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Original Research Article

A RETROSPECTIVE COMPARATIVE STUDY OF PERIOPERATIVE OUTCOMES IN LAPAROSCOPIC VERSUS OPEN CHOLECYSTECTOMY AT A TERTIARY CARE CENTRE

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ABSTRACT

Background: Cholecystectomy is a routinely performed procedure for a variety of gallbladder pathologies. While laparoscopic cholecystectomy (LC) has become the standard of care, open cholecystectomy (OC) continues to be used in select cases. This study was undertaken to compare the perioperative outcomes of LC and OC in a tertiary care institute.

Materials and Methods: This retrospective study was conducted over 18 months and included 60 patients who underwent cholecystectomy for various benign gallbladder diseases. 60 patients (30 who underwent OC and 30 patients who underwent LC) were included in this study on the basis of a predefined inclusion and exclusion criteria. Preoperative assessment, surgical technique, postoperative recovery, and complications were analysed from electronic hospital records and case papers. Data were analyzed using appropriate statistical tests. P value less than 0.05 was considered statistically significant.

Results: The LC group had a shorter mean operative time (70.34 \pm 15.2 minutes) as compared to the OC group (95.46 \pm 18.6 minutes; p < 0.001). Time to oral intake and duration of hospital stay were also markedly reduced in the LC group (8.6 \pm 2.4 hours and 1.8 \pm 0.6 days, respectively) compared with the OC group (17.3 \pm 3.1 hours and 4.2 \pm 1.1 days; p < 0.001 for both). Postoperative wound infection occurred in only 1 patient (3.3%) in the LC group, whereas 6 patients (20%) in the OC group developed wound infection (p <0.05). Conversion to open surgery was done in 2 patients (6.7%) in the LC group. A single case of bile duct injury was documented in the OC group with no such injury observed in the LC group.

Conclusion: Laparoscopic cholecystectomy provides better perioperative outcomes as compared to open cholecystectomy in patients undergoing cholecystectomy for various gallbladder pathologies. However, LC must be offered as first line after ascertaining suitability for LC so that the threshold for conversion remains low.

Keywords: Cholecystectomy, Laparoscopy, Open Surgery, Gallbladder Disease, Surgical Outcomes.

INTRODUCTION

Cholecystectomy is one of the most commonly performed abdominal surgeries worldwide and is the definitive treatment for a variety of gallbladder pathologies.^[1] While symptomatic cholelithiasis is the most frequent indication for cholecystectomy, it is also routinely indicated for acute and chronic cholecystitis, gallbladder polyps, gallbladder

empyema, mucocele, porcelain gallbladder and suspected malignancy.^[2] With the rising incidence of gallbladder diseases in both developed and developing countries the overall incidence of cholecystectomy continues to grow. In tertiary care settings, cholecystectomy is performed not only for routine symptomatic gallstone disease but also for complicated and atypical presentations.^[3]

The evolution of surgical techniques has significantly changed the approach of surgeries such as cholecystectomy. Open cholecystectomy (OC) which was first performed in the late 19th century remained the gold standard until the advent of laparoscopic cholecystectomy (LC) in the late 1980s. [4] Since its advent LC has revolutionized gallbladder surgery due to its minimally invasive nature, significantly reduced postoperative pain, shorter hospital stay, faster recovery and better cosmetic outcomes.^[5] Today, LC is considered the preferred approach for most elective and emergency gallbladder conditions. However, OC continues to be relevant in specific clinical scenarios that include gangrenous cholecystitis, Mirizzi syndrome, unclear anatomy or when conversion from laparoscopy is necessitated by intraoperative complications or patient factors like dense adhesions or history of prior abdominal surgery.[6]

Despite the clear advantages of LC, the choice between laparoscopic and open approaches in routine practice is influenced by multiple factors. These factors include surgeon experience, equipment availability, intraoperative findings and presence of patients comorbidities in undergoing cholecystectomy.^[7] In resource-limited settings and among surgeons trained primarily in open techniques OC may still be favoured or necessitated. Moreover, while LC is routinely used in elective settings its use in emergency situations such as acute cholecystitis, empyema or gallbladder perforation may be technically demanding and may be associated with a higher risk of complications. [8] These complications are more common as well as more serious in inexperienced hands. Therefore, the surgical community continues to debate the comparative merits of LC versus OC across the spectrum of gallbladder disease. This is more so particularly in institutions serving diverse patient populations with varying levels of disease complexity.

