surgeries [ot] OR surgical[ot] OR "Natural Orifice Endoscopic Surgery"[ot] OR NOTES[ot]))))) AND ((("Gallstones" [Mesh] OR "Gallbladder"[Mesh]) OR (Gallstone*[tiab] OR Gall?Stones[tiab] OR "Biliary Calculi"[tiab] OR gallbladder[tiab] OR Gall?Stone*[tiab] OR "Common Bile Duct Calculi"[tiab] OR "Common Bile Duct Gallstone*"[tiab]) OR (Gallstone* [ot] OR Gall?Stones [ot] OR gallbladder[ot] OR Gall?Stone* [ot] OR "Common Bile Duct Calculi" [ot] OR "Common Bile Duct Gallstone*"[ot]))))))) AND ((("Outcome and Process Assessment (Health Care)"[Mesh] OR "Outcome Assessment (Health Care)"[Mesh:NoExp] OR "Treatment Outcome"[Mesh:NoExp] OR "Early Termination of Clinical Trials"[Mesh] OR "Treatment Failure"[Mesh] OR "Pain Measurement"[Mesh] OR "Quality of Life" [Mesh] OR "Body Image"[Mesh] OR "Return to Work"[Mesh] OR "Patient Satisfaction"[Mesh] OR "Cicatrix"[Mesh]) OR (cosmesis[tiab] OR "post operative pain scores"[tiab] OR "post operative pain score" [tiab] OR "body image"[tiab] OR Cicatri*[tiab] OR scars[tiab] OR scarring[tiab] OR "patient reported outcomes"[tiab] OR "patient reported outcome"[tiab] OR "PRO"[tiab] OR "body schema"[tiab] OR "back to work"[tiab] OR "return to work"[tiab] OR "Outcome Assessments"[tiab] OR "Outcome Assessment"[tiab] OR "Outcomes Research"[tiab] OR "Outcome Study" [tiab] OR "Outcome Studies"[tiab] OR "Outcome Measures"[tiab] OR "Outcome Measure"[tiab] OR " Patient Relevant Outcomes"[tiab] OR "Patient Relevant Outcome"[tiab] OR "patient satisfaction"[tiab] OR "Treatment Effectiveness"[tiab] OR "Treatment Efficacy"[tiab] OR "Rehabilitation Outcomes"[tiab] OR "Rehabilitation Outcome"[tiab] OR "Pain assessments"[tiab] OR "Pain assessment"[tiab] OR "Pain measurements"[tiab] OR "Pain measurement"[tiab] OR "quality of life"[tiab] OR "pain scores"[tiab] OR "pain score" [tiab]) OR ("pain scores"[ot] OR "pain score"[ot] OR "return to work"[ot] OR "patient reported outcomes"[ot] OR "body image"[ot] OR scars[ot] OR scarring[ot] OR "Outcome Measure"[ot] OR "Outcome Measures"[ot] OR "Patient Relevant Outcome"[ot] OR "Rehabilitation Outcome"[ot] OR "Rehabilitation Outcomes"[ot] OR "Pain assessment"[ot] OR "Pain assessments"[ot] OR "Pain measurement"[ot] OR "Pain measurements"[ot] OR "quality of life"[ot] OR cosmesis[ot] OR "patient reported outcomes"[ot] OR "patient reported outcome"[ot] OR "PRO"[ot] OR "body schema"[ot] OR "Outcome Assessment"[ot] OR Cicatri*[ot] OR "Outcomes Research"[ot] OR "patient satisfaction"[ot] OR "Outcome Study"[ot] OR "Outcome Studies"[ot]))))) AND (((((randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial [ti] NOT (animals[mh] NOT humans [mh]))))))))

