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30-day Morbidity and Mortality After Cholecystectomy for Benign Gallbladder Disease (AMBROSE)

A Prospective, International Collaborative Cohort Study

Geoffrey Yuet Mun Wong, MBBS, MSc, ChM,✉ Himanshu Wadhawan, MBBS, MPhil,† Victor Roth Cardoso, PhD,‡ Laura Bravo Merodio, PhD,§ Yashasvi Rajeev, MBBS,‖ Ricardo David Maldonado,¶ Alessandro Martinino, MD,# Vignesh Balasubaramaniam, MBBS, MSc,** Aabid Ashraf, MS,†† Adeela Siddiqui,‡‡ Ahmad Ghassan Al-Shkirat, MBBS,§§ Ahmed Mohammed Abu-Elfatth, MD,‖‖¶¶ Ajay Gupta, PhD,## Akram Alkaseek, MBBCh,*** Amel Ouyahia, PhD,††† Amira Said, MBBCh, MSc,‡‡‡ Anshuman Pandey, MBBS, MS,§§§ Ashwani Kumar, MBBS,‖‖‖ Baila Maqbool, MD,¶¶¶ Carlos Alberto Millán, MD,### Cheena Singh, MBBS, MS,**** Diana Alejandra Pantoja Pachajoa, MD,†††† Dmitry Mikhailovich Adamovich,‡‡‡‡ Enrique Petracchi, MD,§§§§ Fariha Ashraf, MBBS,‖‖‖‖ Marco Clementi, MD,¶¶¶¶ Francesk Mulita, MD, PhD,#### Gad Amram Marom, MD, MSc,***** Gamaleldeen Abdulaal,††††† Georgios-Ioannis Verras, MBBS, MSc,‡‡‡‡‡ Giacomo Calini, MD,§§§§§ Gianluigi Moretto, MD,‖‖‖‖‖ Hossam Elfeki, MD, PhD,¶¶¶¶¶ Hui Liang, MD, PhD,##### Humam Jalaawiy, MBChB,****** Ibrahim Elzayat, MD,†††††† Jayanta Kumar Das, MS,‡‡‡‡‡‡ Jose Miguel Aceves-Ayala, MD,§§§§§§ Kazi T. Ahmed,‖‖‖‖‖‖ Luca Degrate, MD,¶¶¶¶¶¶ Manisha Aggarwal, MBBS, MS,###### Mohammed Ahmed Omar, MD, PhD,******* Mounira Rais, PhD,††††††† Muhammed Elhadi, MBBCh, MSc,‡‡‡‡‡‡‡ Nasser Sakran, MD,§§§§§§§ Rajesh Bhojwani, MS, MCh,‖‖‖‖‖‖‖ Ramesh Agarwalla, MBBS, MS,¶¶¶¶¶¶¶ Samir Kanaan, MD,####### Sarnai Erdene, MD, MSc,******** Serge Chooklin, MD, DrSc,†††††††† Suhail Khuroo, DNB,‡‡‡‡‡‡‡‡ Surrendar Dawani, MBBS,‡‡ Syed Tanseer Asghar, MBBS, MS,§§§§§§§§ Tak Kwan James Fung, MBBS,‖‖‖‖‖‖‖‖ Taryel Omarov, PhD,¶¶¶¶¶¶¶¶ Valentin Titus Grigorean, MD, PhD,********* Zdenko Boras, MD, PhD,######## Georgios V. Gkoutos, PhD, DIC,********* Rishi Singhal, MD,††††††††† Kamal Mahawar, MBBS, MS, MSc,‡‡‡‡‡‡‡‡‡ and AMBROSE Collaborative*

From the *Royal North Shore Hospital, St Leonards, Australia; †Forth Valley Royal Hospital, Larbert, United Kingdom; ‡University of Birmingham, Birmingham, United Kingdom; §University of Birmingham, Birmingham, United Kingdom; ‖Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; ¶Power Stats Statistical Consulting, West Ryde, Australia; #University of Illinois Chicago, Chicago, IL; **Ysbyty Gwynedd Hospital, Bangor, United Kingdom; ††Maharishi Markandeshwar Medical College and Hospital, Solan, India; ‡‡Jinnah Postgraduate Medical Centre, Karachi, Pakistan; §§Jordan University Hospital, Amman, Jordan; ‖‖Assiut University Hospital, Assiut, Egypt; ¶¶Aljazeera Hospital, Alriyadh, Saudia Arabia; ##Queen Elizabeth Hospital, Gateshead, United Kingdom; ***Gharyan Central Hospital, Gharyan, Libya; †††Medical Research Institute Hospital, Université Ferhat Abbas, Setif, Algeria; ‡‡‡Darent Valley Hospital, Dartford, United Kingdom; §§§Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India; ‖‖‖Government Medical College, Patiala, India; ¶¶¶University of New Mexico, Albuquerque, NM; ###Hospital San José, Bogota, Colombia; ****Maharishi Markandeshwar Medical College and Hospital, Solan, India; ††††Clinica Universitaria Reina Fabiola, Córdoba, Argentina; ‡‡‡‡Gomel State Medical University, Gomel, Belarus; §§§§Hospital Dr. Cosme Argerich, Buenos Aires, Argentina; ‖‖‖‖Patel Hospital, Karachi, Pakistan; ¶¶¶¶San Salvatore L'Aquila, University of L'Aquila, L'Aquila, Italy; ####General University Hospital of Patras, Patras, Greece; *****Department of General Surgery, Hadassah Hebrew University Medical Center, Jerusalem, Israel; †††††Southend University Hospital, Southend-on-Sea, United Kingdom; ‡‡‡‡‡General Hospital of Patras, Patras, Greece; §§§§§University Hospital of Udine - Santa Maria della Misericordia, Udine, Italy; ‖‖‖‖‖Pederzoli Hospital, Peschiera del Garda, Italy; ¶¶¶¶¶Mansoura University Hospital, Mansoura, Egypt; #####Second Affiliated Hospital of Nanchang University, Nanchang, China; ******Ad Dewania Teaching Hospital, Ad Dewania, Iraq; ††††††Aswan University Hospital, Aswan, Egypt; ‡‡‡‡‡‡Nazareth Hospital, Shillong, India; §§§§§§Hospital Civil de Guadalajara Dr. Juan I. Menchaca, Guadalajara, Mexico; ‖‖‖‖‖‖Darent Valley Hospital, Dartford, United Kingdom; ¶¶¶¶¶¶Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy; ######Jain Multispeciality Hospital, Khanna, India; *******Qena University Hospital, Qena, Egypt; †††††††Saadna Abdenour De Sétif, Setif, Algeria; ‡‡‡‡‡‡‡Tripoli University Hospital, Tripoli, Libya; §§§§§§§Faculty of Medicine, Bar-Ilan University, Ramat Gan, Israel; ‖‖‖‖‖‖‖Santokba Durlabhji Memorial Hospital, Jaipur, India; ¶¶¶¶¶¶¶Fortis Hospital, West Bengal,