The existing body of literature mostly comprise on comparison of LC and OC in the context of specific indications that include uncomplicated gallstone disease or acute cholecystitis. Many Studies have reported that even in re-operative cases such as completion cholecystectomy laparoscopic techniques offer significant perioperative benefits over open surgery in terms of faster recovery and better cosmetic outcomes. ^[9] One of the important limitations of such studies is that they often concentrate on narrowly defined patient populations or unique surgical scenarios thereby limiting the generalizability of their findings. There remains a paucity of randomised controlled trials evaluating LC and OC across all indications. ^[10]

Therefore, this study was undertaken to address this existing knowledge gap by retrospectively analysing the outcomes of laparoscopic and open cholecystectomy performed for various indications. By evaluating key parameters such as operative time, postoperative recovery time, complication rates and duration of hospital stay this study aims to provide

comprehensive data that can assist in making informed surgical decision-making.

MATERIALS AND METHODS

This retrospective comparative study was conducted in the Department of General Surgery at a tertiary care teaching hospital. The duration of study was 18 months which extended from January 2024 to June 2025. 60 patients who had previously undergone cholecystectomy for various gallbladder pathologies were included in this study on the basis of a predefined inclusion and exclusion criteria. The participants were divided into two equal groups of 30 patients each. Group A consisted of patients who underwent laparoscopic cholecystectomy (LC) while Group B comprised of patients who underwent open cholecystectomy (OC). As this was a retrospective study, no prior sample size calculation was performed. All consecutive patients who met the predefined inclusion and exclusion criteria during the study period were included, yielding a total sample of 60 cases (30 LC and 30 OC). Since this study involved retrospective analysis of anonymized patient data without any direct patient interaction or intervention ethical committee approval was waived in accordance with institutional policy. The confidentiality of all patient records was strictly maintained throughout the study.

All patients whose records documented symptomatic gallbladder disease such as cholelithiasis, acute or chronic cholecystitis, gallbladder polyps, mucocele, empyema or acalculous cholecystitis were screened for eligibility. Clinical examination notes, laboratory investigations (complete blood count, liver function tests, renal function tests) and ultrasonography findings were retrieved from the hospital's electronic and manual archives. Based on the operative notes, surgeon's assessment and intraoperative findings documented at the time of surgery patients were categorized into the LC or OC group accordingly. Laparoscopic procedures had been performed under general anesthesia using a standard four port technique while open cholecystectomies had been carried out through a right subcostal Kocher incision using conventional methods. Intraoperative details, conversion rates, operative duration complications were extracted from electronic medical records or case papers.

For LC cases documentation included the method of pneumoperitoneum creation, dissection of Calot's triangle, clipping of the cystic duct and artery and removal of the gallbladder from the liver bed. For OC cases the corresponding open surgical steps were noted. Records of drain placement were reviewed. Postoperative monitoring parameters included time to oral intake, duration of hospital stay, wound status and postoperative complications such as wound infection or bile leak. Incidence of these complicates were obtained from inpatient papers as well as from electronic patient data. Follow up entries at two

weeks (for wound review) and four weeks (for postoperative recovery assessment) were also analyzed.

SPSS version 23.0 was used for data analysis. Quantitative variables such as operative time, postoperative pain scores, duration of hospital stay, time to return to normal activities and blood loss were expressed as mean ± standard deviation. Qualitative variables including postoperative complications, conversion to open surgery and demographic characteristics were presented as frequencies and percentages. The comparison of these quantitative and qualitative variables between these 2 groups was done using the Chi-square test or Fisher's exact test. P value less than 0.05 was taken as statistically significant.

Inclusion Criteria:

- Patients who had undergone either laparoscopic or open cholecystectomy within the study period were included.
- Patients aged between 18–65 years at the time of surgery.
- Only patients whose medical records contained complete operative and postoperative details necessary for analysis were included.

Exclusion Criteria:

- Age less than 18 or above 65 years at the time of cholecystectomy.
- Patients with proven or suspected gallbladder malignancy.
- Patients with known bleeding disorders, as recorded in their medical files, were excluded.
- Patients with a history of previous upper abdominal surgery documented in their records
- Patients with incomplete postoperative or follow up data.

