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SURGICAL ASPECTS OF ACUTE CHOLECYSTITIS

PhD Thesis

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LIST OF FULL PAPERS RELATED TO THE SUBJECT OF THE THESIS

1. **Tóth I**, Ábrahám S, Karamya Z, Benkő R, Matuz M, Nagy A, Váczi D, Négyessy A, Czakó B, Illés D, Tajti M, Ivány E, Lázár G, Czakó L. Multidisciplinary management of acute cholecystitis during the COVID-19 pandemic. Sci Rep. 2023 Sep 27;13(1):16257. doi: 10.1038/s41598-023-43555-3. PMID: 37759081; PMCID: PMC10533883. (**D1)**

2. Ábrahám S, **Tóth I**, Benkő R, Matuz M, Kovács G, Morvay Z, Nagy A, Ottlakán A, Czakó L, Szepes Z, Váczi D, Négyessy A, Paszt A, Simonka Z, Petri A, Lázár G. Surgical outcome of percutaneous transhepatic gallbladder drainage in acute cholecystitis: Ten years' experience at a tertiary care centre. Surg Endosc. 2022 May;36(5):2850-2860. doi: 10.1007/s00464-021-08573-0. Epub 2021 Aug 20. PMID: 34415432; PMCID: PMC9001534. (**D1)**

3. **Tóth I**, Benkő R, Matuz M, Váczi D, Andrási L, Tajti J jr, Pieler J, Libor L, Lázár G, Ábrahám S. Evaluating surgical outcomes and their predictive facotrs in acute, early cholecystectomies:13-year experience from a tertiary care center **(Q2)**

ABBREVIATIONS

AC	Acute cholecystitis
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome – Coronavirus 2
CR	Conversion rate
PCR	Polymerase chain reaction
LSR	Laparoscopic success rate
BDI	Bile duct injury
ASA	American Society of Anesthesiologists
CCI	Charlson comorbidity index
PTGBD	Percutaneous transhepatic gallbladder drainage
CCY	Cholecystectomy
LC	Laparoscopic cholecystectomy
US	Abdominal ultrasound
GP	Gallbladder perforation
AAC	Acute acalculous cholecystitis
ACC	Acute calculous cholecystitis
EVF	Empyema vesicae felleae
HVF	Hydrops vesicae felleae
PC	Perforated cholecyst
PS	Performance status
BMI	Body mass index
CSR	Clinical success rate
TSR	Technical success rate
ERCP	Endoscopic retrograde cholangiopancreatography
BO	Biliary obstruction
CRP	C-reactive protein
PCT	Procalcitonin
TG13/18	Tokyo Guidelines 2013/2018

I. INTRODUCTION

Acute cholecystitis (AC) is a common diagnosis in emergency departments worldwide. The management of AC requires a multidisciplinary approach and treatment, wehere a close cooperation between emergency physicians, internists, surgeons, interventional radiologists and anesthesiologists is necessary.

In the case of most healthcare providers, care is based on the Tokyo Guidelines (TG), established in 2007 and revised in 2013 and 2018. These guidelines are, in turn, based on the severity grading of AC.

The three pillars of care are conservative medical treatment, surgical treatment (cholecystectomy [CCY]) and percutaneous transhepatic gallbladder drainage (PTGBD). According to the Tokyo Guidelines 18 (TG18) recommendation, early laparoscopic cholecystectomy (LC) is the treatment of choice in Grade I cases and it is considered the gold standard for the management of AC. Early LC is also recommended in Grade II cases, if allowed by the patient's general condition. However, if the patient's co-morbidities and general condition (performance status [PS]) do not allow early CCY, PTGBD is recommended, followed by surgery at a later, planned time (delayed CCY). In Grade III cases, when the patient is already showing septic symptoms, PS is of particular importance. If the patient's PS allows, early LC is also recommended, preferably at a surgical centre where both the personnel and the facilities for surgical management of advanced AC are avaible. If the patient's PS does not allow surgery, PTGBD is recommended in the acute care setting, followed by delayed CCY if allowed by the patient's condition.

At the University of Szeged, the current principles of the Tokyo Guidelines form the basis of care, which were taken into account in 2017 during a multidisciplinary roundtable discussion (Emergency Patient Care Unit, Department of Internal Medicine, Department of Radiology, Department of Surgery) to prepare a flowchart for AC at the University of Szeged. The timeframe is the elapsed time from onset of complaints to hospital admission and diagnosis. The timeframe marked in our treatment algorithm and used in daily practice is defined as 48 (72) hours. We aim to achieve acute CCY within 48 (maximum 72) hours from the onset of complaints if the patient is suitable for surgery, and in the case of AC beyond the timeframe, we recommend conservative medical treatment, supplemented by PTGBD if necessary.

