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The Rolling Stones: A Systematic Review and Meta-Analysis of the Management of Gallstone Ileus

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Rezumat

Un review sistematic și o meta-analiză privind managementul ileusului biliar

Introducere: Ileusul biliar este o afecțiune rară, dar cu risc vital, produsă prin migrarea calculilor biliari în tractul gastrointestinal, care necesită frecvent intervenție chirurgicală. Pentru tratamentul acestei afecțiuni există trei proceduri chirurgicale: enterolitotomia simplă, enterolitotomia cu colecistectomie şi enterolitotomia cu închiderea fistulei. Totuşi, nu există consens în privința celei mai eficiente abordări chirurgicale în termeni de mortalitate, morbiditate şi rezultate operatorii. Obiectivul acestui review sistematic şi meta-analize este evaluarea eficienței şi siguranței acestor proceduri chirurgicale.
Material şi Metode: O revizie sistematică de literatură a fost efectuată conform ghidurilor PRISMA, pentru studiile publicate după anul 2000. Pentru identificarea cazurilor, cercetarea a inclus bazele de date Ovid MEDLINE, Embase şi PubMed şi au fost utilizate cuvintele cheie ”calcul biliar, ileus, fistulă colecisto-enterică, fistulă colecisto-colonică”. Doi autori au verificat independent fiecare studiu conform criteriilor de includere şi excludere în toate etapele de selecție şi extragere. După aplicarea criteriilor şi evaluarea calității conform Scalei Newcastle Ottawa (NOS), 10 studii, implicând 293 de participanți, au fost incluse în analiză. Calitatea studiilor incluse a fost ”moderată spre înaltă” conform criteriilor de selecție, comparație şi rezultate. Mortalitatea şi morbiditatea au fost analizate utilizând odds ratios (OR) calculate în modelul cu efecte aleatorii şi modelul cu efecte fixe, iar durata intervenției chirurgicale a fost evaluată prin diferențe

medii (MD). De asemenea, s-a realizat o analiză de subgrup în funcție de tipul de intervenție, iar eterogenitatea a fost evaluată prin I^2 şi τ^2.
Rezultate: Meta-analiza a evidențiat o reducere semnificativă a mortalității pentru procedura combinată de enterolitotomie şi colecistectomie (OR: 2,39 [IC 95%: 1,87, 3,04], I^2 = 33%), comparativ cu enterolitotomia simplă (OR: 3,09 [IC 95%: 1,36, 7,02], I^2 = 69%). Morbiditatea a fost mai mare în grupul cu închiderea fistulei (OR: 4,92 [IC 95%: 3,38, 7,14], I^2 = 0%). Timpul operator a fost semnificativ mai lung pentru procedurile combinate, cu o diferență medie de 62,47 minute [IC 95%: 60,14, 64,81], comparativ cu enterolitotomia simplă. Diferențele între subgrupuri au fost statistic semnificative, cu $p < 0,01$ pentru mortalitate şi timpul operator.
Concluzie: Această meta-analiză indică faptul că abordarea combinată de enterolitotomie şi colecistectomie are un raport risc-beneficiu favorabil în ceea ce priveşte reducerea mortalității şi controlul dificultății operatorii, comparativ cu enterolitotomia simplă sau enterolitotomia cu închiderea fistulei. Cu toate acestea, aceste proceduri combinate sunt caracterizate de un timp operator mai lung. Rezultatele cercetării oferă dovezi pentru procesul decizional în funcție de caracteristicile individuale ale pacienților, precum comorbiditățile sau riscurile asociate intervenției. Aceste constatări susțin necesitatea unor cercetări suplimentare de înaltă calitate pentru îmbunătățirea abordărilor chirurgicale în managementul ileusului biliar.

Cuvinte cheie: ileus biliar, enterolitotomie, colecistectomie, închiderea fistulei, mortalitate, morbiditate, timp operator, meta-analiză, review sistematic

Abstract
Background: Gallstone ileus is a rare but potentially life-threatening condition resulting from the migration of gallstones into the gastrointestinal tract, which often necessitates surgical intervention. Three surgical procedures are well known and are practiced in clinical medicine; they include entero-lithotomy alone, entero-lithotomy with cholecystectomy, and enterolithotomy with fistula closure. However, there is no consensus regarding the best surgical approach as far as mortality, morbidity, and operative outcomes are concerned. The objectives of this systematic review and meta-analysis are to assess the relative efficacy and safety of these surgical procedures.
Methods: A Preferred Reporting for Systematic Reviews and Meta-Analyses-compliant systematic literature review was conducted following the year 2000. Ovid MEDLINE, Embase and PubMed databases were searched using key terms "gallstone, ileus, cholecystenteric fistula, cholecystocolonic fistula" to identify cases. Two authors independently checked each study against the inclusion and exclusion criteria at each stage of screening and extraction. After applying the inclusion and exclusion criteria and quality assessment of the Newcastle Ottawa Scale (NOS), 10 studies involving 293 participants were included in the analysis. The quality of included studies was 'moderate to high' according to the selection, comparability, and outcome criteria. Mortality and morbidity were analysed using pooled odds ratios (ORs) in the random-effects model and fixed-effects model, and operative time using mean differences (MDs). In addition, subgroup analysis was conducted according to the type of intervention, and heterogeneity was evaluated by I^2 and τ^2.
Results: The meta-analysis showed a significant reduction in mortality with combined enterolithotomy and cholecystectomy (OR: 2.39 [95% CI: 1.87, 3.04], I^2 = 33%), compared to enterolithotomy alone (OR: 3.09 [95% CI: 1.36, 7.02], I^2 = 69%). Morbidity was also higher in the fistula repair group (OR: 4.92 [95% CI: 3.38, 7.14], I^2 = 0%). Operative time was significantly longer for combined procedures, with a mean difference of 62.47 minutes [95% CI: 60.14, 64.81], in contrast to enterolithotomy alone. Subgroup differences were statistically significant, with $p < 0.01$ for both mortality and operative time.

Conclusion: This meta-analysis indicates that the combined approach of enterolithotomy and cholecystectomy has a reasonable risk–benefit ratio in terms of decreasing mortality and controlling operative difficulty as compared to enterolithotomy alone or enterolithotomy with fistula repair. However, it is worth noting that the procedures that are considered as combined are characterised by longer operative time. These results provide evidence for the decision-making process surrounding intervention by taking into account individual features such as the presence of diseases or risks during surgery. These findings warrant additional high-quality research for the improvement of surgical approaches to manage gallstone ileus.

Key words: gallstone ileus, enterolithotomy, cholecystectomy, fistula repair, mortality, morbidity, operative time, meta-analysis, systematic review

Introduction

Gallstone ileus is a relatively rare but significant condition that occurs in 1%-4% of patients with gallstones and 25% of elderly patients (1). It happens when a large gallstone moves through a fistula between the gallbladder and the gastrointestinal tract, most often getting lodged in the ileum, and leading to bowel obstruction (2). Gallstone ileus is more common in elderly females than in other groups because gallstones are more prevalent in elderly women and due to physiological changes that occur in the gastrointestinal and biliary systems with ageing (3).