Objective: This study aimed to assess 30-day morbidity and mortality rates following cholecystectomy for benign gallbladder disease and identify the factors associated with complications.

Background: Although cholecystectomy is common for benign gallbladder disease, there is a gap in the knowledge of the current practice and variations on a global level.

Methods: A prospective, international, observational collaborative cohort study of consecutive patients undergoing cholecystectomy for benign gallbladder disease from participating hospitals in 57 countries between January 1 and June 30, 2022, was performed. Univariate and multivariate logistic regression models were used to identify preoperative and operative variables associated with 30-day postoperative outcomes.

Results: Data of 21,706 surgical patients from 57 countries were included in the analysis. A total of 10,821 (49.9%), 4263 (19.7%), and 6622 (30.5%) cholecystectomies were performed in the elective, emergency, and delayed settings, respectively. Thirty-day postoperative complications were observed in 1738 patients (8.0%), including mortality in 83 patients (0.4%). Bile leaks (Strasberg grade A) were reported in 278 (1.3%) patients, and severe bile duct injuries (Strasberg grades B–E) were reported in 48 (0.2%) patients. Patient age, American Society of Anesthesiologists physical status class, surgical setting, operative approach, and Nassar operative difficulty grade were identified as the 5 predictors demonstrating the highest relative importance in predicting postoperative complications.

Conclusions: This multinational observational collaborative cohort study presents a comprehensive report of the current practices and outcomes of cholecystectomy for benign gallbladder disease. Ongoing global collaborative evaluations and initiatives are needed to promote quality assurance and improvement in cholecystectomy.

Keywords: benign gallbladder disease, bile duct injury, cholecystectomy, complications, morbidity, mortality

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Cholecystectomy is one of the most commonly performed abdominal surgical procedures worldwide and is primarily indicated for benign gallbladder diseases such as biliary colic, acute and chronic cholecystitis, gallstone pancreatitis, choledocholithiasis, and cholangitis.[1–3] Less common indications include gallbladder polyps and biliary dyskinesia. Laparoscopic cholecystectomy has become the standard surgical treatment for gallstones and is the preferred approach owing to its lower complication rate, shorter length of hospital stay, and faster recovery than open cholecystectomy.[4–6] Although primary open cholecystectomy has declined substantially since its introduction of laparoscopic cholecystectomy, current data regarding practices and outcomes in settings where the open approach remains the standard procedure are lacking.[7]

The primary aim of cholecystectomy is to ensure a safe procedure and prevent bile duct injury.[8] Although most procedures are uneventful, and severe complications, such as bile duct injury and death, are infrequent at the hospital level, the cumulative effect of a high volume of cholecystectomy procedures can magnify the scale of the problem at the health system level. Several national registries and collaborative studies have successfully captured the variations and outcomes of cholecystectomy at a national level.[9–13] However, an international knowledge gap still exists, particularly in low-income and middle-income countries. Furthermore, the reported incidence of important outcomes, such as bile duct injury, varies widely depending on the definition or criteria utilized for assessment.

Variations in the treatment of benign gallbladder diseases have been observed, which can be influenced by factors such as patient comorbidities, disease severity, technical expertise, and available resources. A recent global survey of surgeons demonstrated significant variations in preoperative, operative, and postoperative practice.[14] Understanding the areas of clinical variation and the extent to which warranted and unwarranted variations occur can help to identify areas of safety and quality for improvement and achieve better patient outcomes through improved surgical care.[15]

Capturing data and clinical variation on a large scale is necessary to detect low-frequency complications and implement effective strategies for patient safety and quality improvement. Therefore, a prospective international study is required to address these gaps and improve our understanding of cholecystectomy practices and outcomes. This study aimed to describe 30-day morbidity and mortality rates following cholecystectomy for benign gallbladder disease. In addition, this study aimed to identify factors that may influence patient outcomes and contribute to evidence-based improvements in surgical practice.

METHODS

Study Design and Setting

The AMBROSE audit was a prospective, international, observational, collaborative cohort study of patients who underwent cholecystectomy for benign gallbladder disease. Data on preoperative risk factors, intraoperative factors, and 30-day postoperative morbidity and mortality were collected for a 6-month study interval from January 1, 2022, to June 30, 2022. The study was open to any hospital performing cholecystectomy.

Participants and Population

The expression of interest to participating centers and surgeons was shared through The Upper Gastrointestinal Surgeons

India; #######Tishreen University Hospital, Latakia, Syria; ********Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; ††††††††Lviv Regional Clinical Hospital, Lviv, Ukraine; ‡‡‡‡‡‡‡‡Narayana Superspeciality Hospital, Katra, India; §§§§§§§§Kulsum International Hospital, Islamabad, Pakistan; ||||||||||||||||John Radcliffe Hospital, Oxford, United Kingdom; ¶¶¶¶¶¶¶¶Azerbaijan Medical University, Baku, Azerbaijan; ########Clinical Hospital Osijek, Osijek, Croatia; ********Bagdasar Arseni Emergency Clinical Hospital, Bucharest, Romania; ********Centre for Health Data Science, University of Birmingham, United Kingdom; †††††††††University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; and ‡‡‡‡‡‡‡‡‡South Tyneside and Sunderland NHS Trust, Sunderland, United Kingdom.