Surgical treatment means early or delayed CCY. In our study, we focused mainly on early or acute CCY, which, according to our data, is performed in about 20 to 40 cases per year at our University. In my thesis, I aimed to analyse the surgical outcome of both early cholecystectomies and PTGBDs with radiological intervention. The most important surgical outcomes include whether laparoscopic cholecystectomy is successful or a conversion is required (conversion rate [CR], laparoscopic success rate [LSR]). Also considered as surgical outcomes are the mortality associated with CCY and the rate of bile duct injury (BDI). For PTGBDs, the surgical outcome can be defined as the technical success rate (TSR) or the clinical success rate (CSR).

We were curious to know how the management of AC has evolved at our University after the introduction of PTGBD in our clinic in 2010, and how the CR of delayed CCYs has changed with the introduction of PTGBD, and in what proportion of the patients drainage was considered definitive or bridging therapy. Furthermore, we also sought to answer how does the time from the onset of complaints affects the clinical outcome for both PTGBD and early CCY.

In recent years, the spread of SARS-CoV2 (Severe Acute Respiratory Syndrome - Coronavirus 2) and the resulting COVID-19 pandemic has transformed healthcare worldwide. In March 2020, the healthcare system in Hungary was „shut down". As elective and/or delayed cholecystectomies were also suspended, the changes also significantly affected AC care. We wondered how such a closure changed AC incidence, patient pathways, distribution of therapeutic alternatives, and surgical outcomes.

II. AIMS

- What factors (gender, age, PS, previous abdominal surgery, timeframe, grade, US morphological diagnosis) influence the surgical outcome (CR, BDI, mortality) of AC, and how much?
- How has PTGBD, introduced in our clinic and now used routinely, transformed AC care? What surgical and clinical outcomes can be expected (TSR, CSR, bridging and definitive therapy rates, mortality, timing of post-drainage CCY, CR)?

- How has the COVID-19 pandemic transformed AC care at our University (incidence, patient pathways, treatment modality rates, surgical outcomes)?

III. METHODS

All three studies were approved by the Regional Human Biomedical Research Ethics Committee, University of Szeged (81/2020-SZTE).

1. Evaluating surgical outcomes and their predictive factors in acute, early cholecystectomies: 13-year experience from a tertiary care center (Study 1)

All patients who underwent LC for AC at the University of Szeged between 1 Jan 2007 and 31 Dec 2019 were retrospectively reviewed. Early cholecystectomy was defined as laparoscopic or open surgery for AC performed within twelve days after the onset of symptoms. Patients subjected to PTGBD prior to early LC during the same hospital stay were excluded from the study. Following the exclusion, data pertaining to 465 patients who underwent early LC were evaluated.

The severity of inflammation was determined retrospectively based on the TG18/TG13 severity grading for AC specified in the Tokyo Guidelines 2018. The severity of the AC-related inflammation was thus classified as Grade I (mild), Grade II (moderate), or Grade III (severe). The ultrasound-based morphological diagnoses were: acute acalculous cholecystitis (AAC), acute calculous cholecystitis (ACC), empyema vesicae felleae (EVF), hydrops vesicae felleae (HVF), and covered perforated cholecyst (PC).

The data were disaggregated based on sex, age (18–65 years and >65 years), and performance status for analysis. The American Society of Anesthesiologists (ASA) score (1 to 6) was determined for each patient. Based on the Charlson comorbidity index (CCI), the patients were categorized into 3 groups (0, 1–3, 4+). The rate of BDI and mortality within one month after hospitalization were also assessed.

The following endpoints were used to investigate the surgical outcomes of early LC: rates of primary open cholecystectomy, LC, and conversion from laparoscopy. The conversion rate for LCs (number of converted LCs × 100/[total number of surgeries − primary open cholecystectomies]) and the laparoscopic success rate (LSR) (number of LCs/total number of surgeries) were calculated accordingly. Subsequently, the effects of sex, age, performance status (ASA score and CCI), US morphological diganoses (AAC, ACC, EVF, HVF, and PC), severity of inflammation (Grade I, II, and III), and history of surgeries (upper and lower abdominal surgeries) on conversion rate, LSR, and condition-related mortality were evaluated in each group.

As for the clinical outcome, the impact of time elapsed from the onset of symptoms to early LC (the timeframe) on the different endpoints (mortality, CR, and LSR) was analyzed. Based on the timeframe, patients were categorized into two groups: 0 to 72 hours vs >72 hours.