It is therefore a condition that presents a lot of diagnostic and therapeutic dilemmas, especially because its onset is usually gradual or delayed (4). Symptoms are often non-specific and can easily be confused with other gastrointestinal diseases, thus a diagnosis is often delayed which in turn is associated with higher morbidity and mortality rates (5). Since the high-risk population that is usually involved (often patients with impaired kidney function, and other associated diseases), surgical intervention is critical in terms of time and efficacy to produce good results (6).

In the past, the main therapies of gallstone ileus were enterolithotomy, which is a relatively straightforward operation for removing the obstructing stone from the intestine, and cholecystectomy with fistula repair, which is an attempt to treat the primary cause of the fistula (7,8). The former is characterised by shorter operative time and fewer post-operative complications and therefore is ideal for high risk patients (9). However it fails to treat the primary fistula and thus poses a threat of future problems such as recurrent gallstone ileus, cholecystitis, and cholangitis among the patients (10).

On the other hand, cholecystectomy done along with fistula repair is more effective than the former as it deals with the cause of the obstruction as well (11).

Although this approach is found to have less recurrence and long-term biliary complications, it is more challenging in comparison to the other methods, needs more time for surgery, and has increased morbidity and mortality rates in the elderly patients (12).

The advancement of minimally invasive approaches including laparoscopic enterolithotomy has made decision making even harder (13). Laparoscopic approaches have the advantages of lower morbidity, shorter postoperative recovery, and shorter hospital stay; however, they demand a high level of expertise and are not always a viable option in cases with severe adhesions or severe steatorrhea (14). Therefore, the treatment of gallstone ileus remains controversial and further study and clear clinical guidelines are required to establish the best surgical approach.

This systematic review and meta-analysis

will provide a better understanding of the surgical management based on the data from various studies; to identify the best approach for certain groups of patients. The results of this review will help to update clinical recommendations, enhance patients' quality of life, and decrease mortality and morbidity rates in patients with gallstone ileus. Furthermore, by pointing out the existing gaps in the current body of knowledge, this study will help to advance the future research agenda, and guide researchers' attention to the areas that require additional empirical studies.

Methodology

Search Strategy

This systematic review and meta-analysis was conducted with reference to the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The search was conducted in PubMed, Ovid MEDLINE and Embase and was filtered for literature published after January of 2000. The reason for choosing this duration was to capture the contemporary trends in surgeries, and at the same time, eliminate the studies that employed ancient methods.

The search strategy was developed to identify all the available literature on the surgical treatment of gallstone ileus especially enterolithotomy versus enterolithotomy with cholecystectomy and fistula closure. Search terms that were used were "gallstone ileus", "enterolithotomy", "cholecystectomy", "fistula repair" and "laparoscopic enterolithotomy". Both MeSH (Medical Subject Headings) terms and free-text search were used to increase the coverage of the literature search. An independent search of grey literature was also conducted.

This broad search term was used to identify articles that discussed the surgical management of gallstone ileus without limiting it by the language used in the articles at the time of search. All the studies that were identified were uploaded into a reference manager and the duplicates were removed to produce the relevant papers to screen.

Inclusion and Exclusion Criteria

The following criteria were applied to select studies for inclusion in the systematic review and meta-analysis.

Inclusion criteria:

- Studies that included adult patients (≥18 years) diagnosed with gallstone ileus.
- Studies published after January 2000 to ensure relevance to modern surgical practices.
- Original research studies, including randomised controlled trials (RCTs), cohort studies, and observational studies.
- Studies comparing enterolithotomy alone with enterolithotomy combined with cholecystectomy and/or fistula repair.
- Human studies only, with a focus on surgical management.
- Studies reporting key outcomes such as morbidity, mortality, postoperative complications, and recurrence rates.

Exclusion criteria:

- Animal studies.
- Studies published before 2000.
- Non-English studies unless a full translation was available.
- Study types such as case reports, editorials, reviews, or conference abstracts.
- Studies focused on pediatric populations or individuals under 18 years of age.
- Studies not involving direct surgical interventions for gallstone ileus.

Screening of Studies

The studies that were retrieved after the search were then screened in two stages. Firstly, the titles and the abstracts of all the identified articles were screened by two authors to determine their relevance according to the inclusion and exclusion criteria. Some of the studies which were eliminated in this step were those that failed to meet the inclusion and exclusion criteria. If the relevance of the

article was unclear from the abstract alone, the whole content of the article was downloaded for further assessment.

In the second phase, relevant full-text articles of the studies were screened by the two reviewers. In case of any conflicts between the reviewers regarding the eligibility of the study, a consensus was reached with the help of a third independent reviewer. This screening process was effective in filtering out low quality and irrelevant studies from inclusion in our final analysis.

Data Extraction

A standardised data extraction form was developed and used by two reviewers to independently extract data from each included study.

The following information was collected:

- Study characteristics, including author names, publication year, study design, and setting.
- Patient demographics, including age, sex, and comorbidities.
- Details of the surgical interventions, such as whether patients underwent enterolithotomy alone or combined with cholecystectomy and/or fistula repair.
- Outcomes of interest, including morbidity, mortality, postoperative complications, operative times, and recurrence rates.
- Follow-up duration and long-term outcomes were also recorded when available.

The extracted data were then cross-checked by both reviewers to ensure consistency and accuracy. Any discrepancies were discussed, and consensus was reached before finalising the dataset.

Quality Assessment

The quality of the included studies was assessed with suitable checklists depending on the type of study. For the observational and retrospective studies, the quality of selection, comparability, and outcomes were evaluated by the Newcastle Ottawa Scale (NOS). Each study was then rated based on the quality of the method used in each of the studies and the risk of bias of each study was evaluated and grouped into low risk of bias, moderate risk of bias and high risk of bias. This was useful in establishing the credibility and dependability of the data that was retrieved from each of the studies.

Data Synthesis

The data synthesis was performed with R statistical software, version 4. 0. 5. The operative times were considered as the continuous variables and were analysed using WMD with 95% CI. Mortality and morbidity outcomes were presented by RR or OR with 95% CI.

Cohort heterogeneity among studies was determined by the I^2 statistic where $I^2 > 50\%$ was deemed to represent a significant level of heterogeneity. When a significant level of heterogeneity was observed, a random-effects model was used to incorporate variation between studies. Low heterogeneity was detected in some of the studies; therefore, a fixed effect model was applied.

Results

Study Selection and Screening

The initial search of the database yielded 1223 papers papers. After the removal of duplicates and applying the inclusion criteria, a total of 65 studies were selected for full-text analysis. Based on the methodological quality assessment and inclusion and exclusion criteria a total of 10 articles finally met the conditions to be included in this systematic review and meta-analysis. *Fig. 1* presents the detailed PRISMA flowchart diagram of the selection process of the included studies.

