Population-Based Analysis of 4113 Patients With Acute Cholecystitis

Defining the Optimal Time-Point for Laparoscopic Cholecystectomy

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Objective: To compare clinical outcomes after laparoscopic cholecystectomy (LC) for acute cholecystitis performed at various time-points after hospital admission.

Background: Symptomatic gallstones represent an important public health problem with LC the treatment of choice. LC is increasingly offered for acute cholecystitis, however, the optimal time-point for LC in this setting remains a matter of debate.

Methods: Analysis was based on the prospective database of the Swiss Association of Laparoscopic and Thoracoscopic Surgery and included patients undergoing emergency LC for acute cholecystitis between 1995 and 2006, grouped according to the time-points of LC since hospital admission (admission day (d0), d1, d2, d3, d4/5, d $\geq$6). Linear and generalized linear regression models assessed the effect of timing of LC on intra- or postoperative complications, conversion and reoperation rates and length of postoperative hospital stay.

Results: Of 4113 patients, 52.8% were female, median age was 59.8 years. Delaying LC resulted in significantly higher conversion rates (from 11.9% at d0 to 27.9% at d $\geq$6 days after admission, $P < 0.001$), surgical postoperative complications (5.7% to 13%, $P < 0.001$) and re-operation rates (0.9% to 3%, $P = 0.007$), with a significantly longer postoperative hospital stay ($P < 0.001$).

Conclusions: Delaying LC for acute cholecystitis has no advantages, resulting in significantly increased conversion/re-operation rate, postoperative complications and longer postoperative hospital stay. This investigation—one of the largest in the literature—provides compelling evidence that acute cholecystitis merits surgery within 48 hours of hospital admission if impact on the patient and health care system is to be minimized.

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Each year, 1–4% of patients with gallstones will go on to develop gallstone-related complications, such as acute cholecystitis.[1] In the prelaparoscopic era, prospective randomized studies showed the superiority of early versus delayed open cholecystectomy for acute cholecystitis with regard to hospital stay and time to full recuperation.[2,3] With the revolution of laparoscopic surgery in the early 1990s it seemed reasonable to apply the knowledge acquired from open gallbladder surgery to the laparoscopic technique, although many authors remained rather skeptical.[4–6] Out of fear of higher complication rates due to increased local inflammation obscuring optimal view and dissection of Calot's triangle, a large proportion of surgeons in the early 2000s still preferred delaying laparoscopic cholecystectomy (LC) for 6 weeks or more if a patient presented with acute gallstone-related cholecystitis.[7] However, more recent data by Campbell et al has shown an encouraging trend toward an increased rate of urgent (44%) and same-admission (23%) LC for patients admitted with acute cholecystitis.[8]

More recent meta-analyses are clearly in favor of early (within 1 week of symptom onset) LC, which seems safe and feasible.[9,10] Although there is some disagreement on the annual risk of developing symptoms such as recurrent cholecystitis, obstructive jaundice or biliary pancreatitis after an episode of acute cholecystitis—reported rates range from 14% to 31% annually[11,12]—it seems that early LC can help cut costs by avoiding subsequent emergency re-admissions and complications. With resources being ever more shortened in the health care systems across Europe and North America, cost-effectiveness becomes nearly as important as overall patient safety. A cost–utility analysis comparing early versus delayed LC for acute cholecystitis suggests that early LC is not only less expensive but also results in better quality of life when compared to delayed LC.[13]

Although subgroup evaluation in the meta-analysis by Gurusamy et al failed to show any difference for patients operated within 4 or 7 days after symptom onset,[9] the exact time-point of LC remains a matter of great debate. Therefore, the objective of this analysis is to compare various outcomes of LC for acute cholecystitis at different time points after hospital admission in a large, prospective cohort of patients.

METHODS

This analysis was based on the prospective database of the Swiss Association of Laparoscopic and Thoracoscopic Surgery (SALTS) and included all patients aged $\geq$16 years requiring emergency LC (or LC converted to open surgery) for acute uncomplicated cholecystitis between 1995 and 2006. Our cohort of patients undergoing emergency LC only included patients admitted to hospital in a nonplanned manner (via the emergency department) undergoing surgery within the same hospital stay. Acute cholecystitis was diagnosed based on clinical, laboratory and radiological findings. Histological work-up is not available from the SALTS database.