RESULTS

The analysis of the gender distribution of the studied cases showed that in the LC group, females were more prevalent (60%) as compared to males (40%). Similarly, in the OC group, females also slightly outnumbered males with 17 cases (56.7%) compared to 13 males (43.3%). The difference in gender distribution between the two groups was not statistically significant (p=0.796) [Table 1].

Table 1: Demographic and Baseline Characteristics

Gender	Distribution	LC Group (n=30)	OC Group (n=30)	P Value
Male, n (%)	12 (40%)	13 (43.3%)	0.796
Female, r	n (%)	18 (60%)	17 (56.7%)	

The analysis of the age group distribution of the studied cases showed that the most commonly affected age group in both the LC and OC groups was 51–60 (30%). This was followed by the 41–50 year age group, with 9 cases (30%) in the LC group and 8 cases (26.7%) in the OC group. The 31–40 year group accounted for 7 cases (23.3%) in the LC group and 6

cases (20%) in the OC group. Least common age group was above 60 years, with 2 cases (6.7%) in LC and 3 cases (10%) in OC. The mean age of both the groups was found to be comparable with no statistically significant difference (P=0.4363) [Table 2].

Table 2: Age Distribution of studied cases.

Table 2. Age Distribution of studied cases.				
Age Group (Years)	LC Group (n=30)	OC Group (n=30)	P Value	
18–30	4 (13.3%)	3 (10%)	P = 0.4363	
31–40	7 (23.3%)	6 (20%)		
41–50	9 (30%)	8 (26.7%)		
51–60	8 (26.7%)	10 (33.3%)		
Above 60	2 (6.7%)	3 (10%)		
Total	30 (100%)	30 (100%)		
Mean Age	44.27 ± 11.64 years	46.63 ± 11.68 years		

The analysis of co-morbidities among the studied cases showed that the majority of patients in both groups had no comorbidity, with 18 patients (60%) in the LC group and 16 patients (53.3%) in the OC group. The most common comorbid condition was diabetes mellitus alone, affecting 4 patients (13.3%) in the LC group and 5 (16.7%) in the OC group. Hypertension alone was seen in 3 patients (10%) in LC and 4 (13.3%) in OC. Both diabetes and hypertension were present in 2 cases (6.7%) from the LC group and 3 (10%) from the OC group. Less conditions frequently reported included hypothyroidism, bronchial asthma, and ischemic heart disease, each found in 1 patient (3.3%) per group or fewer, with bronchial asthma absent in the OC group. Prevalence of co-morbidities was found to be comparable in both the groups with no statistically significant difference (P=0.794) [Figure 1].

The analysis of indications for cholecystectomy among the studied cases showed that cholelithiasis was the most common indication in both groups which was seen in 18 patients (60%) in the LC group and 17 patients (56.7%) in the OC group. This was followed by acute cholecystitis, reported in 5 cases (16.7%) in the LC group and 7 cases (23.3%) in the OC group. Chronic cholecystitis was indication in 3 patients (10%) in the LC group and 2 (6.7%) in the OC group. Other less frequent indications included

mucocele (2 cases [6.7%] in LC vs. 1 case [3.3%] in OC), empyema (1 case [3.3%] in LC vs. 2 cases [6.7%] in OC), and gallbladder polyp, which was reported in 1 patient (3.3%) in each group [Figure 2].

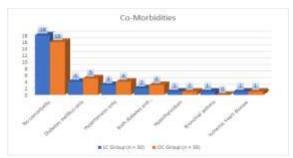


Figure 1: Co-morbidities in studied cases.

The analysis of intraoperative parameters revealed that the mean operative time was significantly shorter in the LC group (70.34 ± 15.2 minutes) as compared to the OC group (95.46 ± 18.6 minutes). The operative time was less in LC group as compared to OC group and the difference was highly significant

(P<0.001). Intraoperative adhesions were observed in 5 cases (16.7%) in the LC group and 8 cases (26.7%) in the OC group (p = 0.532). Bile duct injury occurred in only 1 patient (3.3%) in the OC group and none in the LC group (P=1.0). A surgical drain was placed in 4 cases (13.3%) in the LC group and 6 cases (20%) in the OC group (p = 0.730). Additionally, conversion to open surgery was required in 2 patients (6.7%) within the LC group [Table 3].