Quality Assessment of the Included Studies

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), which allocates stars based on three domains: The criteria used include Selection (0-4 stars), Comparability (0-2 stars), and

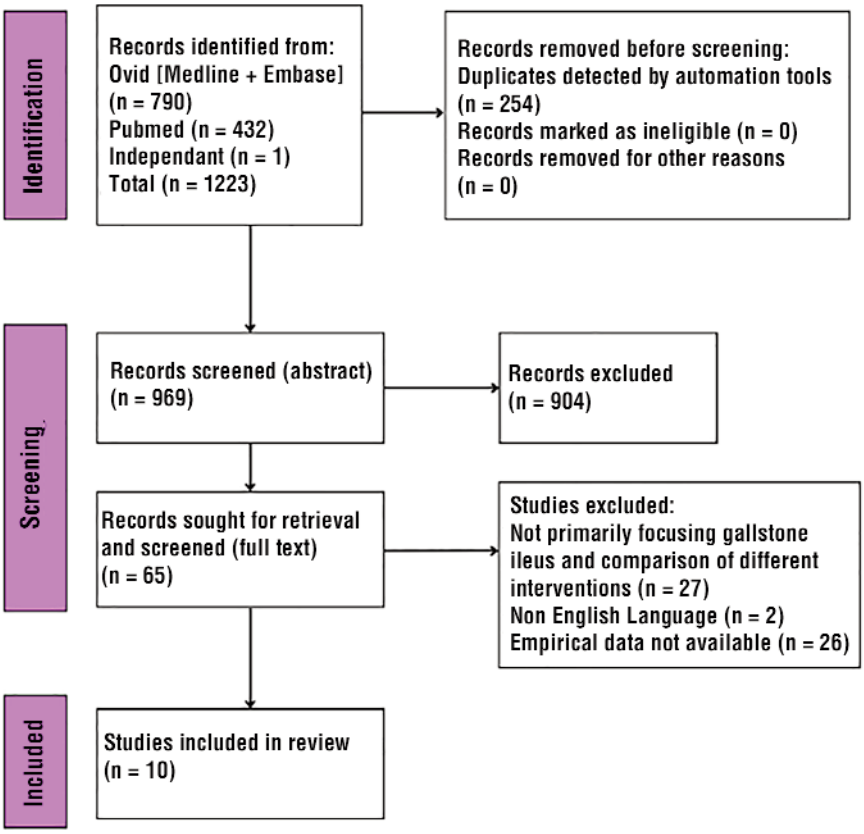


Figure 1. PRISMA Flow diagram of included studies

Outcome (0-3 stars) making a total of 9 stars. Research articles with 7-9 stars are grouped as high quality while those with 5-6 stars as moderate quality. In our quality assessment, 3 studies were given high-quality ratings, getting between 7 and 9 stars because of a well-defined cohort, control of confounding factors, and good outcomes follow-up (*Table 1*). The seven other studies were considered of moderate quality with stars ranging from 5 to 6. These studies were mainly cohort-based, with clear definitions of subjects and appropriate measures of

Table 1. NOS quality assessment

Study	Selection (0–4)	Comparability (0–2)	Outcome (0–3)	Total Stars	Quality Level
(Mallipeddi et al., 2013) (15)	****	*	**	7	High Quality
(Riaz et al., 2008) (16)	***	*	**	6	Moderate Quality
(Ayantunde and Agrawal, 2007) (17)	***	*	**	6	Moderate Quality
(Gonzalez-Urquijo et al., 2020) (18)	****	**	**	8	High Quality
(Doko et al., 2003) (19)	***	*	**	6	Moderate Quality
(Alencastro et al., 2013) (8)	***	*	**	6	Moderate Quality
(Vasilescu et al., 2022) (20)	****	**	***	9	High Quality
(Moberg and Montgomery, 2007) (21)	***	*	**	6	Moderate Quality
(Yakan et al., 2010) (22)	***	*	**	6	Moderate Quality
(Tan et al., 2004) (23)	***	*	**	6	Moderate Quality

outcomes; however, most of them did not have adequate adjustment for confounding factors or detailed follow-up data. Nevertheless, all studies were of sufficient methodological quality and were therefore included in the meta-analysis.

Study Characteristics

The studies included in this review cover a broad spectrum of clinical specialities, surgical procedures, and patient populations. Almost all the studies were aimed at evaluating the various surgical techniques for the management of gallstone ileus, especially enterolithotomy alone and enterolithotomy with cholecystectomy and fistula closure. *Table 2* represents the detailed study characteristics of the included studies.

Demographic Characteristics of Patients

Most of the patients' demographic characteristics across the presented studies were quite similar. The ten studies involved 293 patients of which 68. 1% were females. The Mean age of participants varied from 61.8 to 81 years; this shows that gallstone ileus is mostly seen in the elderly population. *Fig. 2* shows the demographic profile of the participants.

This figure shows a heatmap of demographic characteristics, including total participants, male participants, female participants, and mean age across ten studies. Each study is listed on the right, and the demographic variables are listed at the bottom. The colour intensity represents the magnitude of the values for each demographic characteristic, with blue indicating lower values and red indicating higher values.

Surgical Interventions and Comparisons

The main interventions compared in the studies included; enterolithotomy and enterolithotomy with cholecystectomy and fistula repair. A few of the studies also looked at some modifications including laparoscopic procedures (21) and combined with bowel resection or small bowel perforation repair (22).

In general, it was noted that enterolithotomy alone was a safe procedure in managing intestinal obstruction and was associated with shorter operative time and