✉ tugs.ambrose@gmail.com.

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Society (TUGSS) membership database, national or professional organizations in general surgery and surgical specialties, social media, and personal networks. This study included all adult patients (aged 18 years and above) who underwent elective, emergency, or delayed cholecystectomy for benign gallbladder disease. Open and minimally invasive (laparoscopic and robotic) cholecystectomy approaches were considered eligible. Patients who underwent concurrent abdominal surgery and those with gallbladder cancer (preoperative or incidental diagnosis) were excluded from the study.

Variables of Interest and Outcomes

Anonymized study data were collected and managed using REDCap electronic data capture tools hosted at the Institute of Translational Medicine Birmingham, United Kingdom.[16,17] A data collection instrument with 73 data fields, including preoperative, operative, and postoperative variables, was created in REDCap (Supplementary Material, Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F15). Emergency cholecystectomy was defined as gallbladder surgery performed during the index admission. Delayed cholecystectomy was defined as gallbladder surgery scheduled >2 weeks following a patient's discharge from emergency admission in keeping with the guidelines and audit standards for the management of gallstone pancreatitis and common bile duct stones in the United Kingdom.[18–20] Elective cholecystectomy was defined as gallbladder surgery organized following an outpatient encounter. Thirty-day outcome data were collected in accordance with the protocols of each participating hospital. The Clavien-Dindo (CD) classification was used to define and grade postoperative adverse events. This system has a high degree of agreement in identifying and ranking complications and enables reliable and accurate classification of various complications.[21] The Strasberg classification was used to define and grade bile duct injuries, as this is the most widely adopted classification system.[22] Subtotal cholecystectomy and the fenestrating and reconstituting subtypes were defined based on the description by Strasberg et al.[23] Bile leaks following subtotal cholecystectomy were considered separately from Strasberg type A bile duct injuries following total cholecystectomy. The operative difficulty was defined according to the Nassar operative difficulty scale.[24]

At the end of the study period, the data entered into the REDCap were examined for accuracy, completeness, and consistency. The collaborators were contacted to clarify or verify the data as necessary. The final data set was downloaded and analyzed on December 30, 2022, when all the data queries were resolved.

Statistical Analysis

The results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[25] Descriptive statistics were used to summarize the data. Continuous data were assessed for distribution and summarized as mean (SD) or median (interquartile range) using appropriate parametric or nonparametric tests. Categorical data were expressed as frequencies and percentages, and differences were tested using the χ^2 or Fisher exact test, as appropriate. Univariate and multivariate logistic regression analyses were used to investigate the relationship between 30-day morbidity and mortality rates and the variables studied. The strength of the association between the identified risk factors for complications was determined by calculating unadjusted and adjusted odds ratios with 95% CIs. For all analyses, the threshold for 2-sided statistical significance was set at $P<0.05$. Effect estimates were summarized as odds ratios with 95% CIs. Analyses were performed using Stata Statistical Software Release 17.[26]

Predictive Modeling for Complications

A predictive model based on preoperative and operative factors was developed to predict postcholecystectomy complications. The log-likelihood ratio test was used to compare the fit of the models with and without specific predictors. Predictors that did not significantly enhance model fit were removed from the final model. The aim of the model reduction was to obtain a parsimonious model in which only predictors related to the response at a statistically significant level (adjusted by other predictors in the model) were kept. Dominance analysis was conducted to determine the importance of the predictors in the regression model and further understand the contribution of each predictor to the model's predictive power.[27] Lasso analysis for logistic regression was performed to validate the findings. The data set was split into a testing sample (75%) and a validation sample (25%) with random allocation. A standard LASSO for logistic regression was conducted on the testing sample, with K folds set to 10 to assess out-of-sample prediction performance. The variables included in both models were ranked from the most to the least important.

Ethics and Governance

The project was registered as a multinational audit (Audit Code CARMS-17645) at the University Hospitals Birmingham NHS Foundation Trust, United Kingdom. The study protocol did not require changing the treatment, care, or services from the accepted standards for the patients or service users. Each participating center was responsible for complying with the appropriate health research authority requirements for approval and data sharing. Site collaborators were responsible for obtaining and documenting patients' consent to share their data. Collaborators agreed to these terms electronically before being granted access to data in the REDCap.

RESULTS

Cohort Characteristics

This study collected data on 21,706 patients who underwent cholecystectomy for benign gallbladder disease between January 1, 2022, and June 30, 2022, from 57 countries (Supplementary Material, Table 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F15). Tables 1 and 2 and Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/SLA/F15 summarize the characteristics of the patients who underwent cholecystectomy. The patients were categorized into 3 groups based on the setting of their surgery: elective (n = 10,821, 49.9%), emergency (n = 4263, 30.5%), and delayed (n = 6622, 19.6%). Patients admitted electively were younger, with a median age of 47 years compared with emergency and delayed admissions, with median ages of 52 and 50 years, respectively. Females represented the majority of cases in all categories. Males were more commonly admitted for emergency surgery, accounting for 41.1% (n = 1753) of all emergency admissions. The majority of patients across all categories had American Society of Anesthesiologists (ASA) 1 and ASA II physical statuses. The emergency category had the highest proportion of patients with ASA III and above (15.6% of all emergency admissions) and a greater prevalence of comorbidities, including a body mass index >30, type 2 diabetes mellitus, ischemic heart disease, and stroke.

The main indications for surgery differed among the groups (Table 2). Biliary colic was the most common indication in the elective group (64.5%), whereas cholecystitis was the most common in the emergency (64.3%) and delayed (37.0%) groups. Eight cases of Mirizzi syndrome were recorded: type I: 1, type II: 2, type III: 2, type V = 1, unclassified. Of the 1195 cholecystectomy patients admitted for pancreatitis, 436 (36.5%) underwent emergency surgery, 664 (55.6%) underwent delayed procedures, and 95 (7.9%) underwent elective surgery. Cholecystectomy during the index admission was performed in 2739 of 7989 (34.2%) patients with acute cholecystitis. Preoperative interventions included endoscopic retrograde cholangiopancreatography and percutaneous cholecystostomy, which were performed in 9.1% and 1.4% of patients, respectively.

