SURGICAL ASPECTS OF ACUTE CHOLECYSTITIS

PhD Thesis

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Szeged

2025

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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 in acute cholecystectomies: 13-year experience from a tertiary center
(Accepted for publication in JSLS, Journal of the Society of Laparoscopic and Robotic Surgeons on Dec 11, 2024) (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. At the University of Szeged, on average, 75 to 135 cases of AC are treated annually. 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 [1], [2], [3]. These guidelines are, in turn, based on the definition and severity grading of AC [4]. The diagnosis of AC requires the evaluation of the following factors:

A. Local signs of inflammation

- Murphy's sign
- RUQ (right upper quadrant) mass/pain/tenderness

B. Systemic signs of inflammation

- fever
- elevated CRP
- elevated WBC (white blood cell) count

C. Imaging findings

-Imaging findings characteristic of acute cholecystitis.

Suspected AC diagnosis: one item in A + one item in B.

Definite AC diagnosis: one item in A + one item in B + C.

TG severity grading for acute cholecystitis:

- Grade III (severe) acute cholecystitis is associated with dysfunction of any one of the following organs/systems:
  - cardiovascular dysfunction: hypotension requiring treatment with dopamine ≥5 μg/kg per min, or any dose of norepinephrine
  - neurological dysfunction: decreased level of consciousness
  - respiratory dysfunction: PaO2/FiO2 ratio <300
  - renal dysfunction: oliguria, creatinine >2.0 mg/dl
  - hepatic dysfunction: PT-INR >1.5
  - hematological dysfunction: platelet count <100,000/mm3
- Grade II (moderate) acute cholecystitis:
  - elevated white blood cell count (>18,000/mm3)

- palpable tender mass in the right upper abdominal quadrant
- duration of complaints >72 hours
- marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis)

* Grade I (mild) acute cholecystitis:
  - does not meet the criteria of "Grade III" or "Grade II" acute cholecystitis
  - acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure.

The three pillars of care are conservative medical treatment, surgical treatment (cholecystectomy [CCY]) and percutaneous transhepatic gallbladder drainage (PTGBD). According to the Tokyo Guidelines 2018 (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 [5], [6]. 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. The TG18 recommendations are shown in Figures 1 to 3.

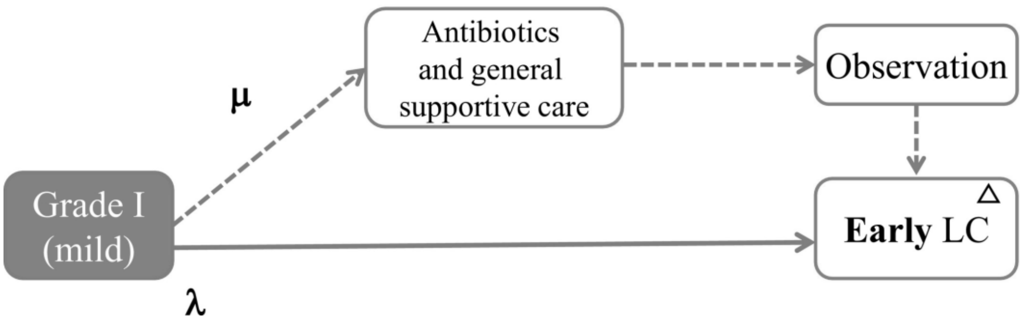

Figure 1. TG18 flowchart for the management of acute cholecystitis Grade I. λ, CCI 5 or less and/or ASA class II or less (low risk); μ, CCI 6 or greater and/or ASA class III or greater (not low risk); ▵, in case of serious operative difficulty, bail-out procedures including conversion should be used. ASA-PS American Society of Anesthesiologists physical status. CCI Charlson comorbidity index

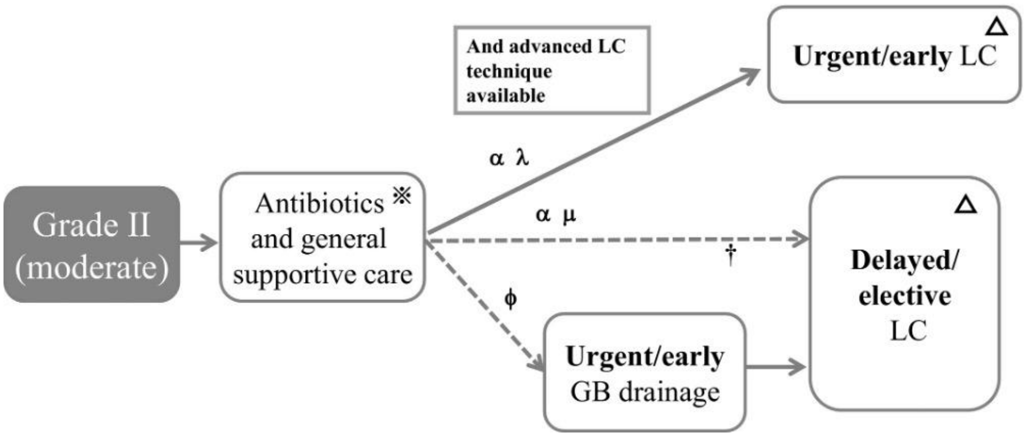

Figure 2. TG18 flowchart for the management of acute cholecystitis Grade II. α, antibiotics and general supportive care successful; ϕ, antibiotics and general supportive care fail to control inflammation; λ, CCI 5 or less and/or ASA-PS class II or less (low risk); μ, CCI 6 or greater and/or ASA-PS class III or greater (not low risk); ※, performance of a blood culture should be taken into consideration before initiation of administration of antibiotics; †, a bile culture should be performed during GB drainage; ▵, in case of serious operative difficulty, bail-out procedures including conversion should be used. ASA-PS: American Society of Anesthesiologists physical status, CCI: Charlson comorbidity index, GB: gallbladder, LC: laparoscopic cholecystectomy.