Patients with an elective admission for LC, planned open cholecystectomy, or reasons other than gallstone-related acute gallbladder inflammation (e.g., acalculous cholecystitis), as well as patients with cholecystitis with concomitant choledocholithiasis, biliary pancreatitis or cholangitis were excluded from the study.

The database is centralized (Qualicare, Qualidoc, Liebefeld, Berne, Switzerland), and all patient details were entered by a data manager working independently from the authors. The SALTS database includes information from 53 regional, 27 cantonal, 4 university hospitals, and 33 private practices in Switzerland.

Missing datasets were individually chased up by the data manager to ensure that the database is as complete as possible. This is

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reflected in a very small number of excluded patients (13 patients, 0.3%) due to missing variables.

Baseline demographic data were extracted from the database and the following outcomes analyzed: (1) rate of intraoperative complications, (2) rate of surgical postoperative complications (e.g., wound infection, hematoma), (3) conversion rate (from LC to open cholecystectomy), (4) rate of reoperation, (5) length of postoperative hospital stay (days), and (6) duration of operation (minutes).

The effect of surgical experience on the above listed outcomes was analyzed separately. Definition of surgical experience was based on the previous number of laparoscopic procedures performed by the lead surgeon (<10, 10–50, 51–100, and >100). Patients were divided into 6 different groups according to the time point, at which surgery was performed after hospital admission. Group 1: day of surgery = day of admission (d0); Group 2: day of surgery = day 1 after hospital admission (d1); Group 3: day of surgery = day 2 after hospital admission (d2); Group 4: day of surgery = day 3 after hospital admission (d3); Group 5: day of surgery = days 4 or 5 (d4/5) after hospital admission; and Group 6: day of surgery on or after day 6 after hospital admission (≥6). Patients operated on day 4 and 5 were combined to obtain a sufficiently large enough group, thereby creating a more even distribution of group sizes for further statistical analysis.

Time-point of hospital admission to operation was chosen as a surrogate marker for time of symptom onset to the time point of operation as this information is readily available and clearly documented in the SALTS database.

STATISTICAL ANALYSIS

In a first step the data set was prepared to satisfy the inclusion and exclusion criteria described above. Continuous outcomes were summarized using median and range and categorical outcomes using counts and frequencies. Complication and conversion rates were analyzed using logistic regression models and postoperative length of stay using a linear regression model on log-transformed data. All models were adjusted for age, gender and American Society of Anesthesiologists (ASA) score. A P value of ≤0.05 was considered statistically significant. All statistical analyses were performed using R, version 2.9.2.[14]

RESULTS

The initial database included 7566 patients with acute cholecystitis (inclusion criterion 1) of whom 5707 required an emergency operation (inclusion criterion 2). Fifteen hundred and eighty-one patients with 1 or more exclusion criteria were also removed from further analysis, as were 13 patients in whom 1 or more variables were incomplete.

Overall, 4113 patients who underwent a LC for acute cholecystectomy were included for further analysis. Median age at the time point of surgery was 59.8 (range 16.9–95.7) years with 52.8% of all patients being female. Median postoperative hospital stay was 6 (range 1–88) days. Median ASA risk was II (2084 patients), with a range of I–IV. Basic patient demographics are summarized in Table 1.

Most patients either had surgery on admission day (n = 1416, 34.4%) or on d1 after hospital admission (n = 1542, 37.5%). A total of 225 patients (5.5%) had documented intraoperative complications. There were no significant changes in number (Fig. 1A–D, second panel) of intraoperative complications for patients operated immediately (d0) versus later (d ≥ 6), $P = 0.737$.

The overall rate of surgical postoperative complications was 6.1%. Significantly more surgical postoperative complications were seen in patients with delayed LC (increase from 5.7% on admission day to 13% after 6 and more days since admission, $P < 0.001$), Figure 1A–D, third panel). A summary of all the intraoperative and local postoperative complications is given in Table 2.