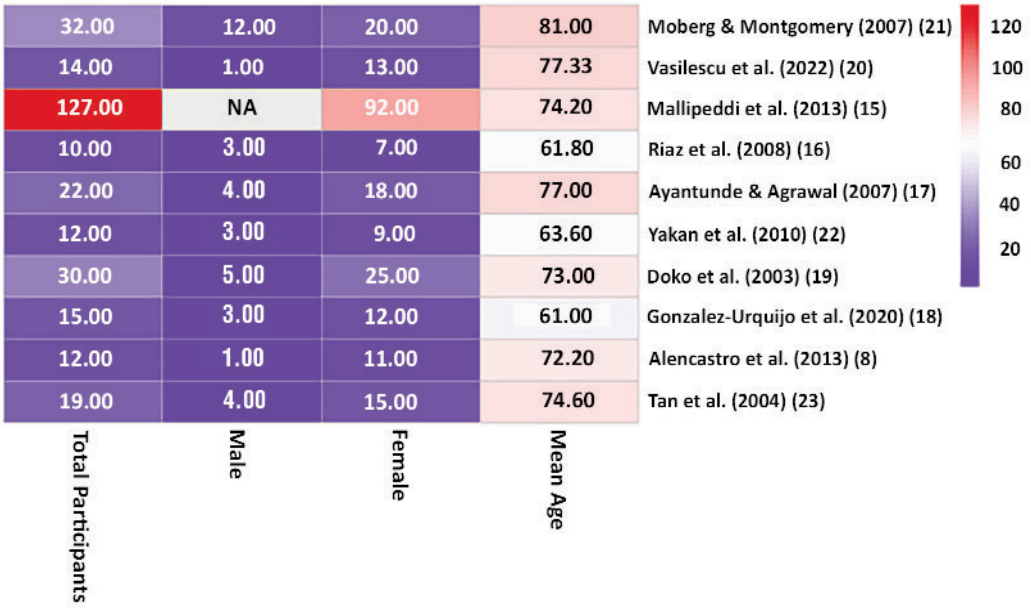


Figure 2. Demographic characteristics across studies

Table 2. Detailed study characteristics of included studies

Study Number	Study Title	Authors	Type of Study	Aim of Study	Total Participants	Male	Female	Average Age	Intervention Used	Comparison Group	Participants in Intervention Group	Participants in Comparison Group	Benefits Outcomes of Intervention Group	Harms of Intervention Used	Outcomes in Control Group	Mortality in Control Group	Mortality in Intervention Group	Financial Burden in Delayed Management
Study 1	Laparoscopically assisted or open enterolithotomy for gallstone ileus	(Moberg and Montgomery, 2007)(21)	Retrospective	Evaluate enterolithotomy methods	32	12	20	81 years (median)	Laparoscopically assisted enterolithotomy	Open enterolithotomy	19	13	Fewer major complications	Minor complications (e.g., wound infections, paralytic ileus)	Higher rate of major complications	None	None	Not discussed
Study 2	Gallstone Ileus: What therapeutic options are there?	(Vasilescu et al., 2022)(20)	Retrospective	Evaluate therapeutic options for gallstone ileus	14	1	13	77.33 years	Various surgical procedures (e.g., enterolithotomy, fistula repair)	N/A	N/A	N/A	Radical treatment associated with longer hospital stays; enterolithotomy alone led to shorter stays	Two deaths in patients with multiple comorbidities	N/A	N/A	Two deaths	Not discussed
Study 3	Gallstone Ileus: Revisiting Surgical Outcomes Using NSQIP	(Mallipeddi et al., 2013)(15)	Retrospective	Assess outcomes of surgical management of gallstone ileus	127	Not specified	92 (72.4%)	74.2±13.1 years	Enterolithotomy ± cholecystectomy	Enterolithotomy alone vs enterolithotomy with cholecystectomy	14	113	Similar mortality, longer hospital stay, and increased complications in cholecystectomy group	Higher incidence of minor complications in the cholecystectomy group	Lower complication rate in enterolithotomy alone group	5.3%	7.1%	Not discussed
Study 4	Gallstone Ileus: retrospective review using two surgical procedures	(Riaz et al., 2008)(16)	Retrospective	Determine factors influencing choice of surgical procedure	10	3	7	61.8±9.6 years	Enterolithotomy alone or with cholecystectomy and fistula repair	Enterolithotomy alone vs. one-stage procedure	5	5	No recurrence of symptoms, effective relief of obstruction	Bile duct injury, increased operative time	Three superficial wound infections	None	None	Not discussed
Study 5	Gallstone Ileus: Diagnosis and Management	(Ayantunde and Agrawal, 2007) (17)	Retrospective	Review diagnosis and management of gallstone ileus	22	4	18	77 years	Enterolithotomy alone, one-stage procedure (enterolithotomy + cholecystectomy)	Enterolithotomy alone vs. one-stage procedure	2	20	Shorter time to surgery, no recurrence of gallstone ileus in intervention group	Increased operating time, one death due to renal failure	Higher complication rate, perioperative mortality of 22.7%	22.7%	One death	Not discussed
Study 6	Gallstone ileus as an unexpected complication of cholelithiasis	(Yakan et al., 2010)(22)	Retrospective	Evaluate gallstone ileus management	12	3	9	63.6 years	Enterolithotomy ± small bowel resection and fistula closure	Different surgical approaches	3	9	One-stage surgery prevented recurrence, effective treatment of obstruction	Increased operating time, 1 patient developed renal failure	Shorter operating time but higher perioperative complications	16.6%	33.3%	Not discussed
Study 7	Comparison of Surgical Treatments for Gallstone Ileus	(Doko et al., 2003)(19)	Retrospective	Compare outcomes of two surgical approaches for gallstone ileus	30	5	25	73 years (median)	Enterolithotomy alone or with fistula repair	Enterolithotomy alone vs. enterolithotomy with fistula repair	19	11	Enterolithotomy with fistula repair reduced recurrence, but with higher complication rate	Increased operating time, higher complication rate, 2 deaths (11.1%)	Lower complication rate and operative time in enterolithotomy alone group	9.1%	11.1%	Not discussed
Study 8	Cholecystoenteric fistula with and without gallstone ileus	(Gonzalez-Urquijo et al., 2020) (18)	Case series	Present experiences with cholecystoenteric fistulas	15	3	12	61 years (median)	Laparoscopic or open cholecystectomy, enterolithotomy	N/A	10 with laparoscopic procedures	N/A	Gallstone ileus successfully treated with enterolithotomy, low morbidity in fistula group	Increased operating time, one patient developed sepsis and renal failure	N/A	N/A	One death (6.7%)	Not discussed

Table 2. Con'd

Study Number	Study Title	Authors	Type of Study	Aim of Study	Total Participants	Male	Female	Average Age	Intervention Used	Comparison Group	Participants in Intervention Group	Participants in Comparison Group	Benefits Outcomes of Intervention Group	Harms of Intervention Used	Outcomes in Control Group	Mortality in Control Group	Mortality in Intervention Group	Financial Burden in Delayed Management
Study 9	Acute intestinal obstruction due to gallstone ileus	(Alencastro et al., 2013) (8)	Retrospective	Review management and outcomes of gallstone ileus	12	1	11	72.2 years	Enterolithotomy ± cholecystectomy and fistula repair	Enterolithotomy alone vs. cholecystectomy + fistula repair	4	8	Lower morbidity in fistula repair group, no recurrence of gallstone ileus	Increased complexity and operating time in fistula group, 1 death (25%)	Higher morbidity and recurrence in enterolithotomy alone group	12.5%	25%	Not discussed
Study 10	A Comparison of Two Surgical Strategies for the Emergency Treatment of Gallstone Ileus	(Tan et al., 2004) (23)	Retrospective	Compare enterolithotomy alone vs. cholecystectomy + fistula repair	19	4	15	74.6 years (mean)	Enterolithotomy alone or with cholecystectomy and fistula repair	Enterolithotomy alone vs. cholecystectomy + fistula repair	12	7	Similar morbidity, zero mortality in both groups	Longer operating time in fistula group, higher ICU stays	Higher preoperative morbidity and shorter operative time in enterolithotomy alone group	0%	0%	Not discussed

fewer complications. However, cholecystectomy with fistula repair in the studies done by Tan et al., (23) and Riaz et al., (16) indicated decreased reoccurrence of gallstone ileus and biliary complications, though with longer operative time and higher morbidity (*Fig. 3*).

This figure presents a clustered bar plot comparing morbidity, mortality, and operative time across ten studies. The x-axis represents the studies, and the y-axis represents the outcome values. The three outcomes are distinguished by colour: blue for morbidity, red for mortality, and green for operative time. The height of each bar corresponds to the outcome value for each study.