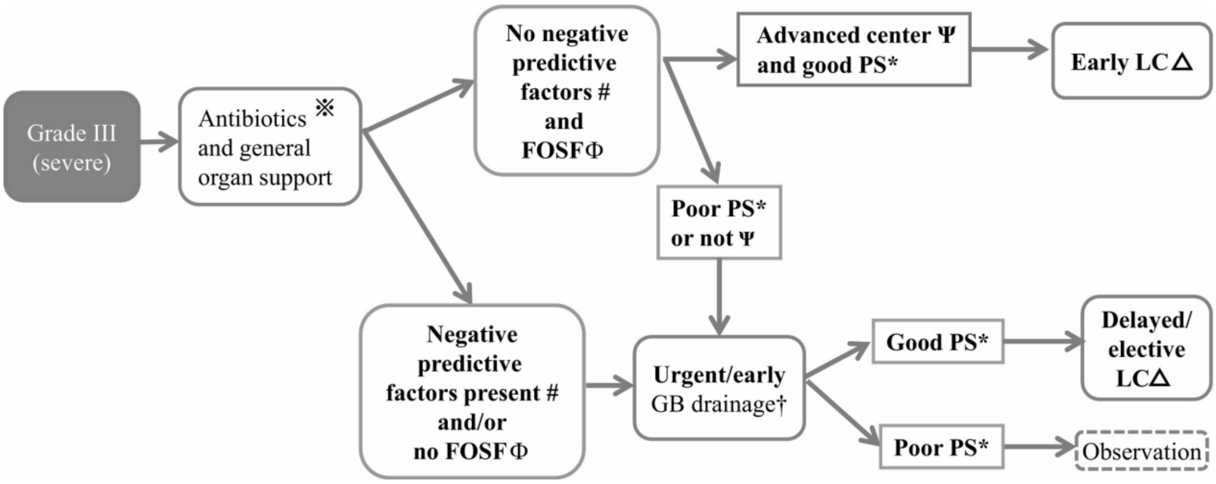

Figure 3. TG18 flowchart for the management of acute cholecystitis Grade III. ※, performance of a blood culture should be taken into consideration before initiation of administration of antibiotics; #, negative predictive factors: jaundice (TBil ≥2), neurological dysfunction, respiratory dysfunction; Φ, FOSF: favorable organ system failure = cardiovascular or renal organ system failure which is rapidly reversible after admission and before early LC in AC; *, in Grade III cases, CCI (Charlson comorbidity index) 4 or greater, ASA-PS 3 or greater are high risk; †, a bile culture should be performed during GB drainage; Ψ, advanced center = intensive care and advanced laparoscopic techniques are available; ▵, in case of serious operative difficulty, bail-out procedures including conversion should be used. GB gallbladder, LC: laparoscopic cholecystectomy, PS: performance status.

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 (Figure 4). 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.

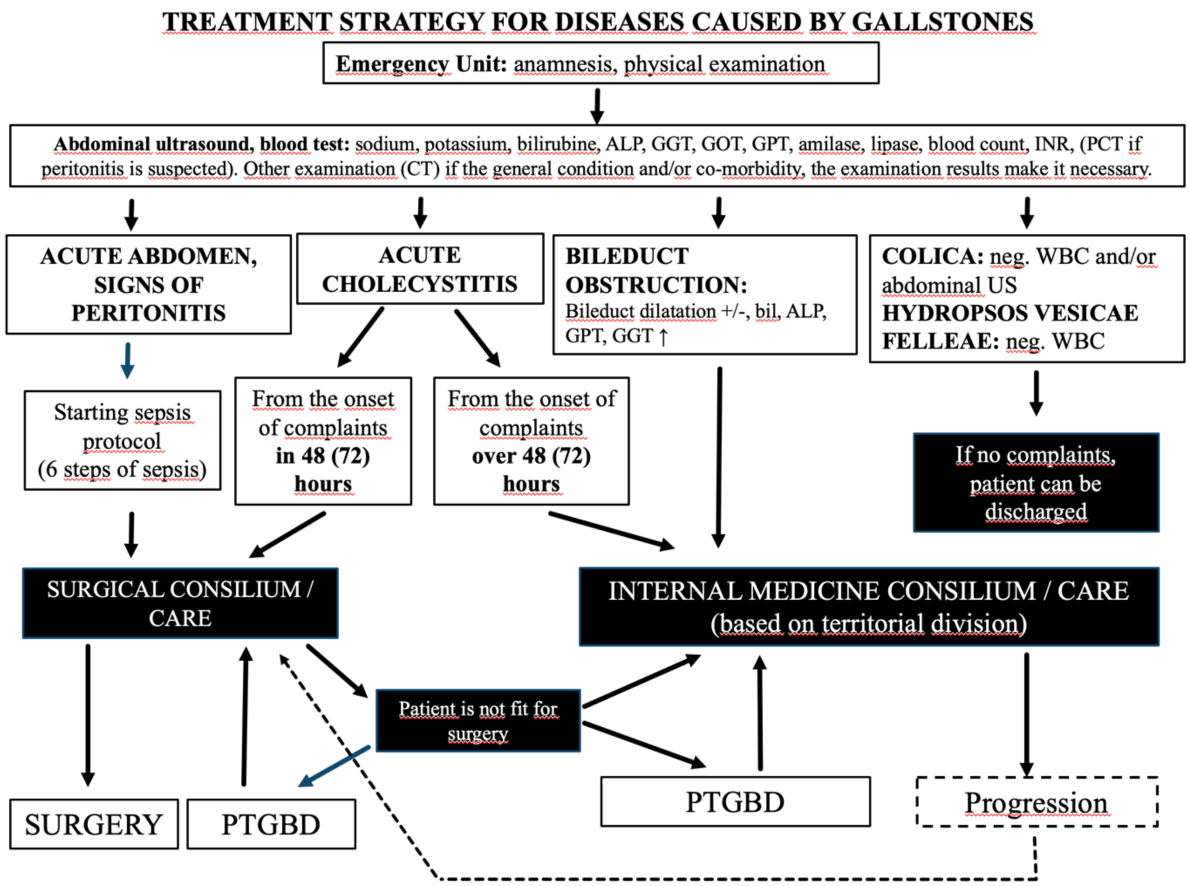

Figure 4. Treatment flowchart for AC at the University of Szeged. ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, GOT: glutamate-oxaloacetate-transaminase, GPT: glutamate-pyruvate-transaminase, INR: international normalized ratio for prothrombine time, PCT: procalcitonine, CT: computed tomography, bil: bilirubin, WBC: white blood cell, US: ultrasound, PTGBD: percutaneous transhepatic gallbladder drainage.

Our aims:

In our studies, we aimed to analyse the clinical and surgical outcomes of surgical treatment (CCY), PTGBD and conservative treatment, which are the main pillars of AC care mentioned above. Furthermore, we sought to determine how the COVID-19 (Coronavirus Disease - 2019) pandemic influenced the aforementioned factors as well as clinical practice.

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). Apart from the technical failure (when drainage cannot be performed for some technical reason), the CSR is of great importance, since in the case of clinical success, CCY can be postponed to a non-inflammatory period or, in some cases, even dispensed with. However, in the case of failure, if the disease progresses, a very high-risk, difficult CCY with a high complication rate may be required immediately.

Prior to 2010, patients beyond the timeframe or ineligible for surgery were largely treated conservatively, and progression was usually followed by a difficult CCY. 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, we have been faced with the COVID-19 pandemic. 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", resources were reallocated and the focus was shifted to the care of COVID patients and to the control of the spread of the disease. Elective and non-urgent procedures and surgeries were postponed, transforming emergency care, including emergency surgical care [7]. As elective and/or delayed cholecystectomies were also suspended, the changes also significantly affected AC care [8]. 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 in acute cholecystectomies: 13-year experience from a tertiary 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 indications for early LC in patients with radiologically confirmed AC were determined based on the recommendations in the Tokyo Guidelines 2007, 2013, and 2018 [2], [3], [9].

The severity of inflammation was determined retrospectively based on the TG18/TG13 severity grading for AC specified in the Tokyo Guidelines 2018 [4]. The severity of the AC-related inflammation was thus classified as grade I (mild), grade II (moderate), or grade III (severe). The morphological diagnoses dtermined by abdominal ultrasound (US) 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 [10]. Based on the Charlson comorbidity index (CCI), the patients were categorized into 3 groups (0, 1–3, 4+) [11]. 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 diagnoses (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.