TABLE 1. Summary of the Patient Characteristics of the Study Population

Patient demographics	
Female, number of patients	2171 (52.8%)
Median age, years (range)	59.8 (16.9–95.7)
ASA classification	
ASA I	1172 (28.5%)
ASA II	2084 (50.7%)
ASA III	795 (19.3%)
ASA IV	62 (1.5%)
Median hospital stay, days (range)	
Overall	6 (1–88)
On day of admission	6 (1–53)
Day 1	6 (2–73)
Day 2	6 (2–31)
Day 3	7 (2–38)
Day 4 or 5	6 (2–23)
Day 6 or more	8 (2–88)
Time to operation in days after admission = N	
On day of admission	1416 (34.4%)
Day 1	1542 (37.5%)
Day 2	530 (12.9%)
Day 3	247 (6.0%)
Day 4 or 5	218 (5.3%)
Day 6 or more	160 (3.9%)

The overall in-hospital mortality rate was 0.8%, equivalent to 32 patients. There was no statistically significant association between time-point of surgery and risk of death ($P = 0.95$). The overall conversion rate from laparoscopic to open surgery was 15.5% (636 patients). The conversion rate was significantly higher (27.9%) for patients operated after 6 and more days since admission compared to those operated on the day of admission (11.9%, $P < 0.001$), Figure 1(A–D), first panel. In total, 48 patients (1.2%) required a reoperation during the same hospital stay, with higher reoperation rates with increasing delay between hospital admission and LC (increase from 0.9% on admission day to 3% after 6 and more days since admission, $P = 0.007$), Figure 1(A–D), fourth panel. Details of the duration of operation as a function of the timing of surgery are given in Figure 1(E). As the time point of surgery is delayed (day of admission versus 6 and more days after admission), significantly more patients undergo a longer operation ($P = 0.036$). This did not reflect in surgical experience of the lead surgeon, expressed as total number of previously completed laparoscopic procedures. Most LC (2692, 65.5%) were carried out by surgeons with previous experience in more than 100 laparoscopic procedures, with only a small minority (n = 87 or 2.1%) of surgeons lacking general experience (less than 10 previous laparoscopic procedures). There was no statistically significant association between time point of surgery and previous surgical experience ($P = 0.06$).

Delaying surgery resulted in a significantly longer postoperative hospital stay from just over 6 days (6.1) for patients operated on the day of admission to 8 days for patients operated on day 6 or thereafter ($P < 0.001$), as is depicted in Figure 1(F).

A complete summary of the unadjusted and risk-adjusted comparisons of outcomes (grouped according to time-point of LC) are displayed in Tables 3 and 4.

DISCUSSION

This is one of the largest population-based studies, including well over 4000 patients, which looks at the effect of the time-point