eTable 1. Summary Table of Included Trials

First author	Year	n	Intervention	Primary PRO	Secondary PRO	Reporting quality	Risk of bias
Hajong[1]	2016	64	Single incision lap chole	–	Postoperative pain, Cosmesis	Poor	Unclear
Borle[2]	2015	60	Single incision Lap chole	Cosmesis	Body Image	Poor	High
Deveci[3]	2013	100	Single incision Lap chole	–	Postoperative pain, Cosmesis	Poor	High
Harju[4]	2007	157	Mini-laparotomy Chole	Health-related QOL	–	Poor	High
Ye[5]	2015	200	Single incision Lap chole	–	Postoperative pain, Cosmesis	Poor	High
Lurje[6]	2015	110	Single incision Lap chole	Cosmesis	Postoperative pain, Body Image, Health-related QOL	Good	Low
Bingener[7]	2015	110	Single incision Lap chole	Postoperative pain	Health-related QOL	Good	Low
Rosenmueller[8]	2013	355	Mini-laparotomy Chole	Postoperative pain	Health-related QOL	Good	Low
Alhashemi[9]	2016	115	Mini-port Lap chole	–	Postoperative pain, Cosmesis, Health-related QOL	Good	Low
Phillips[10]	2012	200	Single incision Lap chole	–	Postoperative pain, Cosmesis, Health-related QOL	Poor	Unclear
Aprea[11]	2011	50	Single incision Lap chole	–	Postoperative pain, Satisfaction	Poor	Unclear
Zheng[12]	2012	58	Single incision Lap chole	–	Postoperative pain, Satisfaction	Poor	Unclear
Keus[13]	2008	257	Mini-laparotomy Chole	Health-related QOL	Body image, Cosmesis	Good	Low
Gupta[14]	2005	80	Mini-port Lap chole	–	Postoperative pain, Cosmesis	Poor	High
Vagenas[15]	2006	88	Mini-laparotomy Chole	–	Cosmesis	Poor	High
Arezzo[16]	2016	600	Single incision lap chole	–	Postoperative pain, Cosmesis, Health-related QOL	Poor	Low
Ostlie[17]	2013	60	Single incision lap chole	Cosmesis	–	Poor	Unclear
Brown[18]	2013	84	Single incision lap chole	Health-related QOL	Postoperative pain	Poor	Unclear
Borchert[19]	2014	97	Transvaginal Lap Chole	Postoperative pain	Health-related QOL	Good	Low
Lai[20]	2011	51	Single incision Lap chole	Postoperative pain	Cosmesis	Poor	Low
Aspinen[21]	2014	60	Mini-laparotomy Chole	Postoperative pain	Health-related QOL, Cosmesis	Poor	Unclear
Liu[22]	2016	245	Three port Lap chole	–	Postoperative pain, Cosmesis, Health-related QOL	Poor	High
Zhang[23]	2014	75	Occult scar incision lap chole	–	Postoperative pain, Cosmesis	Poor	Unclear
Bignell[24]	2013	80	Mini-port lap chole	Postoperative pain	Cosmesis	Good	Unclear
Ellatif[25]	2013	269	Single incision lap chole	Health-related QOL	Postoperative pain, Cosmesis	Good	Low
Khorgami[26]	2014	90	Single incision lap chole	–	Postoperative pain, Cosmesis	Poor	Low
Bucher[27]	2011	150	Single incision Lap chole	Cosmesis	Postoperative pain, Satisfaction, Health-related QOL	Poor	High
Jorgensen[28]	2014	117	Single incision Lap chole	Postoperative pain	Cosmesis	Poor	Low
Lee[29]	2010	70	Single incision Lap chole	Postoperative pain	Cosmesis	Poor	Unclear
Saad[30]	2013	105	Single incision lap chole	Postoperative pain	Health-related QOL, Satisfaction, Cosmesis	Poor	Low
Pietrabissa[31]	2016	60	Single incision robotic chole	Postoperative pain	Cosmesis	Poor	Low

(Continued)