Statistical analysis

Detailed descriptive statistics for continuous and categorical variables are reported. Pearson's chi-square test or Fisher's exact test was used for univariate analysis, as appropriate. Potential factors influencing the need for conversion during early LC were analyzed using logistic regression. Statistical analysis was performed using R 3.5.1.

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. We did these exclusions to provide a homogenous study population in terms of the used interventional radiology method (i.e. only ultrasound-guided PTGBD). 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 [2], [3], [9].

The severity of inflammation was determined retrospectively based on the TG18/TG13 severity grading for acute cholecystitis defined in the Tokyo Guidelines 2018 [4]. 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)[12].

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. As a routine practice, we followed up the patients with control abdominal ultrasound after the PTGBD everyday/every second day or rarely with CT. We

checked the position of the inserted tube/drain and the possible regression of the gallbladder inflammation (thickness of the gallbladder wall, pericholecystic fluid, etc.).
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. Elective surgeries were further divided into two groups according to the time elapsed between PTGBD and the CCY surgery (performed between three to six weeks and after six weeks). In these groups, the previous parameters (CR and LSR) were also determined. 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). We further analysed in-hospital mortality in relation to different patient or intervention characteristics.

Statistical analysis: Detailed descriptive statistics for continuous and categorical variables were reported. Welch’s t-test, one-way ANOVA, Pearson’s chi-squared test or Fischer’s exact test were used for the univariate analysis, as appropriate. We tested the association between negative patient outcomes (in-hospital mortality, clinical progression and emergency cholecystectomy) and patient’s performance status or ACC severity with a univariate method followed by logistic regression. Statistical analysis was performed using R 3.5.1.

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, which predicts ten-year survival taking comorbidities and patient age into account [11]. 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. Based on aspects specified in the 2018 Tokyo Guidelines (TG18/TG13 severity grading for acute cholecystitis [4]), 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). Based on our radiological standards, acute calculous cholecystitis has general US signs as sensitive findings (sonographic Murphy sign, presence of cholelithiasis) and less specific findings (gallbladder wall thickening (over 3 mm), sludge, increased vascularisation of the gallbladder wall, pericholecystic fluid, gallbladder distension, layering of the gallbladder wall). In case of EVF additional to general signs of calculous cholecystitis can be seen: echogenic content within the gallbladder lumen. In case of GP the following signs can be observed: defect in the gallbladder wall with pericholecystic fluid collection, stranding of the omentum, adjacent hepatic abscess. In case of HVF you can see impacted stone in cystic duct, >4 cm transverse diameter of gallbladder, >9 cm longitudinal diameter of gallbladder and convex borders of gallbladder. 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). See Figure 5 for treatment pathways.

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.

Statistical analysis: Welch's test, one-way ANOVA, Pearson's chi-squared test, Fisher's exact test and Independent-Samples Mann-Whitney U Test were used to statistically analyse patient characteristics, surgical treatments, length of hospital stay, mortalities and unexpected readmissions. CCI groups, ultrasound morphological groups, AC severity groups and treatments were analysed statistically using Chi-Square Test with Pairwise Z-Tests with Bonferroni correction.

Figure:

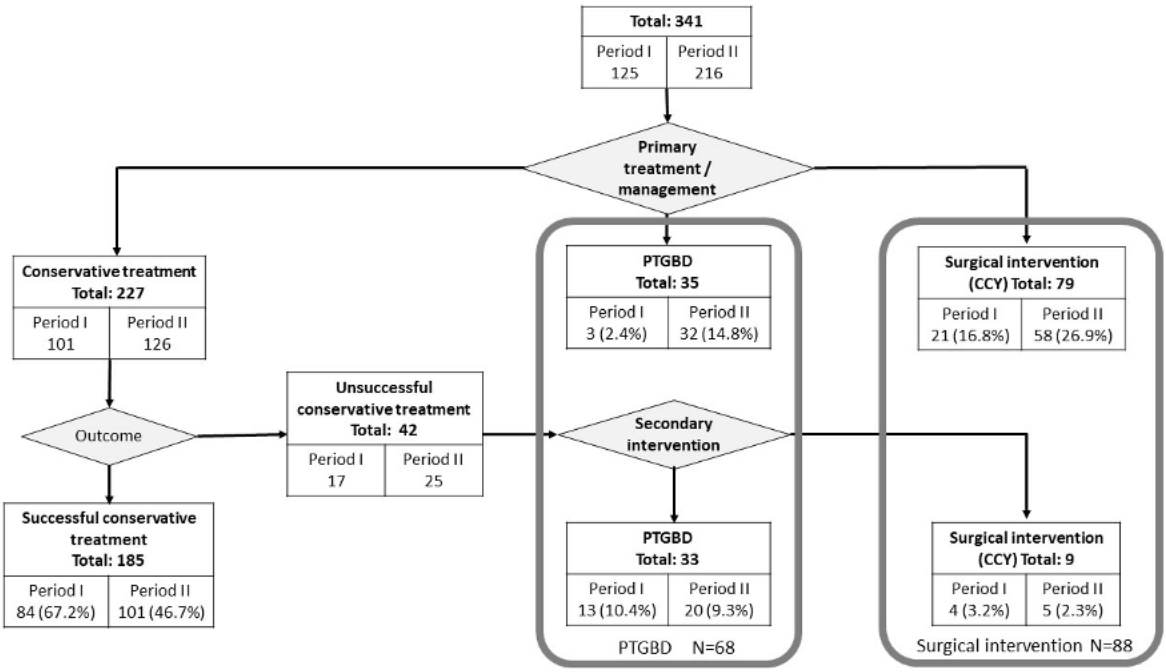

Figure 5. Flowchart for the management and number of patients in each group (Period I: pre-COVID period, Period II: COVID period). COVID: coronavirus disease; PTGBD: percutaneous transhepatic gallbladder drainage; CCY: cholecystectomy.

IV. RESULTS

1. Evaluating surgical outcomes in acute cholecystectomies: 13-year experience from a tertiary center (Study 1)

A total of 465 patients underwent acute, early cholecystectomy during the study reference period. The patient characteristics and surgical details are summarized in Table 1.

The mean age of patients was 57.9 ± 17.2 years, and women accounted for 58.2% of the study population. 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. Data pertaining to CR, LSR, and mortality are presented in Tables 2 and 3. 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 1 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. If surgery was still inevitable for grade III severity, primary open cholecystectomy was performed in almost half (46.1%) of the cases. No increasing trend in CR could therefore be observed compared to the grade II cases.

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%, $p < 0.001$). The results were similar for the ASA score (Table 2).

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 lower abdominal surgery had no significant impact on CR or LSR, but 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) (Table 2).

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. The mean time frame was the shortest in the laparoscopic surgery group (37.94 hours) and the longest in the primary open surgery group (63.35 hours) (Tables 4A and 4B).

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) (Figure 6, Tables 5A and 5B).