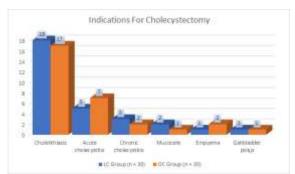


Figure 2: Indications for cholecystectomy in studied cases.

Table 3: Intraoperative Findings and Details in studied cases.

Parameter	LC Group (n=30)	OC Group (n=30)	p-value
Operative time (min)	70.34 ± 15.2	95.46 ± 18.6	< 0.001
Intraoperative adhesions, n (%)	5 (16.7%)	8 (26.7%)	0.532
Bile duct injury, n (%)	0 (0%)	1 (3.3%)	1.0
Drain placed, n (%)	4 (13.3%)	6 (20%)	0.730
Conversion to open, n (%)	2 (6.7%)	_	_

The analysis of postoperative recovery parameters revealed that oral intake was resumed significantly earlier in the LC group $(8.6 \pm 2.4 \text{ hours})$ compared to the OC group $(17.3 \pm 3.1 \text{ hours})$, with the difference being highly significant (P < 0.001). Similarly, the duration of hospital stay was markedly shorter in the

LC group, averaging 1.8 ± 0.6 days, whereas patients in the OC group stayed for 4.2 ± 1.1 days (P < 0.001). The time to ambulation was also significantly less in the LC group (10.4 ± 2.8 hours) compared to the OC group (19.5 ± 3.7 hours) (P < 0.001) [Table 4].

Table 4: Postoperative Recovery Parameters in both the groups.

Parameter	LC Group (n=30)	OC Group (n=30)	p-value
Oral intake (hours post-op)	8.6 ± 2.4	17.3 ± 3.1	< 0.001
Hospital stay (days)	1.8 ± 0.6	4.2 ± 1.1	< 0.001
Time to ambulation (hours)	10.4 ± 2.8	19.5 ± 3.7	< 0.001

The analysis of postoperative complications revealed that wound infection was significantly more common in the OC group, occurring in 6 patients (20%) compared to only 1 patient (3.3%) in the LC group, and this difference was statistically significant (p<0.05). Other complications such as bile leak, respiratory infection, postoperative ileus, and readmission within 30 days were observed exclusively or more frequently in the OC group: bile

leak in 1 case (3.3%), respiratory infection in 2 cases (6.7%), postoperative ileus in 3 cases (10%), and readmission in 1 case (3.3%), whereas the LC group had only 1 case (3.3%) of postoperative ileus and no other complications reported in these categories. The overall complication rate was substantially higher in the OC group as compared to LC group (P < 0.05) [Table 5].

Table 5: Postoperative Complications in studied cases.

Complication	LC Group (n=30)	OC Group (n=30)	p-value
Wound infection, n (%)	1 (3.3%)	6 (20%)	< 0.05
Bile leak, n (%)	0 (0%)	1 (3.3%)	
Respiratory infection, n (%)	0 (0%)	2 (6.7%)	
Postoperative ileus, n (%)	1 (3.3%)	3 (10%)	
Readmission within 30 days	0 (0%)	1 (3.3%)	
Total	2 (6.6%)	13 (43.3%)	

DISCUSSION

In this study comparing laparoscopic cholecystectomy (LC) versus open cholecystectomy (OC) (n = 60, 30 in each arm), we found that the LC group had significantly shorter operative time, earlier resumption of oral intake, shorter duration of hospital stay and fewer wound infections as compared to the OC group. These findings are similar to that reported in existing literature while also offering insights from a tertiary care institute in India.

Regarding operative time and recovery parameters our result of mean operative time for LC (70.34 \pm 15.2) vs OC (95.46 \pm 18.6) were found to be consistent with previous comparative work. For example, Kolla et al reported that the duration of surgery was significantly longer in OC than LC (72.4 min vs 44.7 min) in their cohort. Similarly, other studies have shown LC typically yields faster mobilization, earlier feeding and shorter hospital stay. This supports the minimally invasive advantage of LC in general surgical practice. The shorter hospital stay we observed (mean 1.8 days for LC and 4.2 days for OC) mirrors findings from a systematic review and meta-analysis by Roy DK et al who found the mean difference for hospital stay days between LC and OC was 2.68 (95% CI -3.66 to -1.70) favouring LC.[11] The mechanisms likely include reduced incision size, less pain, earlier mobilisation, and fewer wound related complications in the LC group.