Operative Details

Tables 3 and 4 and Supplementary Table 4, Supplemental Digital Content 1, http://links.lww.com/SLA/F15 summarize the operative details of the patients in the cohort. Laparoscopic cholecystectomy was the operative approach in 19,820 (91.3%) patients, whereas 1231 (5.6%) patients underwent primary open cholecystectomy. Conversion from laparoscopic to open surgery was performed in 655 (3.0%) cases, most commonly in emergency cholecystectomy (235 of 4263 emergency cholecystectomies, 5.5%). The reasons for conversion were failure to progress with minimally invasive cholecystectomy (47.5%), adhesions (26.7%), bleeding (8.3%), bile duct injury (1.9%), and other indications that were not categorized, such as visceral injury (8.9). Intraoperative cholangiography was performed in only 1511 patients (7.0%), with the highest utilization in emergency cholecystectomies, accounting for 578 out of 4263 emergency cases (13.6%). In the delayed cholecystectomy group, cholangiograms were performed in 8.0% of patients (530 of 6622), while in the elective cholecystectomy group, it was performed only in 3.7% of patients (403 of 10,821). The utilization of intraoperative cholangiogram in the current audit is summarized in Supplementary Fig. 3, Supplemental Digital Content 1, http://links.lww.com/SLA/F15. The findings indicate that 349 of 395 (88.4%) collaborative groups had performed intraoperative cholangiograms in <10.0% of their cholecystectomy cases. Operative biliary interventions were conducted in 774 patients, accounting for 3.5% of all cases. These interventions included transcystic common bile duct (CBD) exploration (27.4%), trans-CBD exploration (37.5%), endoscopic retrograde cholangiopancreatography (16.9%), and other procedures such as transcystic biliary stenting (9.1%).

Subtotal cholecystectomy was performed in 424 (2.0%) patients. Among these patients, 296 (69.8%) were categorized as grade 4 according to the Nassar operative difficulty scale, and 100 (23.6%) were categorized as grade 3. Of the 419 documented approaches, 266 (63.4%) were completed laparoscopically, 96 (22.9%) required conversion from laparoscopic to open surgery, and 62 (14.8%) underwent open cholecystectomies. Fenestrating subtotal cholecystectomies were performed in 194 cases (45.8% of all subtotal cholecystectomies), and reconstituting subtotal cholecystectomies were performed in 225 cases (53.1% of all subtotal cholecystectomies).

30-day Morbidity and Mortality

Tables 5 and 6 present the Clavien-Dindo classification of surgical complications and specific complications in patients undergoing cholecystectomy, respectively. In the total cohort, postoperative complications were observed in 1738 patients (8.0%), with 564 (2.6%) having major complications (Clavien-Dindo classification III and above). Emergency cholecystectomy procedures had the highest rate of complications at 14.6%, followed by the delayed cholecystectomy group at 9.6%, and the elective cholecystectomy group had the lowest rate at 4.4%. Clavien-Dindo class II complications were the most common, observed in 653 patients (3.0%), followed by class I in 521 patients (2.4%). Complications of classes III, IV, and V were less frequent, with class III in 348 patients (1.6%), class IV in 133 patients (0.6%), and class V in 83 patients (0.4%). Among day-case cholecystectomies, 225 patients (3.9%) developed complications within 30 days of surgery.

In this cohort of 21,706 patients who underwent cholecystectomy, 384 (1.8%) were diagnosed with a bile duct injury. The incidence of bile duct injuries varied between elective, emergency, and delayed admissions. The highest incidence of bile duct injuries was reported in the delayed setting, with 138 (2.1%). Among 10,821 elective admissions and 4263 emergency admissions, bile duct injuries were identified in 94 (0.9%) and 131 (3.1%) patients, respectively. Type A was the most common bile duct injury diagnosed in 336 patients (87.5% of bile duct injuries). Among these type A cases, intervention was not required in 288 patients, whereas 48 patients required intervention. Strasberg types B, C, D and E1 to E4 were relatively less frequent and identified in 48 patients, accounting for 12.5% of all bile duct injuries and 0.2% of the overall cohort.

Bleeding was reported in 0.8% (n = 164) of the patients and was more common in the emergency setting (1.5%) than in elective procedures (0.4%). Bowel injury was rare, occurring in only 0.1% (n = 15) of the patients, but was more common in delayed cholecystectomies (0.1%) than in elective cases (< 0.1%). In this cohort, emergency cholecystectomy was associated with a higher risk of postoperative complications, including surgical site infections (4.0%), pneumonia (1.5%), cardiac complications (0.9%), venous thromboembolism (0.2%), and stroke (< 0.1%).

Among the 424 subtotal cholecystectomies, minor complications (Clavien-DIndo I and II) were observed in 17.5%, and major complications (Clavien-DIndo III–V) in 15.8%. Fifteen (3.5%) deaths were observed within 30 days among patients undergoing subtotal cholecystectomy. Of the patients who underwent the fenestrating procedure, 26 (13.4%) had postoperative bile leaks, and 2 had bile duct injuries (Strasberg classification D). Among those who underwent the reconstitution procedure, 32 cases of postoperative bile leak and one case of bile duct injury (Strasberg classification D) were recorded. There was no statistically significant difference in postoperative bile leaks between patients who underwent fenestrating and reconstituting subtotal cholecystectomy ($P = 0.372$). The 3 cases of Strasberg D bile duct injuries were classified as grade 3 on the operative difficulty grading scale, necessitated intervention in all cases, and were associated with mortality in one case.