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 (Table 6). Although to a lesser degree, CCI was also found to be a determinant of conversion during surgery (OR: 1.56; CI: 1.28–1.89).

Figure and tables:

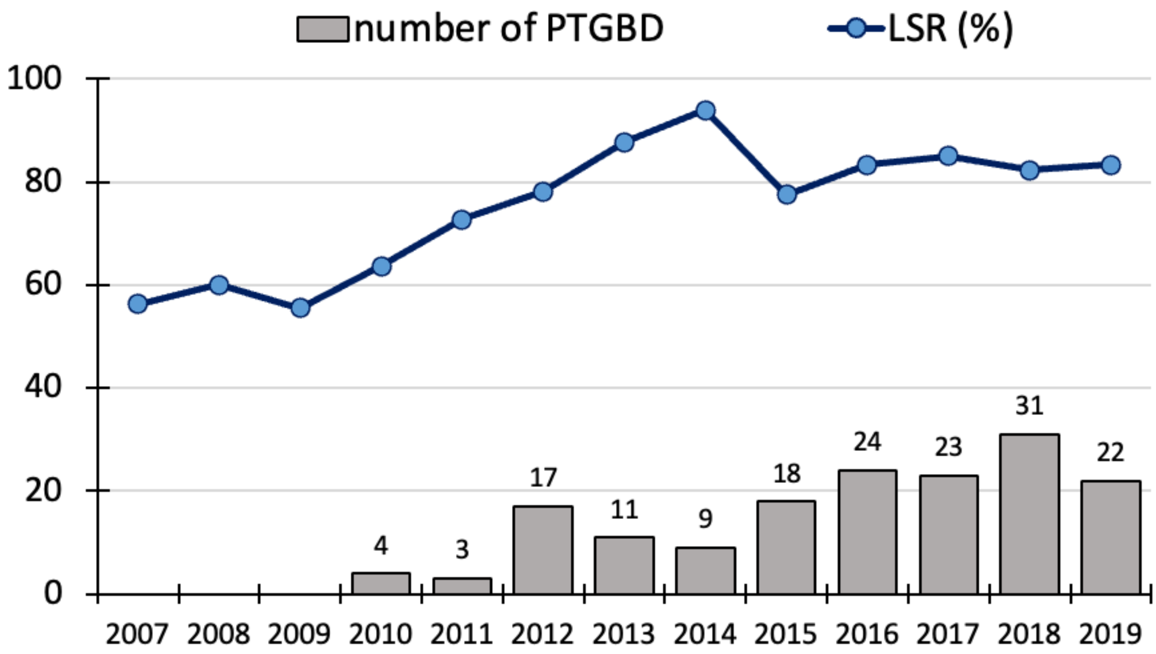

Figure 6. Number of percutaneous transhepatic gallbladder drainage (PTGBD) procedures per year and the annual laparoscopic success rate of the early/urgent cholecystectomies for acute cholecystitis from 2007 to 2019. LSR: laparoscopic success rate (number of LCs/total number of surgeries).

		N	%
Total		**465**	**100**
Age	Mean ± SD	57.97 ± 17.29	
	Min - Max	19-100	
	18–65	298	64.09
	65+	167	35.91
Sex	Female	271	58.28
	Male	194	41.72
ASA score	1	174	37.50
	2	176	37.93
	3	94	20.26
	4	20	4.31
	NA	1	
CCI	CCI 0	143	30.75
	CCI 1–3	219	47.10
	CCI 4+	103	22.15
Time frame*	0–72 hours	355	82.18
	Over 72 hours	77	17.82
	NA	33	
US morphological diagnoses	AAC	27	5.81
	ACC	342	73.55
	EVF	10	2.15
	HVF	35	7.53
	PC	51	10.97
AC severity grade (TG18/TG13)	I	259	57.30
	II	180	39.82
	III	13	2.88
	NA	13	
Period	Pre-PTGBD period	48	10.32
	PTGBD period	417	89.68
BDI		2	0.43

Table 1. Overall data on patients and early cholecystectomies. AAC: acute acalculous cholecystitis; AC: acute cholecystitis; ACC: acute calculous cholecystitis; ASA: American Society of Anesthesiologists score; CCI: Charlson comorbidity index; CR: conversion rate (number of converted LCs × 100/[total number of surgeries – number of primary open cholecystectomies]); EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; LSR: laparoscopic success rate (number of LCs/total number of surgeries); NA: no data; PC: covered perforated cholecyst; PTGBD: percutaneous transhepatic gallbladder drainage; TG13/18: Tokyo Guidelines 2013 and 2018); US: abdominal ultrasound (*between onset of complaints and hospital admission)

		Converted LC	LC	Primary open CCY	Total	CR (%)	LSR (%)	p*
Total		**74**	**364**	**27**	**465**	**16.89**	**78.28**	
Age (years)	18-65	28	260	10	298	**9.72**	**87.25**	>0.001
	65+	46	104	17	167	**30.67**	**62.28**	
Sex	Female	37	217	17	271	**14.57**	**80.07**	0.305
	Male	37	147	10	194	**20.11**	**75.77**	
ASA score	1	13	156	5	174	**7.69**	**89.66**	>0.001
	2	30	136	10	176	**18.07**	**77.27**	
	3	27	60	7	94	**31.03**	**63.83**	
	4	4	11	5	20	**26.67**	**55.00**	
	NA		1		1			
CCI	CCI 0	6	137		143	**4.20**	**95.80**	>0.001
	CCI 1–3	34	175	10	219	**16.27**	**79.91**	
	CCI 4 +	34	52	17	103	**39.53**	**50.49**	
US morphological diagnoses	AAC	4	21	2	27	**16.00**	**77.78**	
	ACC	39	290	13	342	**11.85**	**84.80**	
	EVF	3	7		10	**30.00**	**70.00**	
	HVF	4	31		35	**11.43**	**88.57**	
	PC	24	15	12	51	**61.54**	**29.41**	
AC severity grade (TG18/TG13)	I	18	236	5	259	**7.09**	**91.12**	>0.001
	II	54	110	16	180	**32.93**	**61.11**	
	III	2	5	6	13	**28.57**	**38.46**	
	NA		13		13			
Upper abdominal surgery	No	68	331	21	420	**17.04**	**78.81**	0.037
	Yes	4	13	5	22	**23.53**	**59.09**	
	NA	2	20	1	23			
Lower abdominal surgery	No	51	255	19	325	**16.67**	**78.46**	0.605
	Yes	21	89	7	117	**19.09**	**76.07**	
	NA	2	20	1	23			

Table 2. Characteristics of cholecystectomies (CCY) performed indicated by acute cholecystitis (AC). AAC: acute acalculous cholecystitis; ACC: acute calculous cholecystitis; ASA: American Society of Anesthesiologists score; CCI: Charlson comorbidity index; CR: conversion rate (number of converted LCs × 100/[total number of surgeries – number of primary open cholecystectomies]); EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; LSR: laparoscopic success rate (number of LCs / total number of surgeries); NA: no data; PC: covered perforated cholecyst; TG13/18: Tokyo Guidelines 2013 and 2018); US: abdominal ultrasound (*Fisher's exact test and chi-squared test)