Our postoperative complication profile also supports the superiority of LC in studied cases. wound infection occurred in only 3.3% of LC cases versus 20% in OC. In a similar comparative study done to compare open cholecystectomy and laparoscopic cholecystectomy in patients with cholelithiasis Singh P et al reported a similar higher incidence of wound infection in OC cases as compared to patients who had undergone LC.[12] The rate of surgical site infection reported in this study was 6.5% in OC and 3% in LC respectively. Moreover, a recent comparative study by Khalid A et al found that patients undergoing LC were less prone to low and high grade complications compared to OC.[13] Thus our findings further reinforce that in a tertiary care Indian institute setting the minimally invasive approach yields tangible benefits in terms of surgical site morbidity.

Our study confirms the data on broad safety and feasibility of LC compared to OC across different indications not limited to gallstone disease. For instance, a landmark paper by Lujan et al concluded that LC is a safe and valid alternative to OC even in acute cholecystitis with a lower rate of complications and shorter hospital stay. [14] The fact that our study included various indications (acute/chronic cholecystitis, mucocele, empyema, polyps) rather than only simple cholelithiasis strengthens the external validity of LC in a real world spectrum of gallbladder disease.

However, findings of this study should be interpreted in light of certain caveats and limitations. While LC demonstrated clear advantages in operative time, hospital stay and wound morbidity, our data (and indeed the literature) show that certain scenarios still favour OC or conversion from LC. For example, in cases of dense adhesions, unclear anatomy, prior surgery, empyema or gangrenous cholecystitis OC may be preferred over LC. The systematic review of laparoscopic versus open cholecystectomy by Laurence JM concluded LC had shorter operative times and reduced complication rates but acknowledged heterogeneity and selection bias.^[15] In our cohort, 2 cases (6.7%) required conversion to open. This conversion rate is within acceptable global limits (5-10%). We recommend that LC be offered as first line after ascertaining suitability for LC so that the threshold for conversion remains low.

Finally, from a surgical training and institutional resources perspective, our results highlight key implications for practice in tertiary care settings in India. First, they support the prioritisation of laparoscopic infrastructure and surgeon training given the superior peri operative outcomes. Second, they underscore the importance of appropriate patient selection and intra operative judgement. LC's benefit becomes most meaningful when complications are minimised and conversion decisions are made timely. Third, the results reiterate that open cholecystectomy still has a role in selected patients (complex disease, unstable anatomy, limited laparoscopic experience) and thus the surgical team must remain proficient in both approaches.

This study has certain limitations that needs careful consideration. First is its retrospective design which limits control over confounding variables and also is more prone for selection bias. Second, the analysis was restricted to short-term perioperative outcomes and no long-term follow-up data was analysed. Such an analysis could assess late complications or qualityof-life measures. Lastly a formal cost-effectiveness analysis was not conducted which could have provided additional insight into the economic implications of laparoscopic versus open cholecystectomy.

CONCLUSION

Our study of laparoscopic versus open cholecystectomy demonstrates that the laparoscopic approach offers considerable advantages over the open technique. Patients undergoing laparoscopic cholecystectomy experienced shorter operative durations, earlier resumption of oral intake, reduced duration of hospital stay and significantly fewer wound infections compared to those who underwent open cholecystectomy. Therefore, laparoscopic cholecystectomy should be advocated as the standard approach for most gallbladder surgeries in modern surgical practice. However, LC be offered as first line

after ascertaining suitability for LC so that the threshold for conversion remains low.