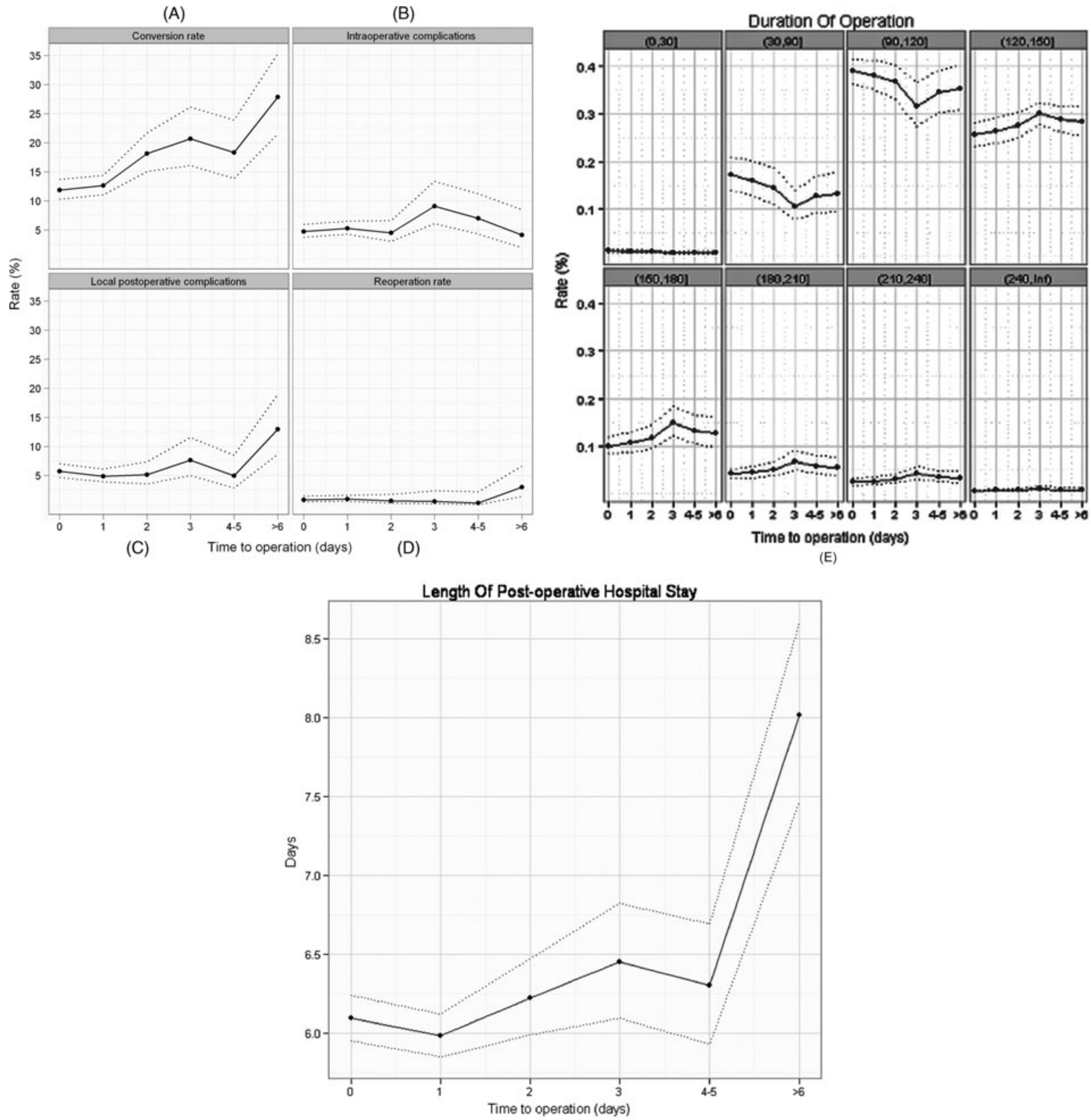

FIGURE 1. For all analyses the reference subject is female, ASA I, 58.8 years old and was operated on d0. (A–D) show the relationship between time to operation (in days) on the x-axis and the rate of conversion from laparoscopic to open surgery, the rate of intraoperative and surgical postoperative complications and the rate of reoperation as a function of time, risk-adjusted for gender, age and ASA classification. The y-axis denotes rate in percentage. The dotted lines correspond to the 95% confidence interval. Patient groups are divided into Group 1: day of surgery = day of admission (d0); Group 2: day of surgery = day 1 after hospital admission (d1); Group 3: day of surgery = day 2 after hospital admission (d2); Group 4: day of surgery = day 3 after hospital admission (d3); Group 5: day of surgery = days 4 or 5 after hospital admission (d4/5) and Group 6: day of surgery = day 6 or more after hospital admission ($\geq$6). Panel (E) looks at the effect of the time from admission to operation (in days) on the x-axis on the duration of the operation (in minutes, grouped into duration of $<$30 minutes, 30 to 90 minutes, 90 to 120 minutes, 120 to 150 minutes, 150 to 180 minutes, 180 to 210 minutes, 210 to 240 minutes and $>$240 minutes), where the y-axis denotes rates. The duration of operation is a categorical outcome and a proportional odds logistic regression is used. Panel (F) shows the relationship between time to operation (in days) on the x-axis and the length of hospital stay in days in relationship to the time-point of LC, risk-adjusted for gender, age and ASA classification. The y-axis denotes mean time in days. The dotted lines correspond to the 95% confidence interval.