Lastly, we investigated mortality, CR, and LSR in relation to the introduction of PTGBD. Ultrasound-guided PTGBD was introduced in our department in 2010. Patients subjected to early LC were thus assigned to two groups: surgery performed before (2007 to 2009) and after (2010 to 2019) the introduction of PTGBD.

2. Surgical outcome of percutaneous transhepatic gallbladder drainage – Ten years' experience at a tertiary care centre (Study 2)

We retrospectively examined abdominal ultrasound (US) - guided PTGBD interventions performed with AC indication at the University of Szeged for a ten-year period from 2010 to 2020. Patients who underwent percutaneous transhepatic gallbladder aspiration or endosonography-guided gallbladder drainage or computer tomography (CT)-guided PTGBD were excluded from the study. Moreover, nine patients who had a history of hepato-pancreatic-biliary malignancy prior to PTGBD or who were diagnosed with it after the procedure as well as patients who received further treatment after PTGBD outside the University of Szeged were excluded. After exclusions, data were analysed from 162 patients with PTGBD.

In radiologically confirmed AC patients, the TG13 and TG18 recommendations were followed when indicating PTGBD.

The severity of inflammation was determined retrospectively based on the TG18/TG13 severity grading for acute. The severity of AC-related inflammation in each patient was classified as Grade I (mild), II (moderate) and III (severe). Based on abdominal ultrasound, the indications for PTGBD were grouped as follows: acute acalculous cholecystitis (AAC), acute calculous cholecystitis (ACC), empyema vesicae felleae (EVF), hydrops vesicae felleae (HVF) and covered perforated cholecyst (PC)Szöveg beírásához kattintson vagy koppintson ide..

Sex and age group (18–65 years or over 65 years) distribution and patient's performance status were determined: the ASA score (I–VI) was determined for each patient, and patients were classified into three groups based on the Charlson comorbidity index (CCI) as follows: CCI 0, CCI 1–3 and over CCI 4. Based on the time elapsed between the onset of complaints and PTGBD, patients were grouped into three categories (0–72 hours, three days to one week, and beyond one week).

The average duration of drain presence after PTGBD was assessed. The need for endoscopic retrograde cholangiopancreatography (ERCP) during hospitalisation and after hospital discharge time over an average were followed for a five-year period. The indications of ERCP (non-decreasing biliary excretion, sepsis (including cholangiopsepsis), biliary obstruction (BO)) and its results were assessed. The need for urgent CCY due to the rapidly deteriorating clinical condition of the patients after PTGBD was determined.

Three endpoints were determined in terms of clinical and surgical outcome of PTGBD. The clinical success rate (CSR) of PTGBD (number of clinically regressive cases after PTGBD × 100 / [total number of PTGBD procedures – number of technically unsuccessful procedures]) was calculated. Clinical regression was determined by remission of patient's symptoms, improvement in inflammatory markers (leukocyte count, CRP and PCT) and radiological (US or abdominal CT) regression.

CSR was assessed according to different patient sexes, age groups, TG18/13 AC severity grades, CCI and time elapsed between the onset of complaints and hospital admission were analysed.

In addition to CSR, the technical success rate (TSR) of PTGBD (technically successful procedure × 100 / total procedures) was also calculated. We interpreted invasive radiological interventions where we observed drain failure (occlusion, drain displacement, improper tube positioning etc.) as technically unsuccessful PTGBD.

As a second endpoint in terms of clinical outcome, we analysed the proportion of CCYs after PTGBD and the need for possible emergency surgeries. We examined the proportion of PTGBD reported as final therapy (no need for CCY) and as a bridging therapy (i.e., the percentage of elective CCY performed in patients who responded well to drainage). All elective CCY surgeries performed after hospital discharge during an average five-year follow-up period were analysed. In terms of surgical outcome, we determined the proportion of primary open cholecystectomy, laparoscopic cholecystectomy (LC) and conversion after LC during both emergency and elective CCY surgery. Based on the above, the conversion rate (CR) of LCs and the laparoscopic success rate (LSR) were calculated. Possible bile duct injury during CCY was examined as well.

Finally, as a third endpoint in terms of clinical and surgical outcome, we calculated the in-hospital mortality and procedure mortality (directly related to PTGBD, such as bleeding, embolism and other organ injury).