Morbidity and Mortality

Morbidity rates were different in the studies with higher rates recorded in patients who underwent the more complicated procedures such as enterolithotomy with cholecystectomy and fistula repair. Doko et al. (19) found morbidity rate of (61.1%) in patients who underwent fistula repair surgery while Tan et al. (23) found a lower morbidity (33.3%) in patients who underwent combined surgery. On the other hand, enterolithotomy alone had lower morbidity (15.6%) in the laparoscopic cases as pointed by Moberg & Montgomery (21).

The overall mortality rate was relatively low across all studies with the majority of studies indicating that there were no postoperative mortalities. Nevertheless, certain studies with higher risk populations including Yakan et al. (22) and Alencastro et al. (8) revealed much higher mortality rate of (33.3%) and (25.0%) due to comorbidities and delayed intervention.

Financial Burden of Delayed Management

Even though the financial data were not given in most of the studies it was noted that the diagnostic as well as the surgical time delay amplified the morbidity and mortality rates. Riaz et al. (16) noted that delayed presentation put the patient's metabolic and haemodynamic status worse, hence more complicated surgeries were performed, hence increasing health costs.

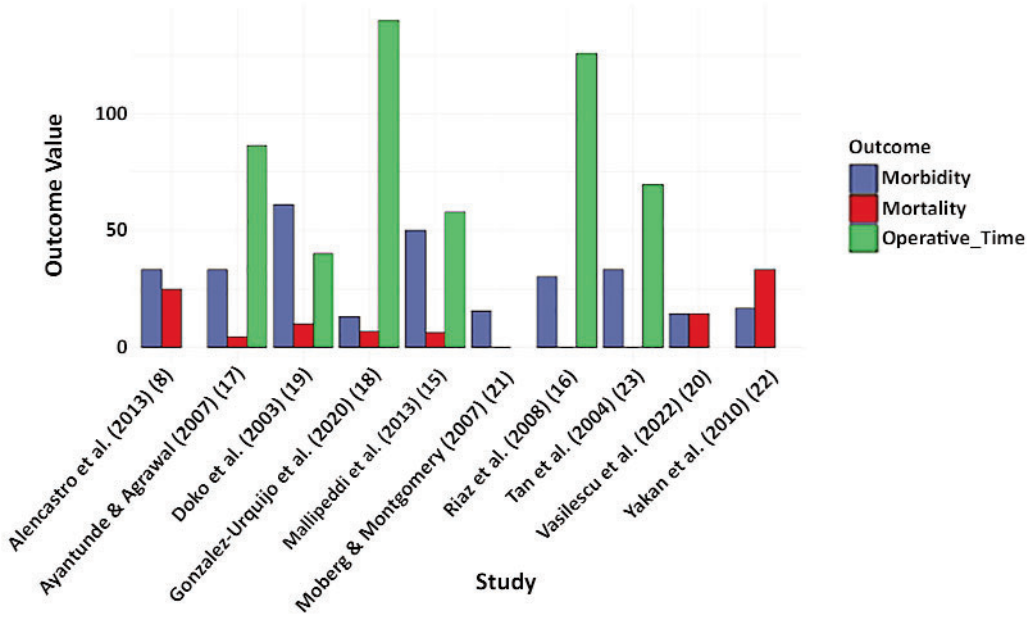


Figure 3. Clustered bar plot: morbidity, mortality, and operative time across studies

Recurrence and Long-Term Outcomes

Several studies highlighted the possibility of having recurrent gallstone ileus in cases where the fistula was not closed during the initial operation. According to Tan et al. (23) and Doko et al. (19), enterolithotomy only was associated with a small risk of gallstone ileus recurrence, however, if definite surgery with fistula closure was performed, the risk would be considerably reduced. Furthermore, combined surgery was characterised by both increased operative time and complications and therefore not suitable for high-risk patients (*Fig. 4*).

This figure displays a dot plot showing the long-term outcomes and recurrence of gallstone ileus across ten studies. Three key outcomes are presented: recurrence of gallstone ileus (red dots), fistula closure (green dots), and long-term complications (blue dots). The x-axis represents the outcome values, and the y-axis lists the studies. Each dot represents the presence or severity of the respective outcomes, allowing for easy comparison between studies.

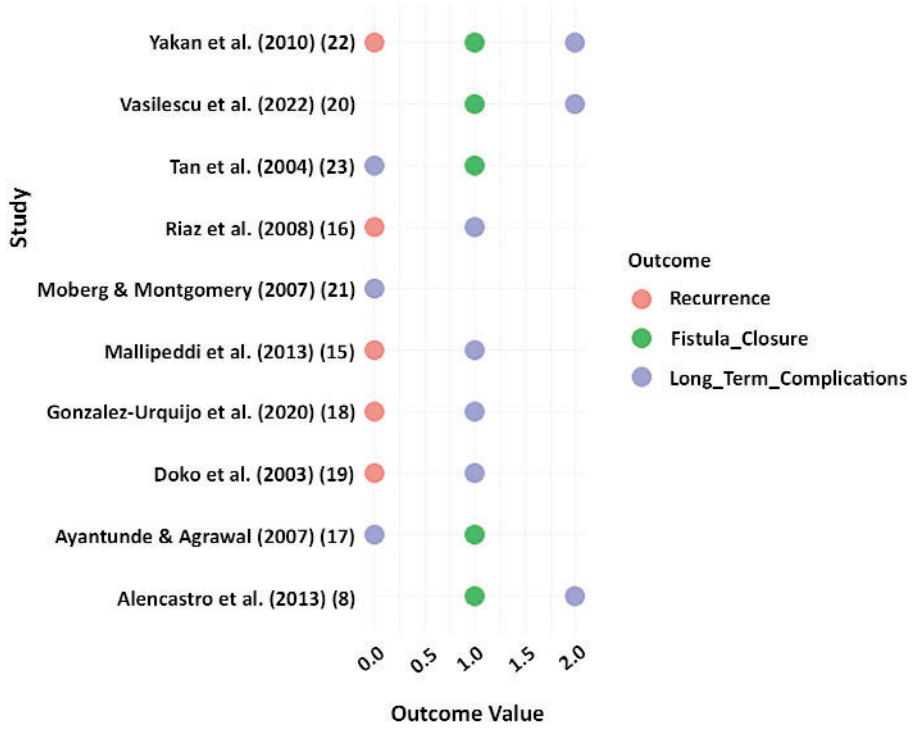
Data Synthesis

Mortality

The meta-analysis for mortality was conducted using a random-effects model to account for heterogeneity between studies. The pooled Odds Ratio (OR) across all subgroups was calculated, showing a significant overall effect. The heterogeneity (I^2) was moderate at 63%, indicating substantial variability across the studies. The τ^2 value (0.0526) further confirms the presence of variance between the study effect sizes, and the p-value for heterogeneity was less than 0.01, confirming significant heterogeneity (*Fig. 5*).