TABLE 2. Summary of All Intraoperative and Local Postoperative Complications

Intraoperative complications: total of 318 complications in 225 patients	
Hematoma/Bleeding	**156**
Abdominal wall	4
Intraabdominal	134
Necessitating a transfusion	18
Trocar/Veress needle injury	**29**
Stomach or intestine	8
Bladder	1
Major vessel	5
Parenchymal injury	7
Others, not defined	8
Other form of organ injury	**20**
Extrahepatic bileduct injury	**14**
Other complications	**99**
Surgical postoperative complications: total of 306 complications in 250 patients	
Hematoma/Bleeding	**78**
Abdominal wall	29
Intraabdominal	32
Necessitating a transfusion	17
Infection	**60**
Superficial wound infection	38
Intraabdominal abscess	12
Generalized peritonitis	10
Biliary complications	**62**
Extrahepatic bileduct injury	3
Temporary jaundice	26
Choledocholithiasis	33
Ileus	**13**
Delayed perforation viscous organ	**8**
Other complications	**85**

of LC on various outcomes in patients admitted with acute calculous cholecystitis. This investigation provides compelling evidence that LC should be performed as soon as possible for patients admitted with acute cholecystitis. Previously reported high conversion rates[15–17] and potentially serious complications[4,5] have usually been the main arguments for postponing early LC in the setting of acute inflammation. Our data suggests that immediate surgery (admission day = day of surgery or at the latest within 24 hours of admission) significantly reduces the risk of a conversion from the laparoscopic to the open approach. Although an overall conversion rate of 15.5% may seem relatively high, this fits in with other studies looking at LC for acute cholecystitis, with rates around 20%.[18–20] Larger cohort studies with lower conversion rates of less than 10% also include LC done in an elective setting,[21] with elective surgery for the non-inflamed gallbladder inevitably resulting in lower conversion rates.[20] These patients will therefore benefit from all the advantages of a laparoscopic intervention, including less postoperative pain, shorter return to normal activities, and reduced blood loss.[22,23]

More recent studies support our findings, as they also fail to show an increase in conversion rate for early LC as opposed to delayed (>6–8 weeks) surgery[18] and certain authors even show more favorable results for early surgery.[24] Although previous studies have shown that surgeons carrying out early LC have to cope with inflammation and edema obscuring Calot's triangle,[25] delayed surgery may result in formation of fibrotic adhesions rendering the operation even more difficult.[24]

Previous trials favoring early LC showed a lower rate of intraoperative complications for early compared to delayed surgery.[18,19,24,26] Analysis of our own results did not show a significant change in intraoperative complications for patients receiving early surgery (d0) compared to those with delayed intervention (d ≥ 6; $P = 0.737$) with the highest number of problems encountered for surgery around d3 after admission and a decrease again thereafter. Lo et al did show that early surgery more frequently required modifications of the usual 4-port technique, such as using a fifth port, gallbladder decompression or enlargement of the periumbilical incision.[24] LC in the setting of acute cholecystitis can prove to be technically more challenging but in the hands of an experienced laparoscopic surgeon does not lead to increased adverse effects.[24]

An increase in the duration of an operation may reflect the complexity and the technical challenges associated with the surgery, as is the case with LC for acute cholecystitis. In our cohort, postponing surgery after hospital admission resulted in a longer operating time. This is likely to be a direct reflection of the surgical complexity encountered as surgery is delayed. Analysis of the timing of surgery and surgical experience (expressed as number of previously completed laparoscopic procedures by the lead surgeon) failed, however, to reveal an association between these 2 factors.