eTable 1. Continued

First author	Year	n	Intervention	Primary PRO	Secondary PRO	Reporting quality	Risk of bias
Marks[32]	2013	200	Single incision lap chole	—	Postoperative pain, Cosmesis, Health-related QOL	Poor	Unclear
Partelli[33]	2016	59	Single incision lap chole	Postoperative pain	Cosmesis, Satisfaction	Poor	Low
Zapf[34]	2013	100	Single incision lap chole	Postoperative pain	Health-related QOL	Poor	Unclear
Leung[35]	2011	79	Single incision lap chole	—	Postoperative pain, Health-related QOL	Poor	Unclear
Pan[36]	2013	102	Single incision lap chole	Postoperative pain	Cosmesis	Poor	Unclear
Villalonga[37]	2012	140	Single incision lap chole	—	Postoperative pain, Satisfaction, Cosmesis	Poor	High
Sasaki[38]	2012	54	Single incision lap chole	—	Postoperative pain, Cosmesis	Poor	High
Harju[39]	2013	157	Mini-laparotomy Chole	Postoperative pain	Cosmesis, Health-related QOL	Poor	Unclear
Kumar[40]	2007	75	Three port lap chole	Postoperative pain	Satisfaction, Cosmesis	Poor	Unclear
Hu[41]	2013	60	Needlescopic Lap Chole	—	Postoperative pain, Satisfaction	Poor	Unclear
He[42]	2015	300	Single incision lap chole	—	Postoperative pain, Cosmesis	Poor	Unclear
Sreenivas[43]	2014	116	Mini-port lap chole	—	Postoperative pain, Cosmesis	Poor	Unclear
Goel[44]	2016	60	Single incision lap chole	—	Postoperative pain, Cosmesis	Poor	High
Rosenmuller[45]	2017	355	Mini-laparotomy Chole	—	Health-related QOL	Poor	High
Aspinen[46]	2017	109	Mini-laparotomy Chole	Health-related QOL	—	Good	Low
Omar[47]	2017	187	Single incision lap chole	Postoperative pain	Cosmesis	Poor	Unclear
Justo-Janeiro[48]	2014	55	One and Two port Lap Chole	Postoperative pain	—	Poor	High
Kudsi[49]	2017	136	Single incision robotic chole	—	Health-related QOL, Cosmesis, Body Image	Good	Low
Xu[50]	2017	105	Single Incision Lap Chole and Lower Abdominal Lap Chole	—	Postoperative pain, Cosmesis	Good	Low

Chole, cholecystectomy; Lap, laparoscopic; PRO, patient-reported outcomes; QOL, quality of life.