Length of Stay and Readmission

A total of 5780 patients (26.6%) underwent cholecystectomy as a day, with the most common indication being biliary colic (51.2%). The median length of stay for non-day case cholecystectomies in emergency, delayed, and elective settings were 3 days (SD 7.7), 2 days (SD 4.0), and 2 days (SD 3.5), respectively. The overall readmission rate for the cohort was 1.8% (392 of 21,706), with the highest unplanned readmission from complications observed in emergency (119 of 4263, 2.8%) cholecystectomy, followed by delayed (174 of 6622, 2.6%), and elective cholecystectomy (99 of 10,821, 0.9%).

Predictors for Complications

Univariate logistic regression demonstrated a statistically significant relationship between 18 preoperative and 6 operative factors and complications following cholecystectomy for benign gallbladder disease (Supplementary Material, Table 5, Supplemental Digital Content 1, http://links.lww.com/SLA/F15 and Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F15 and 2, Supplemental Digital Content 1, http://links.lww.com/SLA/F15). Figure 1 presents the forest plot of the multivariate analysis for preoperative and operative factors associated with postcholecystectomy complications. ASA classes IV and V were combined for the multivariate analysis due to the limited number of observations. The corresponding values for the forest plot are presented in Supplementary Table 6, Supplemental Digital Content 1, http://links.lww.com/SLA/F15. Seven preoperative and 6 operative variables in the multivariate logistic regression were significant predictors of complications: age, surgical setting (elective, emergency, and delayed), previous gallstone disease-related admissions, indication for cholecystectomy, ASA physical status class, type 2 diabetes mellitus, cirrhosis, primary operator, operative approach, subtotal cholecystectomy, Nassar operative difficulty grade, intraoperative cholangiogram, and operative biliary intervention. The operative approach, Nassar operative difficulty grade, ASA physical status class, surgical setting, and patient age were identified as the 5 predictors demonstrating the highest relative importance in predicting postoperative complications for cholecystectomy using dominance analysis and LASSO regression analysis.

DISCUSSION

This prospective observational collaborative cohort study assessed the current management and outcomes of patients in an international cohort who underwent cholecystectomy for benign gallbladder disease. The data indicate that cholecystectomy is generally safe but also highlight that serious complications are an ongoing concern, particularly in emergency cholecystectomies. The overall mortality rates were 0.1% for elective cases, 1.4% for emergency cases, and 0.2% for delayed cases. The overall 30-day mortality rate is higher than 0.1% and 0.2% reported in UK and Swedish population-based cohort studies, respectively.[12,28] However, these variations may arise from differences in case mix and variations in the practice of cholecystectomy for benign gallbladder disease, particularly when considering the inclusion of diverse populations, including low and middle-income countries, in this study. Despite the low mortality rates, these findings warrant consideration, given that cholecystectomy is performed for benign gallbladder disease and underscores the importance of careful patient selection and perioperative management.

Emergency admissions exhibited significantly elevated rates of both major (Clavien-Dindo grades III–V) and minor complications (grades I and II) when compared with elective and delayed admissions. The current study found lower complication rates for elective (4.4%), emergency (14.6%), and delayed (9.6%) cholecystectomy than a previous UK population-based study (7.7%, 15.4%, and 12.8%, respectively).[12] In comparison to the recent CHOLECOVID study that examined patients with cholecystitis globally during the early months of the SARS-CoV-2 pandemic, the current study reported lower rates of minor complications at 15.8% in the CHOLECOVID study. However, major complication rates were comparable at 5.4% in the CHOLECOVID study.[29]

Bile duct injury, which occurred in 1.5% of all cases in this study, is a significant complication owing to its potential to cause long-term morbidity, necessitate repeated interventions, and increase the mortality risk. The results of this study are consistent with the findings of the population-based studies conducted by Gallriks in Sweden and CholeS in the UK. Both studies included Strasberg type A bile duct injuries and reported rates of 1.5% and 1.6%, respectively.[12,30] Studies identifying bile duct injuries by subsequent intervention or surgery may report lower overall rates as most bile leaks resolve without further management. When bile leaks were excluded, the incidence of bile duct injury in the current study was 0.2%, which is comparable to that reported in other national studies.[12,31] This international collaborative study with large sample size and diverse patient populations improves generalizability across various health care settings and addresses the challenge of underpowering associated with the low incidence of bile duct injuries.

The conversion rate from laparoscopic cholecystectomy to open cholecystectomy was 3.0%, which is at least

TABLE 1. Baseline Cohort Characteristics of Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

		Patients, frequency (%)			
		Elective n = 10.821 (49.9%)	**Emergency n = 4263 (30.5%)**	**Delayed (n = 6622, 19.6%)**	**Total**
		10,821 (49.9)	4263 (30.5)	6622 (19.6)	21,706
Age	Median, IQR	47 (36–58)	52 (38–65)	50 (38–62)	—
Sex	Female	7797 (72.1)	2509 (58.9)	4436 (67.0)	14,742
	Male	3014 (27.9)	1753 (41.1)	2185 (33.0)	6952
	Other	10 (< 0.1)	1 (< 0.1)	1 (< 0.1)	12
ASA class	I	3848 (35.6)	848 (19.9)	1575 (23.8)	6271
	II	5902 (54.5)	2378 (55.8)	3985 (60.2)	12265
	III	1052 (9.7)	926 (21.7)	1034 (15.6)	3012
	IV	16 (0.2)	102 (2.4)	25 (0.4)	143
	V	0	8 (0.2)	1 (< 0.1)	9
	Missing	3 (0.0)	1 (< 0.1)	2 (< 0.1)	6
Body mass index	< 18.0	130 (1.2)	36 (0.8)	68 (1.0)	234
	18.0–24.9	3656 (33.8)	1132 (26.6)	1902 (28.7)	6690
	25.0–29.9	4325 (40.0)	1826 (42.8)	2781 (42.0)	8932
	30.0–34.9	1838 (17.0)	804 (18.9)	1261 (19.0)	3903
	35.0–39.9	581 (5.4)	296 (6.9)	394 (6.0)	1271
	> 40.0	266 (2.5)	143 (3.4)	200 (3.0)	609
	Missing	25 (0.2)	26 (0.6)	16 (0.2)	67

IQR indicates interquartile range.