		N	Overall mortality		p*
			N	%	
Total		**465**	**8**	**1.72**	
Age (years)	18–65	298	4	**1.36**	0.466
	65+	167	4	**2.45**	
Sex	Female	271	5	**1.88**	0.554
	Male	194	3	**1.57**	
ASA score	1	174		**0**	0.002
	2	176	2	**1.15**	
	3	94	4	**4.44**	
	4	20	2	**11.11**	
	NA	1			
CCI	CCI 0	143		**0**	0.001
	CCI 1–3	219	2	**0.92**	
	CCI 4+	103	6	**6.19**	
US morphological diagnoses	AAC	27	1	**3.85**	-
	ACC	342	4	**1.18**	
	EVF	10		**0**	
	HVF	35	1	**2.94**	
	PC	51	2	**4.08**	
AC severity grade (TG18/TG13)	I	259	3	**1.17**	0.183
	II	180	4	**2.27**	
	III	13	1	**8.33**	
	NA	13			

Table 3. Overall mortality by patient and intervention characteristics. AAC: acute acalculous cholecystitis; ACC: acute calculous cholecystitis; ASA score: American Society of Anesthesiologists score; CCI: Charlson comorbidity index; EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; NA: no data; PC: covered perforated cholecyst; TG13/18: Tokyo Guidelines 2013 and 2018); US: abdominal ultrasound (*Fisher's exact test and Pearson's chi-squared test)

A		**LC**	**Converted LC**	**Primary open CCY**	**Total**	**p***	**LSR (%)**	**CR (%)**
Time frame (hours)	**Mean ± SD**	37.94 ± 39.65	47.33 ± 45.57	63.35 ± 63.83	40.75 ± 42.54	-		
	Min - Max	2 - 288	5 - 168	7 - 264	2 - 288	-		
Total		**364**	**74**	**27**	**465**	**-**	**78.28**	**16.89**
Time frame#	0–72 hours	290	49	16	355	0.008	81.69	14.45
	Over 72 hours	52	18	7	77		67.53	25.71
	NA	22	7	4	33			

B		N	Overall mortality		**p***
			N	%	
Total		**465**	**8**	**1.72**	**-**
Time frame#	0–72 hours	355	5	**1.41**	0.613
	Over 72 hours	77	2	**2.60**	
	NA	33	1		

Table 4A and 4B. Characteristics and overall mortality of early/urgent cholecystectomies (CCY) for acute cholecystitis based on time between onset of complaints and hospital admission. LSR: laparoscopic success rate (number of LCs/total number of surgeries); CR: conversion rate (number of converted LCs × 100/[total number of surgeries – number of primary open cholecystectomies]) (#time between onset of complaints and hospital admission; *Fisher's exact test and chi-squared test)

A		LC	Converted LC	Primary open CCY	Total	p*	LSR (%)	CR (%)
Total		**364**	**74**	**27**	**465**	**-**	**78.28**	**16.89**
Period	**pre-PTGBD period**	27	14	7	48	>0.001	56.25	34.15
	PTGBD period	337	60	20	417		80.82	15.11

B		N	Overall mortality		**p***
			N	%	
Total		**465**	**8**	**1.72**	**-**
Period	**pre-PTGBD period**	48	3	**6.67**	0.04
	PTGBD period	417	5	**1.21**	

Table 5A and 5B. Characteristics and overall mortality of early/urgent cholecystectomies (CCY) for acute cholecystitis based on the pre–percutaneous transhepatic gallbladder drainage (PTGBD) period and the PTGBD period. LSR: laparoscopic success rate (number of LCs/total number of surgeries); CR: conversion rate (number of converted LCs × 100/[total number of surgeries – number of primary open cholecystectomies]) (*Fisher's exact test and chi-squared test)

			95% CI for OR	
	p	**OR**	**Lower**	**Upper**
CCI	0.000	1.56	1.28	1.89
ASA score	0.328	0.81	0.53	1.23
AC severity grade	0.000	3.77	2.23	6.37
Upper abdominal surgery	0.008	4.30	1.47	12.60
PTGBD period	0.117	0.53	0.24	1.17
Time frame (hours)	0.251	1.00	1.00	1.01
Constant	0.000	0.02		

Table 6. Impact of patient/physician-related characteristics on conversion analysed with multivariate analysis (logistic regression). Overall model fit: NagelkerkeR2 = 0.315; goodness-of-fit: Hosmer–Lemeshow test p = 0.053; classification table: correct predictions = 82.06%; B: regression coefficient; SE: standard error; Wald: df: degree of freedom; OR: odds ratio; CI: confidence interval.

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 (51.23% vs. 48.77%). 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 cases where no surgical procedure was performed, PTGBD served as definitive therapy. Mean age of these patients was 73.81±14.43 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% (Table 7). 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%. The drain inserted was removed 11.65±7.57 days after PTGBD on average. After PTGBD, 62 (42.18%) did not undergo subsequent CCY; drainage therefore proved to be a definitive therapy. 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 (Table 7).

CSR of PTGBD deteriorated significantly in patients over 65 years and in parallel with the increasing severity of the inflammation (Table 8). 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. The clinical regression varied inversely with the ASA score and a similar tendency could be observed for CCI; CSR was 100% for CCI 0, 88.37% for CCI 1–3 and 86.96% for CCI 4+. There was no significant difference in CSR in relation to time elapsed between the onset of complaints and hospital admission (Table 8).

After PTGBD, ERCP was necessary in 15.43% of the cases (25 cases) (Table 9). The most common indication for ERCP was in cases, where no reduction in bile flow through the inserted gallbladder drain was seen. Irrespective of the indication for ERCP, choledocholithiasis was confirmed in 40% of the cases (Table 9).

Comparing emergency and elective CCY surgeries after PTGBD in terms of LSR and CR (Table 10), 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%).

If we further analyse elective and emergency CCYs (Table 11), it can be seen that emergency CCYs were mainly performed in older patients with higher CCI or more severe AC.

In addition to the 0% procedure mortality directly associated with the PTGBD intervention, in-hospital mortality was 11.72% (Table 12). 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. In this scenario, five out of nine patients died with an in-hospital mortality of 55.56%, while mortality was only 6.00% for ACC. Mortality after elective surgery was 0%; however, if emergency CCY was required after PTGBD, we lost 14.29% of the patients.

The logistic regression (Table 13) showed that the severity of AC inflammation had the highest odds for emergency CCY (OR: 14.75; CI: 3.07–70.81). The degree of inflammation also had a significant effect on clinical progression (OR: 7.62; Cl: 2.64–22.05) and on in-hospital mortality (OR: 6.07; CI: 1.79–20.56). CCI had a significant odds ratio only for in-hospital mortality (similarly to the results of the univariate analysis).