REFERENCES

- Gupta V, Jain G. Safe laparoscopic cholecystectomy: Adoption of universal culture of safety in cholecystectomy. World J Gastrointest Surg. 2019 Feb 27;11(2):62-84. doi: 10.4240/wjgs.v11.i2.62.
- Seshadri A, Peitzman AB. The difficult cholecystectomy: What you need to know. J Trauma Acute Care Surg. 2024 Sep 1;97(3):325-336. doi: 10.1097/TA.0000000000004337.
- Argiriov Y, Dani M, Tsironis C, Koizia LJ. Cholecystectomy for Complicated Gallbladder and Common Biliary Duct Stones: Current Surgical Management. Front Surg. 2020 Jul 21;7:42. doi: 10.3389/fsurg.2020.00042.
- Reynolds W Jr. The first laparoscopic cholecystectomy. JSLS. 2001 Jan-Mar;5(1):89-94.
- Odogwu S, Morris S, Addison S, Abbott S. Laparoscopic cholecystectomy performed by a surgical care practitioner: a review of outcomes. Ann R Coll Surg Engl. 2024 Nov;106(8):724-728. doi: 10.1308/rcsann.2023.0058. Epub 2024 Apr 25.
- Jenkins PJ, Paterson HM, Parks RW, Garden OJ. Open cholecystectomy in the laparoscopic era. Br J Surg. 2007 Nov;94(11):1382-5. doi: 10.1002/bjs.5854. PMID: 17654611.
- Mannam R, Sankara Narayanan R, Bansal A, Yanamaladoddi VR, Sarvepalli SS, Vemula SL, Aramadaka S. Laparoscopic Cholecystectomy Versus Open Cholecystectomy in Acute Cholecystitis: A Literature Review. Cureus. 2023 Sep 21;15(9):e45704. doi: 10.7759/cureus.45704.
- AlSaleh N, Alaa Adeen AM, Hetta OE, Alsiraihi AA, Bader MWM, Aloufi AK, ALZahrani FM, Ramadan M, Ageel AH, Alzahrani M. Emergency cholecystectomy: risk factors and impact of delay on electively booked patients, a 5-year experience of a tertiary care center. BMC Surg. 2024 Dec 20;24(1):396. doi: 10.1186/s12893-024-02694-8.

- Alser O, Dissanaike S, Shrestha K, Alghoul H, Onkendi E. Indications and Outcomes of Completion Cholecystectomy: A 5-year Experience From a Rural Tertiary Center. Am Surg. 2023 Nov;89(11):4584-4589. doi: 10.1177/00031348221124331. Epub 2022 Aug 27. PMID: 36031961.
- Ji W, Li LT, Wang ZM, Quan ZF, Chen XR, Li JS. A randomized controlled trial of laparoscopic versus open cholecystectomy in patients with cirrhotic portal hypertension. World J Gastroenterol. 2005 Apr 28;11(16):2513-7. doi: 10.3748/wjg.v11.i16.2513.
- Roy DK, Sheikh R. A Systematic Review and Meta-Analysis of the Outcomes of Laparoscopic Cholecystectomy Compared to the Open Procedure in Patients with Gallbladder Disease. Avicenna J Med. 2024 Feb 1;14(1):3-21. doi: 10.1055/s-0043-1777710. PMID: 38694141; PMCID: PMC11057899.
- 12. Singh, P., Gupta, S. K., & Kumar, M. (2017). A comparative study of open cholecystectomy and laparoscopic cholecystectomy in patients with cholelithiasis. International Surgery Journal, 5(1), 253–256.
- Khalid A, Khalil K, Mehmood Qadri H, Ahmad CZ, Fatima W, Raza A, Asif MA, Luqman MS, Jawariah, Nizami MFK. Comparison of Postoperative Complications of Open Versus Laparoscopic Cholecystectomy According to the Modified Clavien-Dindo Classification System. Cureus. 2023 Aug 17;15(8):e43642. doi: 10.7759/cureus.43642.
- Lujan JA, Parrilla P, Robles R, Marin P, Torralba JA, Garcia-Ayllon J. Laparoscopic Cholecystectomy vs Open Cholecystectomy in the Treatment of Acute Cholecystitis: A Prospective Study. Arch Surg. 1998;133(2):173–175. doi:10.1001/archsurg.133.2.173
- Laurence JM, Tran PD, Richardson AJ, Pleass HC, Lam VW. Laparoscopic or open cholecystectomy in cirrhosis: a systematic review of outcomes and meta-analysis of randomized trials. HPB (Oxford). 2012 Mar;14(3):153-61. doi: 10.1111/j.1477-2574.2011.00425.x. Epub 2012 Jan 18. PMID: 22321033; PMCID: PMC3371197.