TABLE 2. Prior Admissions, Indications for Cholecystectomy, and Interventions Before Cholecystectomy

		Patients, frequency (%)			
		Elective n = 10,821 (49.9%)	Emergency n = 4263 (30.5%)	Delayed (n = 6622, 19.6%)	Total
		10,821 (49.9)	4263 (30.5)	6622 (19.6)	21,706
Prior admissions	0	10,821 (100.0)	2826 (66.3)	0	13,647
	1	—	933 (21.9)	4523 (68.3)	5456
	2	—	343 (8.1)	1322 (20.0)	1665
	≥ 3	—	161 (3.8)	506 (7.6)	667
	Missing	—	0 (< 0.1)	271 (4.1)	271
Indication for cholecystectomy	Cholecystitis	2734 (25.3)	2739 (64.3)	2516 (38.0)	7989
	Biliary colic	6982 (64.5)	463 (10.9)	2235 (33.8)	9680
	Gallstone pancreatitis	95 (0.9)	436 (10.2)	664 (10.0)	1195
	Cholangitis	19 (0.2)	113 (2.7)	144 (2.2)	276
	Choledocholithiasis	338 (3.1)	323 (7.6)	778 (11.8)	1439
	Gallbladder polyps	314 (2.9)	14 (0.3)	73 (1.1)	401
	Biliary dyskinesia	66 (0.6)	7 (0.2)	26 (0.4)	99
	Other	273 (2.5)	167 (3.9)	186 (2.8)	626
	Missing	0	1 (64.3)	0	1
Preoperative ERCP	No	10,556 (97.6)	3730 (87.5)	5435 (82.1)	19,721
	Yes	264 (2.4)	532 (12.5)	1187 (17.9)	1983
	Missing	1 (< 0.1)	1 (< 0.1)	0	2
Preoperative cholecystostomy	No	10,743 (99.3)	4181 (98.1)	6465 (97.6)	21,389
	Yes	77 (0.7)	81 (1.9)	155 (2.3)	313
	Missing	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	4

ERCP indicates endoscopic retrograde cholangiopancreatography.

comparable, if not lower, than the rates reported in previously published studies.[12,32] While conversion is an important quality performance indicator associated with morbidity
and mortality, the approach in itself is not considered a complication. Severe inflammation, adhesions, bleeding, or a combination of these factors may make it necessary to convert to an open approach when it is unsafe or impractical to continue with the minimally invasive approach. Most subtotal cholecystectomies were performed using a laparoscopic approach rather than conversion to the open approach for difficult gallbladders. This may reflect several factors, such as a shift in the traditional paradigm to convert to open surgery in technically difficult cases, improved visualization using a laparoscope, and declining experience in open cholecystectomy.

The identification of significant preoperative and operative predictors of complications allows the dynamic risk of complications to be assessed at different phases of treatment and enables the adaptation of strategies and interventions based on this information. The 5 predictors that demonstrated the highest relative importance in predicting postoperative complications were age, ASA physical status class, surgical setting, Nassar operative difficulty grade, and operative approach. These factors have previously been shown to be independent predictors of complications, emphasizing the importance of considering them during perioperative assessment to determine the most appropriate treatment strategy, particularly for high-risk patients.[12,24,28,32]

TABLE 3. Operative Approach for Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

		Elective n = 10,821 (%)	Emergency, n = 4263 (%)	Delayed n = 6622 (%)	Total n = 21,706
Operative approach	Laparoscopic cholecystectomy	10,319 (95.4)	3532 (82.9)	5969 (90.1)	19,820
	Open cholecystectomy	341 (3.2)	496 (11.6)	394 (6.0)	1231
	Laparoscopic converted to open cholecystectomy	161 (1.5)	235 (5.5)	259 (3.9)	655
Indication for conversion	Adhesions	40 (25.5)	46 (20.1)	89 (35.2)	175
	Bleeding	26 (16.6	23 (10.0)	21 (8.3)	70
	Bile duct injury	8 (5.1	12 (5.2)	5 (2.0)	25
	Failure to progress with laparoscopic or robotic surgery/"difficult" gallbladder	69 (44.0)	133 (58.1)	109 (43.1)	311
	Other	14 (8.9)	15 (6.6)	29 (11.5)	58
	Missing	4 (< 0.1)	6 (0.1)	6 (0.1)	16
Total or subtotal cholecystectomy	Total cholecystectomy	10,747 (99.3	4071 (95.5)	6461 (97.6)	21,279
	Subtotal cholecystectomy.	71 (0.7)	192 (4.5)	161 (2.4)	424
	NA	3 (< 0.1)	0	0	3
Fenestrating or reconstituting subtotal cholecystectomy	Fenestrating	40 (56.3)	81 (42.2)	73 (45.3)	194
	Reconstituting	28 (39.4)	110 (57.3)	87 (54.0)	225
	NA	3 (4.2)	1 (0.5)	1 (0.6)	5

TABLE 4. Operative Details for Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

		Elective n = 10,821 (%)	Emergency n = 4263 (%)	Delayed n = 6622 (%)	Total n = 21,706
Primary operator	Consultant	7875 (72.8)	2951 (69.2)	4732 (71.5)	15,558
	Trainee	2945 (27.2)	1311 (30.8)	1890 (28.5)	6146
	NA	1 (< 0.1)	1 (< 0.1)	0	2
Nassar grade	Grade 1	4937 (45.6)	613 (14.4)	2157 (32.6)	7707
	Grade 2	4170 (38.5)	1211 (28.4)	2486 (37.5)	7867
	Grade 3	1227 (11.3)	1439 (33.8)	1295 (19.6)	3961
	Grade 4	477 (4.4)	1000 (23.5)	683 (10.3)	2160
	NA	10 (0.1)	0	1 (0.0)	11
Intraoperative cholangiogram	No	10,418 (96.3)	3685 (86.4)	6091 (92.0)	20,194
	Yes	403 (3.7)	578 (13.6)	530 (8.0)	1511
	NA	0	0	1 (< 0.1)	1
Operative biliary intervention	Transcystic CBD exploration	27	103	103	233
	Laparoscopic Trans-CBD exploration	82	106	131	319
	ERCP	23	64	57	144
	Other	47	15	16	78
	Not Performed	10,642	3975	6315	20,856
Abdominal drain	Yes	3713 (34.3)	2467 (57.9)	3147 (47.5)	9327
	No	7107 (65.7)	1796 (42.1)	3473 (52.5)	12,376
	NA	1 (< 0.1)	0	2 (< 0.1)	3

CBD indicates common bile duct; ERCP, endoscopic retrograde cholangiopancreatography.