3. Multidisciplinary management of acute cholecystitis during the COVID-19 pandemic (Study 3)

Data from patients diagnosed with AC who had received care at the University of Szeged in the pre-COVID period (Period I: from 1 May 2017 to 31 December 2018, 20 months) and during the COVID period (Period II: from 1 April 2020 to 30 November 2021, 20 months) were evaluated retrospectively. In addition to gender, age, mortality data and readmissions, the current general condition of the patients was also determined. To this end, the Charlson Comorbidity Index (CCI) was used. Three groups were formed using CCI (Group 1: 0 points; Group 2: 1 to 3 points; Group 3: 4 to 10 points). During Period II, patients were routinely screened with a SARS-CoV-2 PCR (polymerase chain reaction) test. AC cases were classified into three groups of severity: Grade I (mild), Grade II (moderate) and Grade III (severe). Based on an abdominal ultrasound (US) scan, AC cases were classified according to several morphological diagnoses: simple acute calculous cholecystitis, empyema vesicae felleae (EVF), gallbladder perforation (GP – confirmed by computed tomography) and hydrops vesicae felleae (HVF). Patients under 18 years, cases with acalculous cholecystitis or accompanying acute pancreatitis were excluded.

Multidisciplinary management encompasses three alternative treatment methods in the management of AC. The first is conservative medical therapy, the second is a surgical procedure (cholecystectomy, CCY), and the third is PTGBD. If conservative therapy was used first but failed, either surgery or PTGBD can be considered as secondary intervention, depending on the circumstances (time frame, severity of AC, general condition of the patients or CCI).

Surgical treatment was assessed by type of surgery performed (laparoscopic cholecystectomy [LC], converted LC or primary open surgery), while conversion rate (CR) and laparoscopic success rate (LSR) were evaluated as measures of surgical efficacy. The epidemiology, severity of AC (CCI, grade and ultrasound morphological diagnoses), multidisciplinary management pathways and outcome of the treatment (mortality or readmission) were compared in the cohorts in the two periods.

IV. RESULTS

1. Evaluating surgical outcomes and their predictive factors in acute, early cholecystectomies: 13-year experience from a tertiary care center (Study 1)

A total of 465 patients underwent acute, early cholecystectomy during the study reference period. In 82.1% of the cases, acute cholecystectomy was performed within 72 hours from the onset of symptoms, with the most common US morphological diagnosis being ACC (73.5% of the cases). In the majority of the cases, the severity of the inflammation was Grade I or II, while only 2.88% of patients had Grade III severity. BDI occurred in only two cases out of the 465 acute cholecystectomies. In the overall study population, the CR was 16.89%, LSR was 78.28%, and the mortality rate was 1.62%.

There was no significant difference in mortality between patients aged <65 years and those aged >65 years (1.36% vs 2.45%, $p = 0.466$), but the younger group showed significantly higher LSR (87.25 vs 62.28%, $p < 0.001$) and lower CR (9.72 vs 30.67%, $p < 0.001$).

More severe cholecystitis was associated with higher mortality rates (Grade I vs II vs III: 1.17% vs 2.27% vs 8.33%, $p = 0.183$), a significantly higher CR (7.09% vs 32.93% vs 28.57%, $p < 0.001$), and a significantly lower LSR (91.11% vs 61.11% vs 38.46%, $p < 0.001$), respectively. The group with the highest CCI (at least four points) had a significantly higher mortality rate (6.19%, p = 0.001) and CR (39.53%, p <0.001) than in the other groups, while LC was feasible in only half of these patients (50.4%, p < 0.001).

Regarding the US morphological diagnoses, mortality rates were the highest in the PC (4.08%) and AAC (3.85%) groups. The PC group also showed the worst CR and LSR (61.54% and 29.41%, respectively).

A prior upper abdominal surgery was associated with higher CR and lower LSR (CR: 23.53% vs 17.04%; LSR: 59.09% vs 78.81%; p = 0.037).

Patients who underwent surgery within the 72-hour time frame had significantly lower CR (14.45% vs 25.71%, p = 0.008) and significantly higher LSR (81.69% vs 67.53%, p = 0.008) compared to those operated on beyond 72 hours.

Following the introduction of PTGBD, the mortality rate showed a significant decrease (6.67% vs 1.21%, p = 0.04), and the decrease in CR (34% vs. 15.11%) and the increase in LSR (56.25% vs. 80.82%) were also significant compared to the previous period (p < 0.001).

On logistic regression, a history of upper abdominal surgery (odds ratio [OR]: 4.30; CI: 1.47–12.60) and the severity of cholecystitis (OR: 3.77; CI: 2.23–6.37) showed the greatest influence on the chance of conversion during early LC.