With local surgical postoperative complication rates ranging from 5.7% for patients operated on the day of hospital admission to 13% for patients undergoing LC after ≥ 6 days, overall morbidity is very low across all groups when compared to the general literature.[24,19] However, within our study population, patients operated on early after hospital admission had significantly fewer complications than patients in whom surgery was delayed for a few days. A much smaller study by Daniak et al included 88 patients.[27] Patients operated on early (within 24 hours of admission) had fewer postoperative complications and a shorter hospital stay, even after adjustment for patient demographics and comorbidities, results which had already been achieved in a study by Brodsky et al, published in 2000.[28]

As an outlook of the current debate about early versus late LC, there is an ongoing phase III surgical randomized control trial (NCT00447304) with the potential to provide level Ib evidence about the importance of very early surgery (LC within 24 hours after presentation) versus delayed LC.[29]

Reoperation rates for missed bile-duct injuries or injuries to other abdominal organs as well as revisions for postoperative bleeding are poorly documented in most published studies but are around 1%,[30,31] which fits in with our own analysis. Our data again clearly favors early LC if reoperation rates are to be kept minimal.

Various studies have shown that prolongation from the time-point of symptom onset to surgery increases length of hospital stay not only in the preoperative, but also the postoperative period.[9,19,24,27] In our analysis, patients who were operated early on had a significantly shorter postoperative hospital stay compared to patients undergoing LC after a prolonged time-period in hospital. As we did risk-adjustment for age and ASA classification, it seems unlikely that these differences in outcomes could be explained by differences in patient demographics.

A recent meta-analysis by Siddiqui et al from 2008 included 4 randomized trials with a total of 375 patients comparing early LC versus delayed LC for acute cholecystitis.[32] Although postoperative complication and conversion rates were similar between the 2 groups, total hospital stay was significantly reduced in patients undergoing early surgery.

The longer the hospital stay, the greater the health costs generated, not to mention the indirect costs and economic burden resulting from longer time spent off work. As Switzerland currently does not have to worry about Disease Related Groups (DRG), the pressure to send people home as quickly as possible after an intervention is not as urgent, partly explaining our relatively long postoperative hospital stay. However, with DRG being implemented in the near future, the pressure to send people home sooner will inevitably increase.

TABLE 3. Comparison of Unadjusted Outcomes. All the Results are Relative to 0 Day, where time of Operation = Day of Admission

Outcome	Time point of surgery	Odds ratio	95% CI	*P*
Intraoperative complications	Day of admission	1		
	Day 1	1.139	0.822–1.578	0.434
	Day 2	0.966	0.605–1.544	0.886
	Day 3	2.004	1.225–3.281	0.006
	Day 4 or 5	1.546	0.880–2.717	0.130
	Day 6 or more	0.893	0.403–1.978	0.781
Local surgical postop. complications	Day of admission	1		
	Day 1	0.857	0.626–1.173	0.335
	Day 2	0.873	0.563–1.355	0.546
	Day 3	1.455	0.884–2.394	0.140
	Day 4 or 5	0.993	0.544–1.813	0.982
	Day 6 or more	2.629	1.606–4.304	<0.001
Conversion rate	Day of admission	1		
	Day 1	1.091	0.880–1.353	0.425
	Day 2	1.628	1.244–2.130	<0.001
	Day 3	2.005	1.429–2.813	<0.001
	Day 4 or 5	1.872	1.304–2.687	0.001
	Day 6 or more	3.090	2.132–4.479	<0.001
Rate of reoperation	Day of admission	1		
	Day 1	1.165	0.590–2.302	0.660
	Day 2	0.710	0.235–2.150	0.545
	Day 3	0.762	0.173–3.355	0.720
	Day 4 or 5	0.430	0.057–3.275	0.416
	Day 6 or more	4.273	1.716–10.643	0.002
Duration of operation	Day of admission	1		
	Day 1	1.096	0.962–1.250	0.168
	Day 2	1.244	1.038–1.490	0.018
	Day 3	1.821	1.441–2.303	<0.001
	Day 4 or 5	1.508	1.169–1.945	0.002
	Day 6 or more	1.417	1.058–1.897	0.019
Length of postoperative hospital stay	Day of admission	1		
	Day 1	0.994	0.959–1.030	0.734
	Day 2	1.007	0.958–1.058	0.777
	Day 3	1.093	1.022–1.169	0.010
	Day 4 or 5	1.088	1.014–1.168	0.020
	Day 6 or more	1.413	1.303–1.533	<0.001

Previous studies have also shown that delaying surgery for a longer period increases costs substantially due to repeat emergency hospital admissions for recurrent cholecystitis or other gallstone-related complications.[11,13]