SUPPLEMENTARY REFERENCES

1. Hajong R, Hajong D, Natung T, et al. A comparative study of single incision versus conventional four ports laparoscopic cholecystectomy. J Clin Diagn Res 2016;10:4–7.
2. Borle FR, Mehra B, Singh A. Comparison of cosmetic outcome between single-incision laparoscopic cholecystectomy and conventional laparoscopic cholecystectomy in rural Indian population: a randomized clinical trial. Indian J Surg 2015;77:3–6.
3. Deveci U, Barbaros U, Kapakli MS, et al. The comparison of single incision laparoscopic cholecystectomy and three port laparoscopic cholecystectomy: prospective randomized study. J Korean Surg Soc 2013;85:275–282.
4. Harju J, Pääkkönen M, Eskelinen M. Comparison of the quality of life after minilaparotomy cholecystectomy versus laparoscopic cholecystectomy: a prospective randomized study. Isr Med Assoc J 2007;9:147–148.
5. Ye G, Qin Y, Xu S, et al. Comparison of transumbilical single-port laparoscopic cholecystectomy and fourth-port laparoscopic cholecystectomy. Int J Clin Exp Med 2015;8:7746–7753.
6. Lurje G, Raptis DA, Steinemann DC, et al. Cosmesis and body image in patients undergoing single-port versus conventional laparoscopic cholecystectomy: a multicenter double-blinded randomized controlled trial (SPOCC-trial). Ann Surg 2015;262:728–735.
7. Bingener J, Skaran P, McConico A, et al. A double-blinded randomized trial to compare the effectiveness of minimally invasive procedures using patient-reported outcomes. J Am Coll Surg 2015;221:111–121.
8. Rosenmuller MH, Ornberg MT, Myrnas T, et al. Expertise-based randomized clinical trial of laparoscopic versus small-incision open cholecystectomy. Br J Surg 2013;100:886–894.
9. Alhashemi M, Almahroos M, Fiore JF, et al. Impact of mini-port laparoscopic cholecystectomy versus standard port laparoscopic cholecystectomy on recovery of physical activity: a randomized trial. Surg Endosc 2017;31:2299–2309.
10. Phillips MS, Marks JM, Roberts K, et al. Intermediate results of a prospective randomized controlled trial of traditional four-port laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy. Surg Endosc 2012;26:1296–1303.
11. Aprea G, Bottazzi EC, Guida F, et al. Laparoendoscopic single site (LESS) versus classic video-laparoscopic cholecystectomy: a randomized prospective study. J Surg Res 2011;166:e109–e112.
12. Zheng M, Qin M, Zhao H. Laparoendoscopic single-site cholecystectomy: a randomized controlled study. Minim Invasive Ther Allied Technol 2012;21:113–117.
13. Keus F, Vries JD, Gooszen HG, Laarhoven CJHM. Laparoscopic versus small-incision cholecystectomy: health status in a blind randomised trial. Surg Endosc 2008;22:1649–1659.
14. Gupta A, Shrivastava U, Kumar P, Burman D. Minilaparoscopic versus laparoscopic cholecystectomy: a randomised controlled trial. Trop Gastroenterol 2005;26:149–151.
15. Vagenas K, Spyrakopoulos P, Karanikolas M, et al. Mini-laparotomy cholecystectomy versus laparoscopic cholecystectomy: which way to go? Surg Laparosc Endosc Percutan Tech 2006;16:321–324.
16. Arezzo A, Passera R, Bullano A, et al. Multi-port versus single-port cholecystectomy: results of a multi- centre, randomised controlled trial (MUSIC trial). Surg Endosc 2017;31:2872–2880.
17. Ostlie DJ, Sharp NE, Thomas P, et al. Patient scar assessment after single-incision versus four-port laparoscopic cholecystectomy: long-term follow-up from a prospective randomized trial. J Laparoendosc Adv Surg Tech A 2013;23:553–555.
18. Brown KM, Moore BT, Sorensen GB, et al. Patient-reported outcomes after single-incision versus traditional laparoscopic cholecystectomy: a randomized prospective trial. Surg Endosc 2013;27:3108–3115.
19. Borchert DH, Federlein M, Fritze-Buttner F, et al. Postoperative pain after transvaginal cholecystectomy: single-center, double-blind, randomized controlled trial. Surg Endosc 2014;28:1886–1894.
20. Lai ECH, Yang GPC, Tang CN, et al. Prospective randomized comparative study of single incision laparoscopic cholecystectomy versus conventional four-port laparoscopic cholecystectomy. Am J Surg 2011;202:254–258.
21. Aspinen S, Harju J, Juvonen P, et al. A prospective, randomized study comparing minilaparotomy and laparoscopic cholecystectomy as a day-surgery procedure: 5-year outcome. Surg Endosc 2014;28:827–832.
22. Liu E, Li Z, Wang N, et al. A prospective, randomized, controlled trial of three-port laparoscopic cholecystectomy versus conventional four-port laparoscopic cholecystectomy: is the fourth port really required? Int J Clin Exp Med 2016;9:3055–3061.
23. Zhang L, Sah B, Ma J, et al. A prospective, randomized, controlled, trial comparing occult- scar incision laparoscopic cholecystectomy and classic three-port laparoscopic cholecystectomy. Surg Endosc 2014;28:1131–1135.
24. Bignell M, Lewis MPN, Cheong ECK, Rhodes M. A prospective, randomized, single-blind trial of 5-mm versus 3-mm ports for laparoscopic cholecystectomy: is smaller better? Surg Endosc 2013;27:3616–3621.
25. Abd Ellatif ME, Askar WA, Abbas AE, et al. Quality-of-life measures after single-access versus conventional laparoscopic cholecystectomy: a prospective randomized study. Surg Endosc 2013;27:1896–1906.
26. Khorgami Z, Shoar S, Anbara T, et al. A randomized clinical trial comparing 4-port, 3-port, and single-incision laparoscopic cholecystectomy. J Invest Surg 2014;27:147–154.
27. Bucher P, Pugin F, Buchs NC, et al. Randomized clinical trial of laparoendoscopic single-site versus conventional laparoscopic cholecystectomy. Br J Surg 2011;98:1695–1702.
28. Jørgensen LN, Rosenberg J, Al-Tayar H, et al. Randomized clinical trial of single- versus multi-incision laparoscopic cholecystectomy. Br J Surg 2014;101:347–355.
29. Lee PC, Lo C, Lai PS, et al. Randomized clinical trial of single-incision laparoscopic cholecystectomy versus minilaparoscopic cholecystectomy. Br J Surg 2010;97:1007–1012.
30. Saad S, Strassel V, Sauerland S. Randomized clinical trial of single-port, minilaparoscopic and conventional laparoscopic cholecystectomy. Br J Surg 2013;100:339–349.
31. Pietrabissa A, Pugliese L, Vinci A, et al. Short-term outcomes of single-site robotic cholecystectomy versus four-port laparoscopic cholecystectomy: a prospective, randomized, double-blind trial. Surg Endosc 2016;30:3089–3097.