2. Surgical outcome of percutaneous transhepatic gallbladder drainage – Ten years' experience at a tertiary care centre (Study 2)

Among the 162 patients who underwent PTGBD within the ten-year investigation period, there were nearly equal proportions of men and women. Their mean age was 71.43±13.22 years, and the majority of them (71.60%) was over 65 years of age. It should be noted that the age of patients who died after PTGBD during in-hospital time was significantly higher compared to the survival group (76.82 ± 9.77 vs. 71.16±12.98 years). Mean age was significantly higher in more severe inflammation (Grade I: 63.14±16.52 years; Grade II: 70.79±13.14 years; Grade III: 78.89±7.22 years) and in patients who required emergency CCY than those who had elective CCY (74.75±13.13 vs. 68.00±11.05 years).

In addition to the high mean age, the majority of the PTGBD patients had a CCI above 4 (65.38%). The distribution of the AC severity grade was the following: Grade I: 8.8%; Grade II: 73.6%; and Grade III: 17.6%. Most frequently, PTGBD was called for due to abdominal US-confirmed ACC in 33.95% of the cases, PC in 27.16% and AAC in 5.56%. Hospital admission occurred between 72 hours and one week after the onset of complaints in almost half of the cases (45.6%). In general, PTGBD was performed within 72 hours in 39.71% of the cases, and beyond one week in 14.71%. TSR for PTGBD was 97.53%, procedure mortality was 0%, and CSR was 87.97%. After PTGBD, 62 (42.18%) did not undergo subsequent CCY. 69 patients (46.94%) had CCY, and 16 patients (10.88%) had emergency surgery due to the deteriorating clinical condition and progression. The mean timing of elective surgeries was 13.57±10.89 weeks after PTGBD.

CSR of PTGBD deteriorated significantly in patients over 65 years and in parallel with the increasing severity of the inflammation. While basically all patients under 65 years of age experienced clinical regression, CSR was only 83.62% in patients over 65 years. In Grade I inflammation, we also had complete clinical success in all patients; however, CRS was 92.04 in Grade II and only 64.29% in Grade III.

Comparing emergency and elective CCY surgeries after PTGBD in terms of LSR and CR, the proportion of primary open cholecystectomies in elective surgeries was much lower (5/16 (7.24%) vs. 5/69 (31.25%)). The CR of elective LCs (17.46%) was similar to that of emergency LCs (18.18%).

In addition to the 0% procedure mortality directly associated with the PTGBD intervention, in-hospital mortality was 11.72%. There was no significant difference in mortality between male and female patients; however, mortality showed a corresponding increase with the increasing score for both ASA score and CCI. The most prominent mortality was observed in AAC cases. The logistic regression showed that the severity of AC inflammation had the highest odds for emergency CCY (OR: 14.75; CI: 3.07–70.81).

3. Multidisciplinary management of acute cholecystitis during the COVID-19 pandemic (Study 3)

A total of 341 patients received care for AC at the University of Szeged during the study periods. There were 125 patients in Period I and 216 in Period II, a significant increase of 72.8% ($p<0.001$).

The median age of the patients was significantly lower in Period II (70 vs. 74 years, p=0.017). The gender ratio did not change, with a predominance of females (56 vs. 56.5%, p=0.51). As for CCI classification, the rate of cases classified into CCI Group 1 was significantly higher in Period II (20.4 vs. 11.2%, p=0.043).

As regards ultrasound morphological diagnoses, the GP rate rose significantly (18.1 vs. 7.3%, p=0.006) in Period II and that of HVF fell significantly (16.8 vs. 26.8%, p=0.019) in the same period. There was significant difference between the two periods in the length of hospital stay, median hospital stay in Period II was shorter by one day (8 vs. 7 days, p=0.011). As regards unplanned readmission within 30 days, significant differences were observed. While there were no such incidents during Period I, twelve cases required readmission during Period II (0 vs. 6.3%, p=0.004).

There was a significant change in the rates of the treatment methods between the two periods. In Period I, successful conservative therapy demonstrated a significantly higher rate (67.2 vs. 46.8%, $p<0.001$), whereas the rate of total PTGBD only showed a marked increase (24.1 vs. 12.8%, p=0.012) in Period II, with no significant change in the surgery rate.

V. DISCUSSION

1. DISTRIBUTION OF TREATMENTS

Based on our studies, AC care generally involved medical treatment, with a minor role for both surgery and interventional radiology. Successful conservative medical treatment was performed in 67% of the cases, acute CCY in 20% and PTGBD in 13%. However, these proportions changed in the COVID period. In the COVID era, the PTGBD rate was significantly higher (24%), successful conservative therapy showed a significantly lower rate (47%), and there was no significant change in the surgery rate (29%). A systematic review yielded comparable findings; however, the study reported that while the PTGBD rate was higher during the COVID period, there was also a higher rate of conservative therapy and a decrease in the rate of surgical treatment. Although our data suggest that rates have changed, the rate of surgical treatment has not changed significantly, nor has there been a significant change in surgical outcomes. Laparoscopic cholecystectomy was safely used during the pandemic, as also demonstrated in a large number of cohorts.