Subtotal cholecystectomy has been advocated for difficult operative conditions when a critical view of safety cannot be achieved, and biliary anatomy cannot be clearly defined.[8,23,33] Although fenestrating subtotal cholecystectomy is associated with a higher incidence of postoperative biliary fistula than the reconstituting subtype, this study did not find a statistically significant difference in bile leak or postoperative intervention between the 2 techniques.[23] These findings suggest that the short-term outcomes of fenestrating and reconstituting subtotal cholecystectomies are comparable. Long-term follow-up is needed to assess the recurrence of gallstones associated with the remnant gallbladder in reconstituting subtotal cholecystectomies. Although avoiding dissection of ductal structures would have an anticipated effect on reducing bile duct injury, it does not eliminate the risk of such injuries, as exemplified by 3 cases of lateral injury to the biliary system without any loss of continuity.[33] The precise mechanism of bile duct injury in these cases remains uncertain based on the collected data. However, potential contributing factors to these injuries may involve misidentification of biliary anatomy during the initial dissection of the hepatocystic triangle or during subtotal cholecystectomy. These factors could be influenced by variations in biliary anatomy, marked acute local inflammation, or chronic biliary inflammatory fusion. Although it remains uncertain whether higher frequency or more severe bile duct injuries would have resulted if surgeons had persisted with total cholecystectomy in these difficult cases, these reports are cautionary reminders about the rare but clinically significant risk of bile duct injury with subtotal cholecystectomy.

TABLE 5. Clavien-Dindo Classification of Surgical Complications for Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

	Elective n = 10,821 (49.9%)	Emergency n = 4263 (30.5%)	Delayed n = 6622 (19.6%)	
	Incidence (%)	Incidence (%)	Incidence (%)	Total
Complications by Clavien-Dindo Classification				
Grade	—	—	—	—
1	160 (1.5)	162 (3.8)	199 (3.0)	521
2	185 (1.7)	218 (5.1)	250 (3.8)	653
3a	44 (0.4)	83 (2.0)	76 (1.2)	203
3b	46 (0.4)	46 (1.1)	53 (0.8)	145
4a	28 (0.3)	44 (1.0)	33 (0.5)	105
4b	6 (0.1)	13 (0.3)	9 (0.1)	28
5	10 (0.1)	58 (1.4)	15 (0.2)	83

Notable variations in the clinical practice of cholecystectomy have been identified within our cohort, specifically the low utilization of intraoperative cholangiogram and the high proportion of drain placement after cholecystectomy.[34,35] The utilization of intraoperative cholangiogram was highly selective in this study, as reflected by the overall rate of cholangiograms performed in relation to the total number of cholecystectomies and the significant percentage of collaborative groups with utilization below 10.0%. The indications for cholecystectomy associated with common bile duct stones such as gallstone pancreatitis, choledocholithiasis, and cholangitis are higher than the use of cholangiogram, which raises concern for suboptimal assessment and management of the bile duct in these conditions. Further investigation is warranted to gain a better understanding of the factors contributing to the remarkably low rates of intraoperative cholangiography and potential areas for improvement in clinical practice. Despite the high-level evidence indicating no additional benefit of routine abdominal drainage for uncomplicated cholecystectomy and possible complications associated with it, the overall percentage of patients who had an abdominal drain still remained high at 43.0% (9327 out of 21,706).[36,37] The incidence reported in this study may indicate a substantial use of routine prophylactic drains to detect bile leaks, particularly considering that 57.8% of these drains were inserted during cholecystectomies classified as having grade 1 and 2 operative difficulties. The incidence of abdominal drain use is not well established from larger multicenter or national studies. The high incidence of abdominal drains presented in this study may reflect unwarranted variation

TABLE 6. Bile Duct Injuries and Other Specific Complications for Patients Undergoing Cholecystectomy for Benign Gallbladder Disease

	Elective n = 10,821	Emergency n = 4263	Delayed n = 6622	
	Incidence (%)	Incidence (%)	Incidence (%)	Total
Bile duct injury grade	90 (0.8)	98 (2.3)	138 (2.1)	326
Strasberg A*	74 (0.7)	84 (2.0)	120 (1.8)	278
Stasberg B	1 (< 0.1)	0	0	1
Strabserg C	1 (< 0.1)	2 (< 0.1)	0	3
Strasberg D	7** (0.1)	6 (0.1)	11** (0.2)	24
Strasberg E1	4 (< 0.1)	3 (0.1)	1 (< 0.1)	8
Strasberg E2	2 (< 0.1)	2 (0.1)	2 (< 0.1)	6
Strasberg E3	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)	4
Strasberg E4	0	0	2 (< 0.1)	2
Bleeding	41 (0.4)	65 (1.5)	58 (0.9)	164
Bowel injury	3 (0.0)	4 (0.1)	8 (0.1)	15
Wound infection	152 (1.4)	170 (4.0)	217 (3.3)	539
Respiratory infection	15 (0.1)	106 (2.5)	55 (0.8)	176
Venous thromboembolism	1 (< 0.1)	10 (0.2)	7 (0.1)	18
Myocardial infarction or cardiac arrest	8 (< 0.1)	37 (0.9)	11 (0.2)	56
Stroke	1 (< 0.1)	4 (0.1)	4 (0.1)	9
Renal failure	5 (0.1)	26 (0.6)	13 (0.2)	44
Urinary tract infection	18 (0.2)	29 (0.7)	29 (0.4)	76

*Bile leaks associated with subtotal cholecystectomy were considered separately.