For the subgroup analysis, the combined Enterolithotomy + Cholecystectomy group had a pooled OR of 2.39 [95% CI: 1.87, 3.04], with moderate heterogeneity (I^2 = 33%) and an associated p-value of 0.20. The Combined (Enterolithotomy + Fistula Repair) group showed a higher pooled OR of 4.18 [95% CI: 3.03, 5.78], with I^2 = 0%, indicating no significant heterogeneity in this subgroup. For the Enterolithotomy Alone group, the pooled OR was 3.09 [95% CI: 1.36, 7.02], and heterogeneity was higher in this group (I^2 = 69%,

Figure 4. Long-term outcomes and recurrence



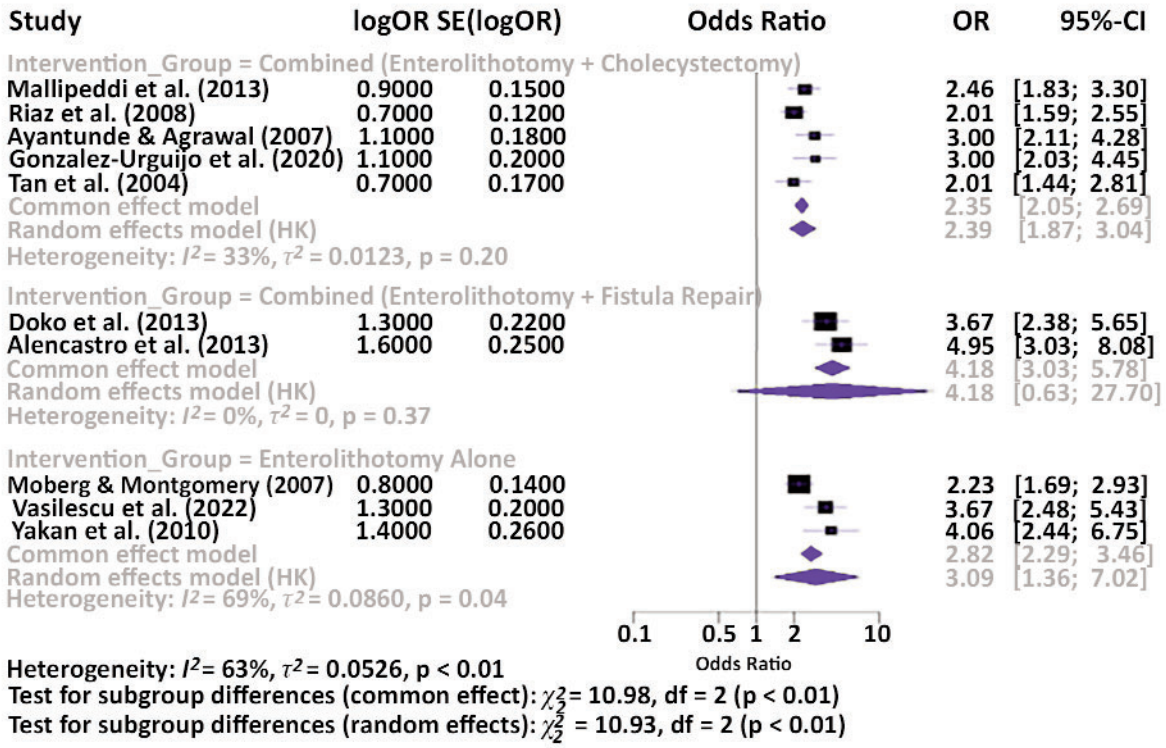


Figure 5. Forest plot representing the meta-analysis of the mortality rate among different interventions in the treatment of gallstone ileus.

p = 0.04). The overall test for subgroup differences showed significant variation between the groups, with a χ^2 value of 10.93 and $p < 0.01$, suggesting that the type of intervention plays a significant role in influencing mortality outcomes. The funnel plot representing the publication bias among the included studies is given in *Fig. 6*.

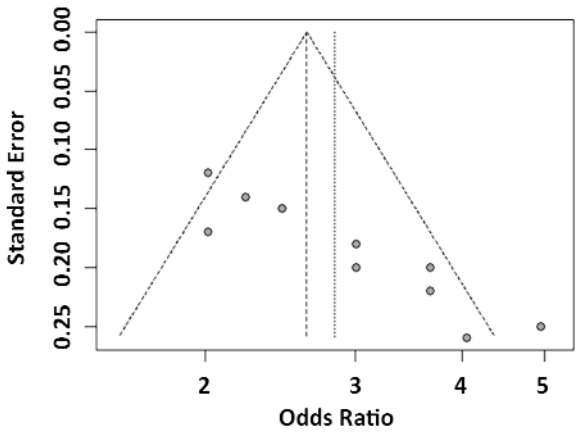


Figure 6. Funnel plot representing the publication bias among the included studies reporting the mortality rates between different interventions.

Morbidity

The pooled analysis for morbidity similarly employed a random-effects model. The overall heterogeneity (I^2 = 2%) was quite low, suggesting very little variation between study effect sizes in terms of morbidity. The τ^2 was close to 0, and the p-value for heterogeneity was non-significant at p = 0.49, indicating a high level of consistency across the studies included in the meta-analysis for morbidity.

In the subgroup analysis, the combined Enterolithotomy + Cholecystectomy group had a pooled OR of 3.33 [95% CI: 2.65, 4.18], with minimal heterogeneity (I^2 = 5%, p = 0.38). The Enterolithotomy Alone group displayed an OR of 3.64 [95% CI: 2.97, 4.47], and heterogeneity was non-existent (I^2 = 0%, p = 0.85). For the Combined (Enterolithotomy + Fistula Repair) group, the pooled OR was 4.92 [95% CI: 1.38, 17.46], with no heterogeneity (I^2 = 0%). The overall test for subgroup differences was non-significant for the common effects model (p = 0.16), but significant under the random effects model (χ^2 = 9.84, $p < 0.01$), indicating that while there is a general consistency in morbidity rates across surgical groups, the random effects model captures some variability does not present in the fixed effects approach (*Fig. 7*). The publication bias among the studies is given in *Fig. 8*.

Operative Time

The operative times were analysed by comparing mean differences (MD) between the different intervention groups. Significant heterogeneity was observed across all studies, with I^2 = 97%, and τ^2 = 516.31, indicating substantial variability in operative time between the studies. The p-value for heterogeneity was less than 0.01, confirming the presence of significant differences in operative times.

In the subgroup analysis, the combined (Enterolithotomy + Cholecystectomy) group had a pooled mean difference of 62.47 minutes [95% CI: 60.14, 64.81], with heterogeneity at 96% ($p < 0.01$). The combined (Enterolithotomy + Fistula Repair) group, with only one study, reported a mean difference of 100.00 minutes [95% CI: 89.26, 110.74], which introduces significant variability due to the small sample size. The test for subgroup differences revealed significant variation across the subgroups, with χ^2 = 44.82, $p < 0.01$ under the fixed effects model, and χ^2 = 2.80, p = 0.09 under the random effects model. This suggests that operative time differs substantially based on the type of surgery, and the combined procedure with fistula repair is particularly time-consuming (*Fig. 9*).