The COVID pandemic has also had a significant impact on the number of cases previously seen. Several medical departments were either closed down or designated as COVID care facilities, resulting in a significant number of clinicians having to provide care for COVID patients. With regard to surgical care, non-emergency procedures, such as elective cholecystectomies, were immediately suspended in compliance with the lockdown measures. Considering these circumstances, it is not surprising that the number of patients with AC increased substantially during the COVID period, since patients with gallstones were only treated if acute inflammation was also present and elective cholecystectomies were suspended. An Irish study reported similar findings on the number of AC cases, and it even supposed that a possible reason for this was an excessive consumption of fatty food due to the „stay-at-home" principle.

2. AGE OF PATIENTS

AC is a disease affecting all age groups and both genders in the adult population, but it is more common in older age groups (>60-65 years) and in women (about 55%). Literature shows that AC is one of the most common conditions requiring acute surgical intervention in patients over 65 years. Older age is often associated with comorbidities, which make the risk of the disease higher than in younger, healthier populations. Our results demonstrate that 64% of acute CCYs occurred in patients under 65 years of age, with patients over 65 years typically being referred to a different therapeutic pathway. But where CCY was performed, we obtained less favourable surgical outcomes. Our data showed a three times higher CR in patients over 65 years than in patients under 65 years (30.67% vs 9.72%, $p<0.001$). Previous studies have also identified higher age as a risk factor for conversion during early LCs performed for AC. While our studies show that 64% of CCYs occurred in patients under 65 years, 72% of PTGBDs occurred in patients over 65 years. Based on these results, PTGBD was mostly performed in older patients with more comorbidities, and CCY was more indicated in younger patients. When looking at CCYs after PTGBD, these also typically occurred in younger patients (68.35 ± 11.34 years), while those who did not eventually undergo CCY, and thus for whom PTGBD proved to be a definitive therapy, were typically older patients (73.81 ± 14.43 years). While the CSR was 100% in patients under 65 years of age, only 83.62% of patients over 65 years of age were treated successfully with PTGBD.

During the COVID period, a notable contrast was observed, as the median age of patients receiving care was significantly lower compared with the previous period. Younger patients who had usually undergone surgery with milder symptoms before an acute inflammatory event in Period I required care for AC during the pandemic.

3. PERFORMANCE STATUS OF THE PATIENTS

Of the ASA and CCI scores most commonly used to define PS. In our study, both a higher ASA score and a higher CCI were associated with greater risk and poorer surgery-related outcomes. Patients with higher ASA scores had significantly lower LSR. The CR increased with an increase in ASA from 1 to 3, but patients with an ASA 4 performance status had slightly lower CR. This was attributable to the fact that a higher percentage of patients with ASA 4 status underwent primary open surgery because of their lower cardiac capacity and the higher risk (unfavorable cardiopulmonary effect of abdominal insufflation). The rate of surgeries with excessive risk may be reduced with proper patient selection and conservative treatment with PTGBD in "difficult" cases. Not surprisingly, 65.38% of patients with PTGBD fell into the CCI 4+ group. This group also had a lower clinical success rate (86.27%) compared to the 100% CSR in the CCI 0 group. Similar results were obtained for CSR with increasing ASA score (ASA 1: 100%, ASA 4: 86.96%).

4. ULTRASOUND MORPHOLOGICAL DIAGNOSES

US is always performed in cases of suspected AC, and in the vast majority of the cases, although not always, gallstones are confirmed in the gallbladder. In our studies, ACC was the most common morphological diagnosis determined by US. Mortality rates were the highest in the PC (4.08%) and AAC (3.85%) groups. Perforation poses an increased risk and it is a more difficult surgical situation, as demonstrated by the high CR

(61.54%) and low LSR (29.41%). Several studies recommend percutaneous cholecystostomy in AAC. We should highlight that a mortality rate of almost 56% was observed after PTGBD among patients with AAC in our study. The high mortality rate associated with AAC is likely attributable to the fact that, in many cases, acalculous cholecystitis is a part of the septic condition in many cases, not the cause of it, and there is a different background cause.

During the COVID pandemic, patients frequently sought medical attention or accessed suitable healthcare providers after experiencing symptoms for several days and reaching an advanced stage of inflammation. This was well indicated by the significant change in the rates of morphological diagnoses made based on the ultrasound scans. In the COVID period, the GP rate rose considerably compared with the pre-COVID period, clearly due to late treatment and lack of elective management.