**Bile duct injuries were observed in 2 cases of elective subtotal cholecystectomy and 1 case of delayed subtotal cholecystectomy.

and an opportunity for quality improvement. Upcoming international prospective cohort studies on cholecystectomy may further clarify this trend.[38]

Although this study contributes valuable data for understanding the outcomes of cholecystectomy, the results should be contextualized within several considerations. First, the study had a follow-up duration of 30 days, considering the practicality and feasibility of conducting a 6-month global audit. Although short-term outcomes are valuable for assessing immediate postoperative recovery and identifying early complications, it is essential to acknowledge that this limited timeframe may not be adequate for assessing certain complications, particularly bile duct injuries. These injuries are infrequent but can lead to prolonged hospital stays, readmissions, the need for repeat interventions, and mortality after 30 days, all of which might not have been captured within this relatively short follow-up window.[39] Second, this study was limited by the absence of a site survey to collect data on hospital-level services and resources during the study period. This information could have provided valuable insights into variations in the practice and outcomes of cholecystectomy across different health care settings. Furthermore, the reallocation of resources, as well as delays and backlogs in surgical procedures resulting from the pandemic, might have influenced patient treatment and outcomes during this specified timeframe.[29] Incorporating site surveys into future studies would offer a more comprehensive understanding of cholecystectomy practice in diverse environments. A third limitation of this study was its inability to independently validate the data, primarily because it was collected from multiple sources or contexts. However, efforts were made to improve data compliance by informing collaborators to record all consecutive cases and to address missing data or inconsistencies at the end of the study. The potential selection and sampling biases may have affected the data set despite these measures.

Several areas that can enhance the understanding of surgical practices and their influence on patient outcomes in future audits have been identified. The experience of the operating surgeons was documented by categorizing primary operators into two groups: trainees and consultants. While this allowed us to describe the association between experience in cholecystectomy and postoperative outcomes at a broad level, incorporating additional factors such as the volume of cholecystectomies performed, surgical specialty, and the level of supervision for trainee-led cholecystectomies in future audits will provide a more comprehensive understanding of the impact of variation in surgical experience on outcomes.[40] The majority (80.3%) of the cohort that underwent elective and delayed cholecystectomy can reasonably be considered a surrogate for daytime procedures, as they are typically performed during regular hours. The timing of emergency cholecystectomy, specifically daytime and nighttime operations, can vary significantly and potentially influence outcomes.[41] Therefore, incorporating the timing of cholecystectomy in future audits is valuable for quality improvement and effective resource allocation. Clinical practice may vary regarding the timing of bile leak intervention,

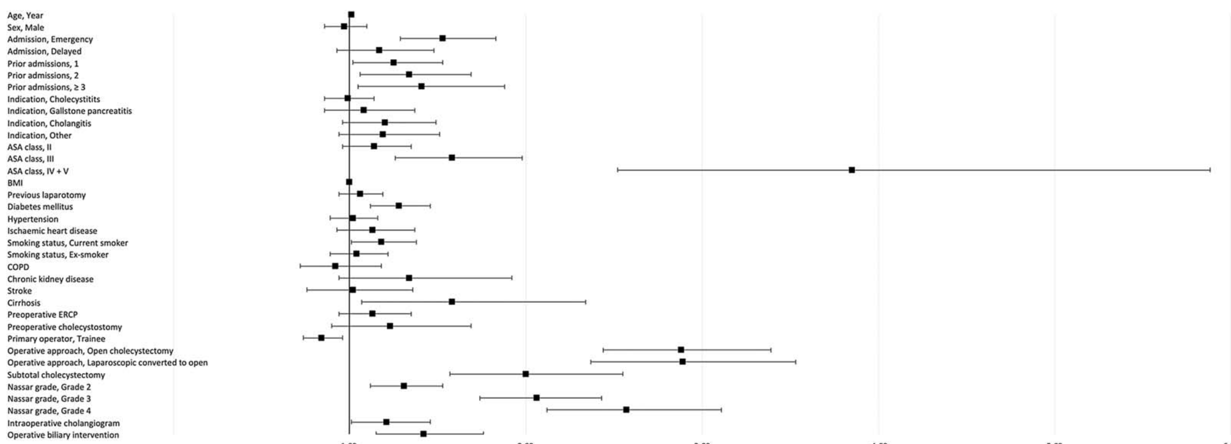

FIGURE 1. Forest plot of multivariate analysis for preoperative and operative factors associated with complications after cholecystectomy for benign gallbladder disease.

with some surgeons basing their decision on factors such as the volume and duration of bile leakage.[42,43] This timing data should be considered for inclusion in future studies to provide a more comprehensive understanding of the management of bile leaks in total and subtotal cholecystectomy. Although the majority of collaborative groups did not routinely perform intraoperative cholangiograms, the absence of specific data, such as indications for selective use, limits the ability to establish any direct associations between cholangiography and bile duct injury.[30,44] Future studies should incorporate information about whether these injuries are diagnosed intraoperatively or postoperatively, as this distinction can provide insights into the management strategies employed in these 2 different settings.

This study presents the 30-day morbidity and mortality outcomes of 21,706 cholecystectomies performed for benign gallbladder disease in a global population. Postoperative complications were observed in 1738 patients (8.0% of the total cohort), including mortality in 83 patients (0.4%) and bile duct injuries (including bile leaks) in 326 patients (1.5%). We showed that the frequency of complications, particularly bile duct injury and death, was relatively low, consistent with the findings of previous observational studies. Nevertheless, it is essential to consider the severity of clinically significant injuries, such as bile duct injuries, given the frequency at which cholecystectomies are performed. The 5 predictors demonstrating the highest relative importance in predicting postoperative complications were operative approach, Nassar operative difficulty grade, ASA physical status, surgical setting, and patient age. Continuous evaluation and ongoing global collaborative initiatives are pivotal for promoting quality assurance and improvements in cholecystectomy.

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