Tables:

		N	%	Mean ± SD	Min–Max
Age (years)	30–65	46	28.4		
	65+	116	71.6		
	Total	162	100	71.43±13.22	33–95
Sex	Female	79	48.77		
	Male	83	51.23		
	Total	162	100		
ASA score	1	16	10.13		
	2	65	41.14		
	3	54	34.18		
	4	23	14.56		
	NA	4			
CCI	CCI 0	8	5.13		
	CCI 1–3	46	29.49		
	CCI 4 +	102	65.38		
	Total	156	100	4.21±2.25	0–10
	NA	6			
Time frame (between onset of complaints and hospital admission)	0–72 hours	54	39.71		
	72 hours–1 week	62	45.59		
	Over 1 week	20	14.71		
	NA	26			
Indication of PTGBD based on abdominal US N=140; 100%	AAC	9	5.56		
	ACC	55	33.95		
	EVF	17	10.49		
	HVF	37	22.84		
	PC	44	27.16		
AC severity grade (TG18/TG13)	I	14	8.81		
	II	117	73.58		
	III	28	17.61		
	NA	3			
PTGBD TSR N=162 100%			97.53		
PTGBD CSR N=162 100%			87.97		
Time of drain removal after PTGBD (days)		88		11.65±7.57	1–42
	NA	*76*			
Mortality after PTGBD	Procedure mortality	0	0		
	In-hospital mortality	17	11.72		
ERCP after PTGBD	During hospital stay	21	13.46		
	After hospital discharge	4	2.56		
	There was no ERCP	131	83.97		
	NA	6			
CCY after PTGBD	Emergency CCY	16	10.88		
	Elective CCY	69	46.94		
	There was no surgery	62	42.18		
BDI during CCY after PTGBD		1	1.17		
Time interval between PTGBD and CCY	Emergency (days)	16	19.05	5.50±12.56	0–52
	Elective (weeks)	68	80.95	13.57±10.89	2–67
	Total	84	100	11.24±10.92	0–67
	NA	*1*			

Table 7. General patients and interventions characteristics. AC: acute cholecystitis; AAC: acute acalculous cholecystitis; ACC: acute calculous cholecystitis; BDI: bile duct injury; CCY: cholecystectomy; CSR: clinical success rate; ERCP: endoscopic retrograde cholangiopancreatography; EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; NA: no data; PC: covered perforated cholecyst; TSR: technical success rate; TG13/18: Tokyo Guidelines 2013 and 2018; US: ultrasound

		Clinical progression after PTGBD	Clinical regression after PTGBD	Technically unsuccessful PTGBD	Total	TSR %	CSR %	p*
Total		19	139	4	162	97.53	87.97	
Age (years)	30–65	0	42	4	46		100	0.003926
	65+	19	97	0	116		83.62	
Sex	Female	11	65	3	79		85.53	0.5053
	Male	8	74	1	83		90.24	
ASA score	1	0	14	2	16		100	-
	2	12	52	1	65		81.25	
	3	4	49	1	54		92.45	
	4	3	20	0	23		86.96	
	NA		4		4			
CCI	CCI = 0	0	7	1	8		100	0.6372
	CCI = 1–3	5	38	3	46		88.37	
	CCI = 4+	14	88	0	102		86.27	
	NA		6		6			
Time frame (between onset of complaints and hospital admission)	0–72 hours	8	46	0	54		85.19	0.8191
	72 hours–1 week	7	52	3	62		88.14	
	Over 1 week	2	17	1	20		89.47	
	NA	2	24		26			
AC severity grade (TG18/TG13)	I	0	14	0	14		100	0.0009995
	II	9	104	4	117		92.04	
	III	10	18	0	28		64.29	
	NA		3		3			

Table 8. Technical success rate and clinical outcomes of percutaneous transhepatic gallbladder drainage (PTGBD) according to patient characteristics. AC: acute cholecystitis; NA: no data (*Pearson's chi-squared test)

	ERCP indication	ERCP outcome	N
During in-hospital stay N=20; 83.33%	Non-decreasing biliary excretion N=12; 50.00%	BO: CBDS	5
		BO: juxtapapillary diverticulum	2
		BO: SOD	2
		BO: sclerosis of Vater's papilla	1
		Irregular pancreatic anatomy	1
		BO: Mirizzi's syndrome	1
	Cholangiosepsis N=4; 16.66%	BO: CBDS	2
		BO: duodenal stenosis	1
		BO: biliary stent obstruction	1
	Increased biliary obstruction enzymes N=3; 12.50%	BO: juxtapapillary diverticulum	2
		BO: CBDS	1
	Sepsis	Abdominal gallbladder perforation	1
After hospital discharge N=4; 16.67%	**Increased biliary obstruction enzymes**	BO: CBDS	2
	Cholangiosepsis	BO: CBDS	1
	Non-decreasing biliary excretion	Intrahepatic minor BDI	1
Total			**24**
NA			1

Table 9. Indications and timing of endoscopic retrograde cholangiopancreatography (ERCP) after percutaneous transhepatic gallbladder drainage (PTGBD). BDI: bile duct injury; BO: biliary obstruction; CBDS: common bile duct stone; NA: no data; SOD: sphincter of Oddi dysfunction

		LC	Converted LC	Primary open CCY	NA	Total	LSR (%)	p* LSR%	CR (%)
Total		**61**	**13**	**10**	1	**85**	**71.76**	-	**17.57**
CCY after PTGBD	Emergency	9	2	5		16	**56.25**	0.1367	18.18
	Planned CCY	52	11	5	1	69	**75.36**		17.46
	- within 3 to 6 weeks	5	1	1		8	**62.50**	0.3969	16.67
	- after 6 weeks	47	10	4		61	**77.05**		17.54

Table 10. Characteristics of cholecystectomies (CCY) performed after percutaneous transhepatic gallbladder drainage (PTGBD). LSR: laparoscopic success rate (number of LCs / total number of surgeries); CR: conversion rate (number of converted LCs × 100 / [total number of surgeries – number of primary open cholecystectomies]) (*Fischer's Exact Test)

		Elective CCY after PTGBD N=69 (100%)	Emergency CCY after PTGBD N=16 (100%)	Total	p
Age (years)	30–65	27 (39.13%)	2 (12.5%)	29	p-value = 0.0762 Fisher's exact test
	65+	42 (60.87%)	14 (87.5%)	56	
Sex	Female	29 (42.03%)	10 (62.5%)	39	p-value = 0.1698 Fisher's exact test
	Male	40 (57.97%)	6 (37.5%)	46	
ASA score	1	6 (8.7%)	2 (12.5%)	8	p-value = 0.7576 Pearson's chi-squared test with simulated p-value (based on 2000 replicates)
	2	37 (53.62%)	10 (62.5%)	47	
	3	23 (33.33%)	3 (18.75%)	26	
	4	3 (4.35%)	1 (6.25%)	4	
CCI	CCI = 0	3 (4.41%)	1 (6.25%)	4	p-value = 0.8236 Pearson's chi-squared test with simulated p-value (based on 2000 replicates)
	CCI = 1–3	29 (42.65%)	5 (31.25%)	34	
	CCI = 4 or 4+	36 (52.94%)	10 (62.5%)	46	
	NA	1		1	
Time frame (between onset of complaints and hospital admission)	0–72 hours	23 (36.51%)	6 (42.86%)	29	p-value = 0.93 Pearson's chi-squared test with simulated p-value (based on 2000 replicates)
	72 hours–1 week	30 (47.62%)	6 (42.86%)	36	
	Over 1 week	10 (15.87%)	2 (14.29%)	12	
	NA	6	2	8	
Indication of PTGBD based on abdominal US	AAC	2 (2.9%)	1 (6.25%)	3	p-value = 0.7836 Pearson's chi-squared test with simulated p-value (based on 2000 replicates)
	ACC	25 (36.23%)	8 (50%)	33	
	EVF	5 (7.25%)	1 (6.25%)	6	
	HVF	16 (23.19%)	2 (12.5%)	18	
	PC	21 (30.43%)	4 (25%)	25	
AC severity grade (TG18/TG13)	I	9 (13.04%)	0 (0%)	9	p-value = 0.0004998 Pearson's chi-squared test with simulated p-value (based on 2000 replicates)
	II	56 (81.16%)	9 (56.25%)	65	
	III	4 (5.8%)	7 (43.75%)	11	