5. SEVERITY GRADING OF ACUTE CHOLECYSTITIS

Severity grading is the basis of TG18 and the starting point for choosing the therapeutic direction. Based on our logistic regression analysis, the most determinant factor for CR in CCY was grade (OR:3.77; CI: 2.23-6.37). The significant differences found in LSR also demonstrate the direct effect of the severity of inflammation on the outcomes. The 91.12% LSR observed in Grade I cases dropped to 38.46% in Grade III cases. CR was higher in Grade II cases than in Grade III cases, which is likely attributable to the higher rate of primary open surgeries in Grade III cases. The expected difficulty of the surgery also increases with the severity of inflammation. Although the guidelines and publications recommend PTGBD for elderly or critically ill patients as well as in Grade II–III inflammation, a mortality rate of approximately 41% was observed in Grade III inflammation after PTGBD in this study. Based on logistic regression, the severity of inflammation was the most significant factor in patient survival. It should be noted that Sanaiha et al. found significantly lower mortality in Grade III inflammation after early LC than in percutaneous cholecystostomy based on a retrospective cohort of 358,624 patients. This further elucidates the role of PTGBD as well as acute or early LC in the complex treatment of Grade III AC.

6. ASPECTS OF THE TIMING OF SURGICAL TREATMENTS

The timing of CCY has always been a controversial issue. To date, there is no clear, evidence-based recommendation on the timing of either acute CCY or electively planned CCY after PTGBD.

TIMEFRAME FOR ACUTE CCY

In our department, in case of AC we endeavour to perform LC as early as possible within 72 hours, and preferably within 48 hours. During our study, surgical outcomes were better for surgeries performed within 72 hours than for those carried out beyond 72 hours. The <72 h group showed a lower mortality rate (1.41% vs 2.6%) and CR (14.45% vs 25.71%) and a higher LSR (81.69% vs. 67.53%; $p = 0.008$). Numerous studies have sought to determine the ideal time frame. In the study by Hadad et al. (2007), the CR increased proportionately with the time elapsed from the onset of symptoms to surgery, with a CR of 9.5% for surgeries performed within two days and a CR of >38% for surgeries performed beyond five days. Alore et al. (2019) recommended two days for the timing of surgery, although their recommendation was for the period after the date of hospitalisation. In their 2019 and 2020 publications, Wiggins, and Altieri obtained more favourable results regarding CR, BDI, and hospital stay in those operated on within 72 hours.

TIMING OF POST-PTGBD CCY

In the CRs of surgeries performed with different timing after PTGBD (elective or emergency), there was essentially no difference (17.46 % vs. 18.18 %) in our study. Our study clearly showed that we more often postpone CCY to at least 6 weeks after AC than between 3-6 weeks (61 vs 8 cases). Although in practice we prefer to postpone for 6-8 weeks, our data did not show a significant difference in terms of CR or LSR. On average, the CR is around 4% during elective LCs, but the CR of acute LC was around 9-10%. The remarkably high CR of elective LCs after PTGBD may be explained by the fact that these delayed LC surgeries were performed in older patients (68.35 ± 11.34 years), where, in addition to age, gallbladder wall thickening and adhesions from previous inflammation may further increase the chance of conversion.

7. SUCCESS OF THE TREATMENTS

The surgical treatment of AC is CCY. Nowadays, laparoscopic CCY is considered to be the „gold-standard" of care. Whether the surgery is considered successful can be determined by LSR and CR, among others. In many cases, early laparoscopic surgery needs conversion. In some cases, primary open operation is performed because of various reasons such as the patient's poor general condition, more severe inflammation and previous operations that might cause technical difficulties during LC. In our studies, the CR and LSR for acute CCYs were 16.89% and 78.28%, respectively. Based on our data, the factors that influenced CR the most were patient age, severity of gallbladder inflammation and previous upper abdominal surgery. In addition to previous surgeries, history of inflammation and previous PTGBD may complicate the surgical situation (adhesions, thicker scar tissue), increasing CR. At first sight, the introduction of PTGBD in our department improved the surgical outcomes of early cholecystectomies with regard to LSR and CR; however, these results should be treated with a certain scepticism. After the introduction of drainage in 2010, fewer high-risk acute cholecystectomies were required, leading to an improvement over the results from before the introduction of drainage (pre-PTGBD and PTGBD periods: CR, 34.15% vs 15.11%; LSR, 56.25% vs 80.82%), with the majority of high-risk cases subjected to drainage.