STRENGTHS AND LIMITATIONS

The key limitation of our study is the choice of time-point of hospital admission to operation as a surrogate marker for time of onset of symptoms to the time point of operation. However, in Switzerland, accessibility to hospitals and other medical facilities is very good, with a high ratio of hospital/patients (4.2 hospitals/100,000 inhabitants) and very short distances to cover between the patients' home and the nearest hospital.[33] Thus, only a minor fraction of patients will have reduced accessibility due to their geographical location. We therefore believe that using the time point of hospital admission as a surrogate marker does not relevantly influence the validity of our findings. Furthermore, the database does not provide us with long-term follow-up information, so that data on late complications, such hernias or small bowel obstruction due to adhesions are not captured in our database. Unfortunately the SALTS database does not include histological work-up. Diagnosis of acute cholecystitis is therefore based on a combination of clinical, laboratory and radiological findings. Finally, although the SALTS database contains information on the type of complication, no grading of the severity of complication can be ascertained.

There are, however, significant strengths to our study. Firstly, our sample size is large and the statistical power to detect even small clinically relevant details is high. Second, all data was collected prospectively and was very complete with few missing values. Last of all, although the analysis comprises a Swiss population only, because the study was population based, our results have excellent generalizability. The authors therefore believe that the results can be generalized to all countries where the standard of laparoscopic surgery is high.

CONCLUSIONS

Our study represents one of the largest population-based analyses evaluating how timing affects various outcomes after LC for acute, calculous cholecystitis. Delaying surgery neither reduces perioperative complications nor shortens postoperative hospital stay. On the contrary, postponing LC in our study population actually results in more unfavorable outcomes compared to immediate surgery. This study provides compelling evidence that early LC should be advocated for patients admitted to hospital with acute cholecystitis.

TABLE 4. Comparison of Adjusted Outcomes. All the Results are Relative to 0 Day, where Time of Operation = Day of Admission

Outcome analyzed	Time point of surgery	Odds ratio	95% CI	*P*
Intraoperative complications	Day of admission	1		
	Day 1	1.124	0.810–1.558	0.485
	Day 2	0.949	0.593–1.519	0.828
	Day 3	2.016	1.230–3.306	0.005
	Day 4 or 5	1.517	0.860–2.676	0.150
	Day 6 or more	0.872	0.393–1.937	0.737
Surgical postop. complications	Day of admission	1		
	Day 1	0.847	0.618–1.161	0.302
	Day 2	0.891	0.573–1.385	0.607
	Day 3	1.366	0.827–2.256	0.223
	Day 4 or 5	0.864	0.471–1.584	0.636
	Day 6 or more	2.450	1.487–4.036	<0.001
Conversion rate	Day of admission	1		
	Day 1	1.071	0.862–1.331	0.537
	Day 2	1.642	1.250–2.157	<0.001
	Day 3	1.930	1.368–2.723	<0.001
	Day 4 or 5	1.665	1.152–2.407	0.007
	Day 6 or more	2.863	1.961–4.180	<0.001
Rate of reoperation	Day of admission	1		
	Day 1	1.139	0.575–2.254	0.709
	Day 2	0.749	0.247–2.275	0.611
	Day 3	0.679	0.153–3.003	0.610
	Day 4 or 5	0.354	0.046–2.707	0.317
	Day 6 or more	3.599	1.430–9.058	0.007
Duration of operation	Day of admission	1		
	Day 1	1.088	0.954–1.240	0.209
	Day 2	1.247	1.040–1.494	0.017
	Day 3	1.779	1.407–2.251	<0.001
	Day 4 or 5	1.428	1.104–1.842	0.007
	Day 6 or more	1.370	1.021–1.837	0.036
Length of postoperative hospital stay	Day of admission	1		
	Day 1	0.982	0.950–1.014	0.271
	Day 2	1.021	0.976–1.069	0.362
	Day 3	1.058	0.995–1.125	0.070
	Day 4 or 5	1.034	0.969–1.103	0.315
	Day 6 or more	1.315	1.221–1.417	<0.001

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