Table 11. The characteristics of emergency and elective cholecystectomies (CCY) performed after percutaneous transhepatic gallbladder drainage (PTGBD). AC: acute cholecystitis; AAC: acute acalculous cholecystitis; ACC: acute calculous cholecystitis; EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; NA: no data; PC: covered perforated cholecyst; US: ultrasound

Total		N	Survival		In-hospital mortality		NA	p
		162	128	(88.28%)	17	(11.72%)	17	-
Age (years)	30–65	46	36	(90.00%)	4	(10.00%)	6	0.7811
	65+	116	92	(87.62%)	13	(12.38%)	11	
Sex	Female	79	58	(87.88%)	8	(12.12%)	13	1
	Male	83	70	(88.61%)	9	(11.39%)	4	
ASA score	1	16	15	(100.00%)	0	(0.00%)	1	sim p-value = 0.001999
	2	65	55	(98.21%)	1	(1.79%)	9	
	3	54	42	(85.71%)	7	(14.29%)	5	
	4	23	15	(68.18%)	7	(31.82%)	1	
CCI	CCI = 0	8	6	(100.00%)	0	(0.00%)	2	sim p-value = 0.02299
	CCI = 1–3	46	41	(100.00%)	0	(0.00%)	5	
	CCI = 4+	102	79	(84.04%)	15	(15.96%)	8	
	NA	6						
Time frame (between onset of complaints and hospital admission)	0–72 hours	54	46	(86.79%)	7	(13.21%)	1	sim p-value = 0.1729
	3 days–1 week	62	52	(96.3%)	2	(3.70%)	3	
	Over 1 week	20	15	(88.24%)	2	(11.76%)	8	
	NA	26						
Indication of PTGBD based on abdominal US	AAC	9	4	(44.44%)	5	(55.56%)	0	-
	ACC	55	47	(94.00%)	3	(6.00%)	5	
	EVF	17	11	(91.67%)	1	(8.33%)	5	
	HVF	37	30	(88.24%)	4	(11.76%)	3	
	PC	44	36	(90.00%)	4	(10.00%)	4	
AC severity grade (TG18/TG13)	I	14	14	(100%)	0	(0%)	0	sim p-value = 0.0004998
	II	117	100	(92.59%)	8	(7.41%)	9	
	III	28	13	(59.09%)	9	(40.91%)	6	
	NA	3						
CCY after PTGBD	Planned	69	66	(100%)	0	(0%)	3	0.0288
	Emergency	16	12	(85.71%)	2	(14.29%)	2	

Table 12. Survival and in-hospital mortality according to patient and intervention characteristics. AAC: acute acalculous cholecystitis; ACC: acute calculous cholecystitis; EVF: empyema vesicae felleae; HVF: hydrops vesicae felleae; NA: no data; PC: covered perforated cholecyst; PTGBD: percutaneous transhepatic gallbladder drainage; TG13/18: Tokyo Guidelines 2013 and 2018; US: ultrasound (*Fischer's exact test and Pearson's chi-squared test)

		B	S.E.	df	p	OR (95% CI)	Model characteristics
In-hospital mortality N=141	CCI	0.562	0.168	1	0.001	1.75 (1.26–2.44)	Nagelkerke R-squared=0.345; Correct predictions=87.2%
	AC severity grade	1.803	0.623	1	0.004	6.07 (1.79–20.56)	
	Constant	-9.154	1.955	1	0.000		
Clinical progression after PTGBD N=152	CCI	-0.001	0.136	1	0.995	1.00 (0.77–1.3)	Nagelkerke R-squared=0.199; Correct predictions=87.5%
	AC severity grade	2.031	0.542	1	0.000	7.62 (2.64–22.05)	
	Constant	-6.533	1.287	1	0.000		
Emergency CCY after PTGBD N=84	CCI	-0.124	0.182	1	0.495	0.88 (0.62–1.26)	Nagelkerke R-squared=0.273; Correct predictions=84.5%
	AC severity grade	2.691	0.800	1	0.001	14.75 (3.07–70.81)	
	Constant	-6.812	1.611	1	0.000		

Table 13. Logistic regression between negative patient outcomes (in-hospital mortality, clinical progression and emergency cholecystectomy) and patient's performance status or AC severity.

AC: acute cholecystitis; B: regression coefficient; CCI: Charlson comorbidity index; df: degree of freedom; OR: odds ratio; CI: confidence interval

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) (Figure 7).

Out of the 216 patients, only six (2.8%) tested positive for COVID. 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) (Table 14).

There was no significant change in the severity of AC, with the rate of Grade II cases being the highest in both groups (55.1 vs. 52.8%). 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 (Table 14). 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) (Table 15). There was no significant difference in mortality either during the hospital stay or within 30 days after the procedure (Table 15). 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) (Table 15).

There was a significant change in the rates of the treatment methods between the two periods (Figure 8). 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. Out of the six COVID-positive patients, two received successful conservative therapy, three underwent PTGBD, and one had a converted LC.

When assessing (both primary and secondary) surgeries, we found no significant difference either in the distribution of surgery types (LC, converted LC and primary open surgery) or in CR (17.4 vs. 20.9%) and LSR (76 vs. 77.8%) between the two periods.