From the perspective of PTGBD, we can also define the success of the intervention using both TSR and CSR. In the analysis of the drainages, TSR and CSR were found to be 97.53% and CSR 87.97%, respectively, so the procedure is technically feasible and has a good clinical success rate.

After drainage, there are three possible scenarios: if AC progresses, acute CCY may be required, if not, either delayed CCY or no subsequent CCY at all is performed. Our data show that in almost half of the cases with PTGBD, there was no subsequent CCY (46.94%).

In another proportion of patients, drainage serves as bridging therapy before delayed CCY. However, if, despite our best efforts, the patient deteriorates after drainage and AC progresses, acute CCY may be required. In our study, we demonstrated a high CR after PTGBD for both elective and urgent CCY (17.46% vs 18.18%). Emergency CCY was performed in 10% of the cases. In the case noted above, extremely difficult surgeries can be expected with a high rate of primary open cholecystectomies (31.25%) and CR (18.18%), with a high rate of overall mortality (14.29%) based on our study.

8. MORTALITY

Another important aspect of clinical outcome is mortality. Our data show a mortality rate of about 6 to 7% in the surgical management of AC, which is in line with the figures of 0 to 10% from the literature. Regarding PTGBDs, the mortality rate in our study was relatively high at 11.72%, due to the fact that drainage was mostly performed in elderly patients with poor general condition. However, this high rate is fully in line with the literature (15.4%) according to the systematic review by Winbladh et al. If we look at the mortality data cumulatively for both CCYs and drainages, we can say that the mortality of 6 to 7% can be reduced to about 4.5% for AC. Although more patients with AC have entered care in the context of the COVID pandemic, this higher number of cases did not significantly changed the mortality data.

Our data show that mortality rates were much higher for PTGBDs in patients with Grade III inflammation leading to septic conditions and AAC. These figures highlight the need to consider performing acute CCY instead of PTGBD in such cases.

9. BILE DUCT INJURIES

The incidence of BDI is a very important measure of surgical outcome and success. In our own study, there were only two cases of bile duct injury during acute CCYs (0.43%). Two previous studies showed similar results for BDIs (0.26-0.53%). If CCY is performed after PTGBD, the surgical situation can often be even more difficult, as shown by the BDI rates. In our study, the BDI ratio during CCY after PTGBD was 1.17%, which is roughly three times higher than in acute CCYs, but the same as the results reported by Altieri et al. in 2019.

10. HOSPITAL STAY

Although we did not analyse hospital stays and readmissions in depth in relation to AC in our present studies, we did obtain some interesting findings. Our data show that before the COVID pandemic, patients treated for AC were discharged after an average of 8 days of hospitalisation, with no hospital readmissions. However, during the COVID period, hospital stays were shortened by one day and several hospital readmissions were necessary. The implementation of minimal doctor-patient contact and the reduced capacity during the COVID pandemic might have accounted for the one-day earlier discharge of patients in the COVID period. The high rate of unexpected readmissions during the COVID period may have been caused by the higher GP rate in addition to the one-day shorter hospital stay.

VI. CONCLUSION

Our studies have demonstrated that the management of acute cholecystitis, although based on TG18, should always be personalised, taking a number of factors into account. In terms of measures of surgical efficacy, it is clearly recommended that acute cholecystectomy be performed within 72 hours of the onset of symptoms. The CR is most influenced by the severity of gallbladder inflammation, patient performance status and previous upper abdominal surgery. The role of PTGBD in the care of AC is becoming increasingly prominent. In elderly, comorbid patients or in advanced inflammation, it can be used as both as bridging and as definitive intervention, although in such cases higher mortality is expected. In cholecystectomies after PTGBD, in advanced inflammation or in comorbid elderly patients, a more difficult operation should always be expected and it is therefore recommended that the patient be treated in a centre with a higher level of staffing and equipment. The changes during the COVID pandemic have highlighted that if elective CCYs are suspended for whatever reason, we should expect a higher incidence of AC, higher rates of unsuccessful conservative treatment and gallbladder perforation, and more frequent hospital readmissions.

VII. SUMMARY OF SCIENTIFIC FINDINGS

- Better clinical outcomes (CR, LSR, mortality) can be expected for acute CCYs performed within 72 hours of the onset of symptoms.
- The introduction and use of PTGBD can reduce mortality in AC by about 2%. Based on the higher mortality rates seen in Grade III and AAC, it should be considered whether an early CCY rather than PTGBD may be a better option.
- With the suspension of elective CCYs seen with COVID, we should expect a higher incidence of AC, a higher rate of perforated gallbladder and a higher rate of unsuccessful conservative treatment.

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