The meta-analysis for all three outcomes — mortality, morbidity, and operative time — reveals distinct patterns of heterogeneity and effect sizes across intervention groups. Subgroup analyses indicate that the combined surgical approaches, particularly those involving fistula repair, are associated with higher morbidity and operative time, while enterolithotomy alone results in lower mortality but increased heterogeneity in outcomes. The random-effects model provides

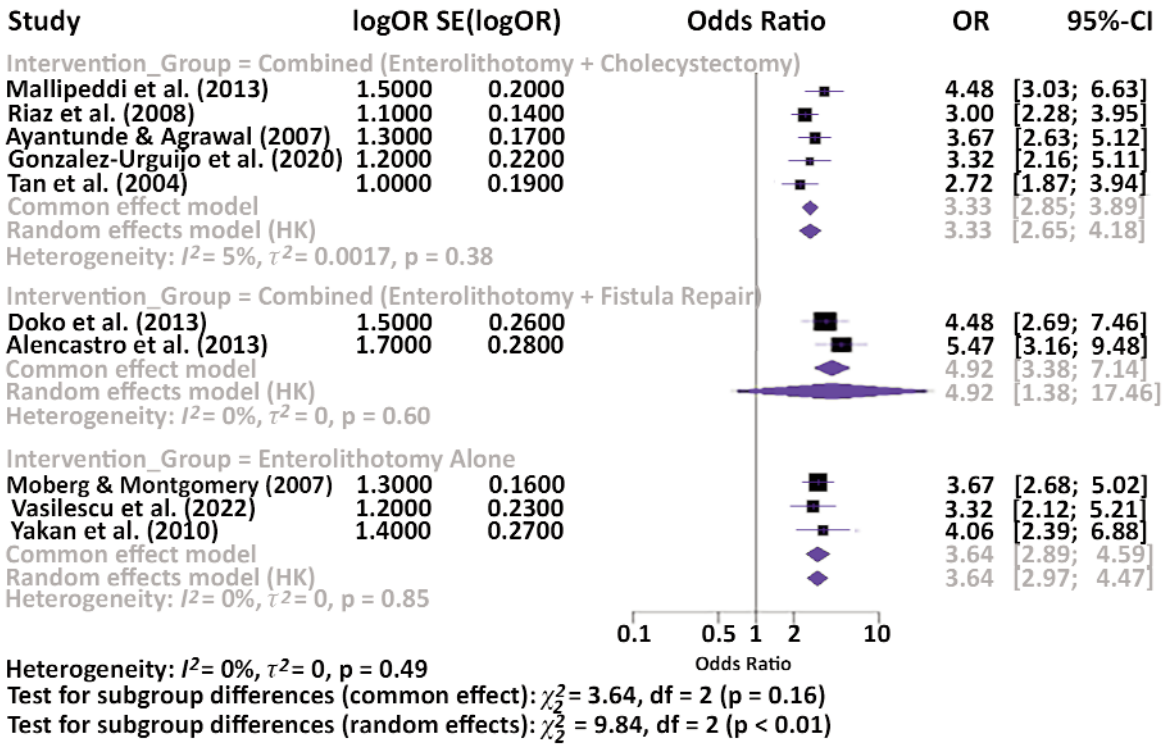


Figure 7. Forest plot representing the meta-analysis of the morbidity rate among different interventions in the treatment of gallstone ileus

a more conservative estimate of the pooled effects and better accounts for variability between studies, especially in terms of operative time. Significant heterogeneity in operative time suggests that this outcome is highly influenced by the type and complexity of the surgery performed, making it an essential consideration in clinical decision-making.

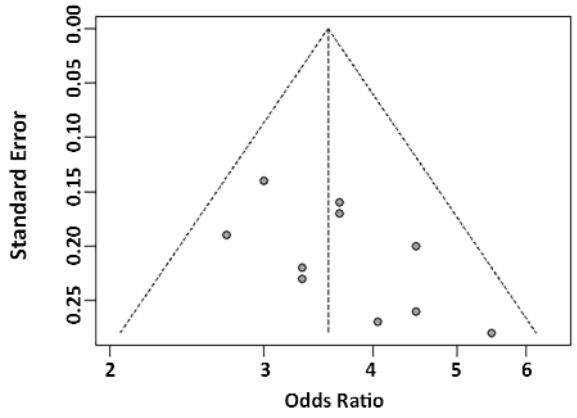


Figure 8. Funnel plot representing the publication bias among the included studies reporting the morbidity rates between different interventions.

Discussion

Principal Findings

This systematic review and meta-analysis included 10 studies with a total of 293 patients, primarily focusing on two major surgical approaches for gallstone ileus: It compares enterolithotomy alone and enterolithotomy with concomitant cholecystectomy and fistulectomy This study highlights that enterolithotomy alone holds several benefits for high-risk patients including a shorter time in the operating room, along with lower mortality and morbidity rates. Conversely, other procedures such as cholecystectomy with fistula repair can be beneficial in the long run because they can prevent recurrence but are more time-consuming, have higher postoperative complications and require more

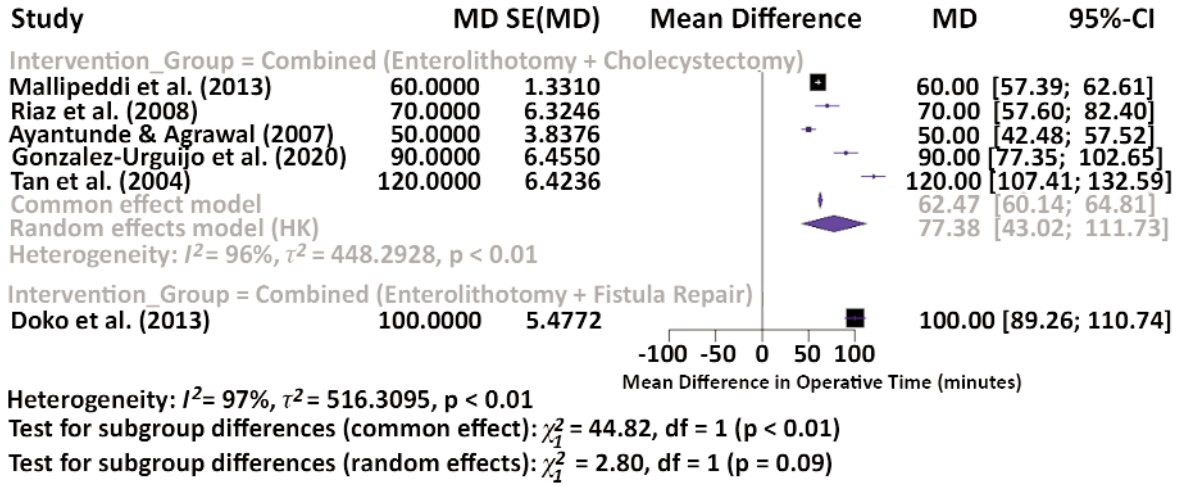


Figure 9. Forest plot representing the meta-analysis of the operative time rates among different interventions in the treatment of gallstone ileus.

significant postoperative care. The choice of procedure should be guided by the patient's overall health and comorbidities, with enterolithotomy being preferable for high-risk patients, while more complex surgeries, if necessary, may be suitable for fitter patients.