32. Marks JM, Phillips MS, Tacchino R, et al. Single-incision laparoscopic cholecystectomy is associated with improved cosmesis scoring at the cost of significantly higher hernia rates: 1-year results of a prospective randomized, multicenter, single-blinded trial of traditional multiport laparoscopic cholecystectomy vs single-incision laparoscopic cholecystectomy. J Am Coll Surg 2013;216:1037–1047.
33. Partelli S, Barugola G, Sartori A, et al. Single-incision laparoscopic cholecystectomy versus traditional laparoscopic cholecystectomy performed by a single surgeon: findings of a randomized trial. Surg Today 2016;46:313–318.
34. Zapf M, Yetasook A, Leung D, et al. Single-incision results in similar pain and quality of life scores compared with multi-incision laparoscopic cholecystectomy: a blinded prospective randomized trial of 100 patients. Surgery 1995;154:662–671.
35. Leung D, Yetasook AK, Carbray J, et al. Single-incision surgery has higher cost with equivalent pain and quality-of-life scores compared with multiple-incision laparoscopic cholecystectomy: a prospective randomized blinded comparison. J Am Coll Surg 2012;215:702–708.
36. Pan M, Jiang Z, Cheng Y, et al. Single-incision vs three-port laparoscopic cholecystectomy: prospective randomized study. World J Gastroenterol 2013;19:394–398.
37. Vilallonga R, Barbaros U, Sümer A, et al. Single-port transumbilical laparoscopic cholecystectomy: a prospective randomised comparison of clinical results of 140 cases. J Minim Access Surg 2012;8:74–78.
38. Sasaki A, Ogawa M, Tono C, et al. Single-port versus multiport laparoscopic cholecystectomy: a prospective randomized clinical trial. Surg Laparosc Endosc Percutan Tech 2012;22:396–399.
39. Harju J, Aspinen S, Juvonen P, et al. Ten-year outcome after minilaparotomy versus laparoscopic cholecystectomy: a prospective randomised trial. Surg Endosc 2013;27:2512–2516.
40. Kumar M, Agrawal CS, Gupta RK. Three-port versus standard four-port laparoscopic cholecystectomy: a randomized controlled clinical trial in a community-based teaching hospital in eastern Nepal. JSLS 2007;11:358–362.
41. Hu H, Xu AA, Huang A. Towards scarless surgery: a novel laparoscopic cholecystectomy by using 2mm needle-shape instruments without trocar. J Laparoendosc Adv Surg Tech A 2013;23:698–701.
42. He G, Jiang Z, Cheng Y, et al. Tripartite comparison of single-incision and conventional laparoscopy in cholecystectomy: a multicenter trial. World J Gastrointest Endosc 2015;7:540–546.
43. Sreenivas S, Mohil RS, Singh GJ, et al. Two-port mini laparoscopic cholecystectomy compared to standard four-port laparoscopic cholecystectomy. J Minim Access Surg 2014;10:190–196.
44. Goel A, Chaubey P, Gupta A, et al. Comparative study of single-incision laparoscopic cholecystectomy with four-port conventional laparoscopic cholecystectomy: a single-center experience. World J Lap Surg 2016;9:9–12.
45. Rosenmuller MH, Nilsson E, Lindberg F, et al. Costs and quality of life of small-incision open cholecystectomy and laparoscopic cholecystectomy- an expertise-based randomised controlled trial. BMC Gastroenterol 2017;17:1–7.
46. Aspinen S, Karkkainen J, Harju J, et al. Improvement in the quality of life following cholecystectomy: a randomized multicenter study of health status (RAND-36) in patients with laparoscopic cholecystectomy versus minilaparotomy cholecystectomy. Qual Life Res 2017;26:665–671.
47. Omar MA, Redwan AA, Mahmoud AG. Single-incision versus 3-port laparoscopic cholecystectomy in symptomatic gallstones: a prospective randomized study. Surgery 2017;162:96–103.
48. Justo-Janeiro JM, Vincent GT, Vazquez de Lara F, et al. One, two, or three ports in laparoscopic cholecystectomy? Int Surg 2014;99:739–744.
49. Kudsi OY, Castellanos A, Kaza S, et al. Cosmesis, patient satisfaction, and quality of life after da Vinci Single-Site cholecystectomy and multiport laparoscopic cholecystectomy: short-term results from a prospective, multicenter, randomized, controlled trial. Surg Endosc 2017;31:3242–3250.
50. Xu L, Tan H, Liu L, et al. A randomized controlled trial for evaluation of lower abdominal laparoscopic cholecystectomy. Minim Invasive Ther Allied Technol 2017:1–8.