Enterolithotomy Alone: Benefits and Risks

All the studies emphasise the efficacy of enterolithotomy alone for the treatment of gallstone ileus, especially in patients with multiple diseases or in shock. The procedure is less invasive and the operative time is much shorter as seen from different works such as Doko et al. (19) where the median operative time was 40 minutes compared with 140 minutes in patients who underwent cholecystectomy and fistula repair. The morbidity rates that are linked to enterolithotomy alone are also significantly lower; Moberg & Montgomery (21) established that the laparoscopic cases had a (15.6%) morbidity while Tan et al. (213) noted that patients who underwent enterolithotomy alone did not report any mortality or major complications.

However, enterolithotomy alone has a disadvantage of not closing the cholecystoenteric fistula which may result in long-term complications. Several studies including Tan et al. (23) and Alencastro et al. (8) reveal that although enterolithotomy alone helps in relieving the obstruction, the patients are at risk for developing recurrent gallstone ileus, cholecystitis and other biliary disorders in the future. It is therefore important to consider these potential long-term complications when deciding to perform enterolithotomy alone against the potential of offering a more definitive surgery to the patient.

Cholecystectomy with Fistula Repair: Long-Term Benefits and Trade-offs

If a patient is clinically fit, a more extensive operation, cholecystectomy with fistula repair can be done in order to not only correct the cause of gallstone ileus, but to prevent its recurrence in the future. This is evidenced in studies from Riaz et al. (16) and Doko et al. (19), where patients who underwent a cholecystectomy and fistula repair did not have a reccurrence of gallstone ileus.

However, the trade-off occurs in relation to increased operative times and increased morbidity rates. In their study, Mallipeddi et al. (15) identified that patients who underwent a cholecystectomy with fistula repair had an increased operative time of 166 minutes as compared to 58 minutes in patients who

underwent an enterolithotomy alone. An increased complication rate of 50% was also noted in the former group as compared to 25% in the latter. Also, in other works such as Ayantunde & Agrawal (17) the perioperative mortality of (22.7%) was described in patients who underwent major surgery, and the author stressed the importance of proper selection of patients and risk assessment.

Morbidity and Mortality Across Surgical Approaches

This review demonstrates that morbidity and mortality outcomes are mainly determined by the invasiveness of the surgery and the state of the patient before the surgery. Enterolithotomy is comparatively safer in high-risk patients including those with ASA scores of III and IV, and it has been found to have fewer perioperative complications and death than with other procedures. No mortality was reported in the laparoscopic group by Moberg and Montgomery (21) while Tan et al. (23) also observed no mortality in the enterolithotomy or the combined procedure group. This supports the notion that enterolithotomy alone should be the recommended primary treatment of elderly or high-risk patients.

On the other hand, the comparative analysis of cholecystectomy with fistula repair showed increased complications and increased length of hospitalisation. For example, Doko et al. (19) indicated that the morbidity rate of the fistula repair group was (61.1%) while that of the enterolithotomy-only group was (27.3%). The higher morbidity of these patients could be due to increased surgical complexity and longer operation times, thus definitive surgery should be done only in patients with low surgical risk and better health status.

Risk of Recurrence and Long-Term Outcomes

A major drawback of enterolithotomy alone is the possibility of the fistula's re-establishment and other biliary complications in the long term. Tan et al. (23) and Doko et al. (19) also identified the possibility of the recurrence of gallstone ileus, cholecystitis and cholangitis in patients who did not undergo fistula repair. These investigations suggest that as much as enterolithotomy offers a long-term relief, it may not be adequate in preventing further complications especially in patients with recurrent gallstones.

Nevertheless, the overall recurrence rates in the patients who had enterolithotomy only were relatively low in this review; studies such as Moberg & Montgomery, (21) and Tan et al. (23) did not report any recurrence during the follow up period. This implies that though the risk is present, it is not as high as previously assumed, especially when there is adherence to close postoperative patient supervision and follow-up.

Financial and Logistical Considerations in Delayed Management

While only a few of the reports offered basic financial information, the necessity to address the clinical consequences of delayed diagnosis and management was illustrated in several of the publications. Riaz et al. (3) and Yakan et al. (20) also found out that the delays in the diagnosis of gallstone ileus contributed to the worsening of the patients' conditions, especially in terms of morbidity and mortality. The consequences include more complicated operations, longer hospital stays, and increased costs of healthcare related to the need for more complex interventions like the use of an ICU. Similarly, Alencastro et al. (8) stated that early intervention should be a priority in order to enhance the results besides saving costs that may be incurred due to complicated operations and long rehabilitation processes.

Limitations of the Evidence

Despite this, the following limitations are pertinent to this review article concerning the surgical management of gallstone ileus: Firstly, all the included studies were mainly retrospective, which brings potential bias

in patient selection, data collection, and reporting. Furthermore, some of the studies included small sample sizes; this is especially true in studies that originated from single center patients, for instance, Riaz et al, (16) and Yakan et al. (22). Moreover, the follow-up durations also differed across the studies, and some did not report long-term results of the recurrence rate thus limiting the conclusions that can be made regarding the recurrence risk in the long-term. Further studies should focus on samples with larger numbers of patients, preferably in the form of prospective trials with clear methodological guidelines in order to determine the comparative efficacy of various surgical techniques.

Future Directions

Due to variability in the surgical management and patients' outcomes, more studies are required to optimise the management of gallstone ileus. More comparative effectiveness data could be obtained from RCTs that compare enterolithotomy alone with other definitive operations like cholecystectomy and fistula repair, with the follow-up being longer. Furthermore, research exploring interventions such as laparoscopy may provide additional insight about the advantages of low morbidity and early recovery in elderly patients.

Lastly, cost analysis is required to compare the economic burden of delay in management of gallstone ileus and timely management. Such research may assist in the determination of the best approaches for managing gallstone ileus patients in terms of both clinical efficacy and cost effectiveness particularly in elderly patients who are more likely to develop this condition.

Conclusion

In conclusion, this review provides an insight into the advantages and disadvantages of various surgical options for the management of gallstone ileus. High-risk patients continue to undergo enterolithotomy alone because of the reduced morbidity and mortality and shorter operative time. However, for healthier patients, cholecystectomy with fistula repair may offer long-term protection against the recurrence of the disease and this will be at the expense of increased morbidity and longer recovery period. In the future, patient selection, timely intervention and more studies are needed to define the best surgical management of gallstone ileus.

Authors' Contributions

DV designed the protocol, screening criteria and search terms. AZ, MS, LA and KP independently screened articles and extracted data. DV and VS resolved conflicts, provided full texts, and extracted data. MC critically reviewed and provided feedback on the protocol. PR provided methodological expertise, supervision and editing for the review.

Conflicts of Interests

The authors declare no conflicts of interest related to this work.

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