Figures and tables:

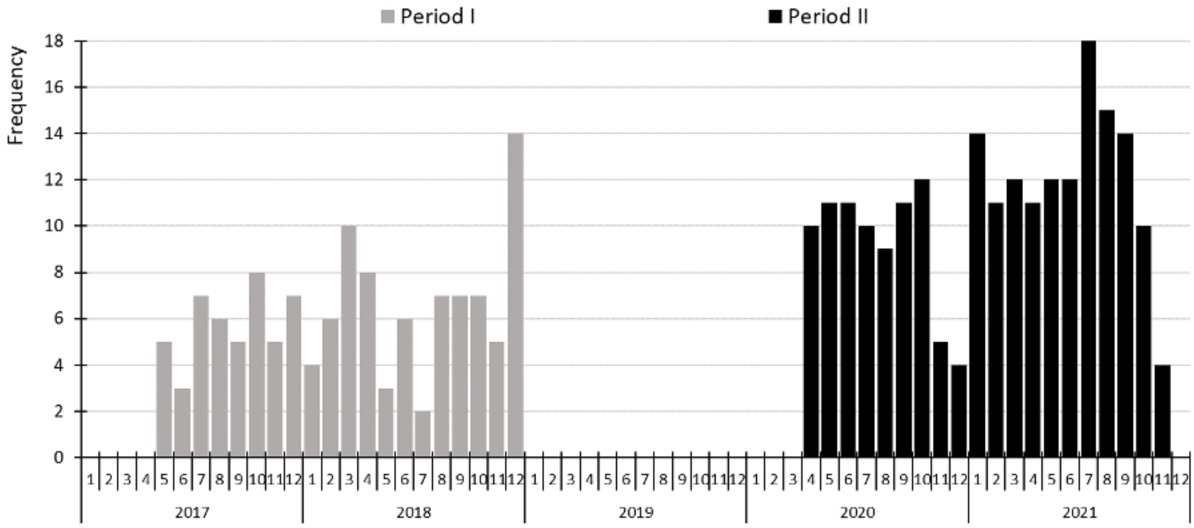

Figure 7. Number of acute cholecystitis diagnoses per month in the two periods.

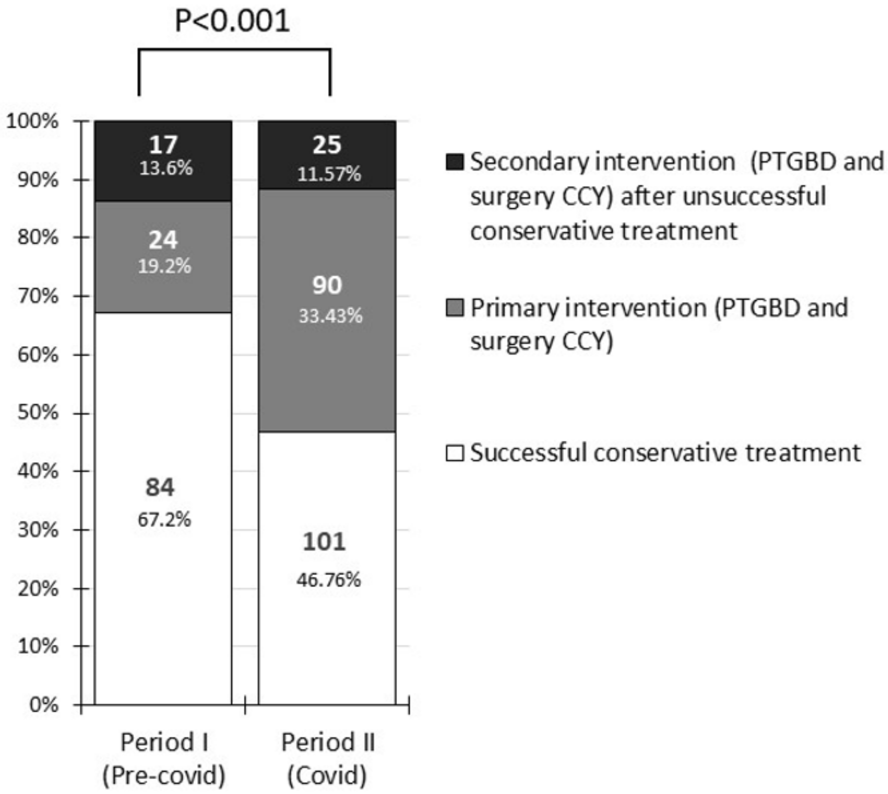

Figure 8. The distribution of treatment types in the two periods. (CCY: cholecystectomy; COVID: coronavirus disease; PTGBD: percutaneous transhepatic gallbladder drainage)

		Period I (pre-COVID)	Period II (COVID)	p value
	N	125 (100%)	216 (100%)	<0.001
Age	median (min–max)	74 (27–101)	70 (24–96)	0.017
Sex	Female	70 (56%)	122 (56.5%)	NS
	Male	55 (44%)	94 (43.5%)	
CCI scores	Group 1 (0)	12 (11.2%)	40 (20.4%)	0.043
	Group 2 (1–3)	36 (33.6%)	57 (29.1%)	NS
	Group 3 (4–10)	59 (55.1%)	99 (50.5%)	NS
	NA	18	20	
AC morphological diagnosis (US)	Calculous cholecystitis	77 (62.6%)	139 (64.4%)	NS
	Empyema vesicae felleae	4 (3.2%)	3 (1.4%)	NS
	Gallbladder perforation	9 (7.3%)	39 (18.1%)	0.006
	Hydrops vesicae felleae	33 (26.8%)	35 (16.2%)	0.019
	NA	2		
AC severity (TG13/18)	Grade I	49 (39.2%)	75 (34.7%)	NS
	Grade II	66 (52.8%)	119 (55.1%)	NS
	Grade III	10 (8%)	22 (10.2%)	NS

Table 14. General patient and cholecystitis characteristics. (AC: acute cholecystitis; CCI: Charlson comorbidity index; COVID: coronavirus disease; NA: no data; TG13/18: Tokyo Guidelines 2013/2018; US: ultrasound; NS: not significant)

		Period I (pre-COVID)	Period II (COVID)	p value
	N	125	216	
Treatment/ management	Successful conservative treatment	84 (67.2%)	101 (46.8%)	<0.001
	Percutaneous drainage	16 (12.8%)	52 (24.1%)	0.012
	primary + secondary	3 + 13	32 + 20	
	Surgical treatment	25 (20%)	63 (29.2%)	NS
	primary + secondary	21 + 4	58 + 5	
Surgical treatment	Laparoscopic cholecystectomy	19 (76%)	49 (77.8%)	NS
	Converted laparoscopic cholecystectomy	4 (16%)	13 (20.6%)	
	Open cholecystectomy	2 (8%)	1 (1.6%)	
	CR (%)	17.4	20.9	NS
	LSR (%)	76	77.78	NS
Length of hospital stay	N	117	201	
	NA	8	15	
	median (min–max)	8 (1–62)	7 (1–60)	0.011
Mortality	No	116 (95.08%)	198 (94.29%)	NS
	Yes	6 (4.92%)	12 (5.71%)	
	NA	3	6	
30-day mortality	No	113 (98.26%)	192 (96.97%)	NS
	Yes	2 (1.74%)	6 (3.03%)	
	NA	10	18	
Unplanned readmission	No	115 (100%)	177 (93.65%)	0.004
	Yes	0 (0%)	12 (6.35%)	
	NA	10	27	

Table 15. Treatments and perioperative data. (CCY: cholecystectomy; COVID: coronavirus disease; CR: conversion rate (number of converted laparoscopic cholecystectomies x 100 / [total number of surgeries – number of primary open cholecystectomies]); LSR: laparoscopic success rate (number of laparoscopic cholecystectomies / total number of surgeries); NA: no data)

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 [13]. A recent article from July 2023 found similar results when examining data from US academic centres (comparing 15 months of the pre-pandemic and the pandemic periods each) [14]. 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. CR and LSR were similar in both periods and the rate of laparoscopic procedures did not fall during the pandemic despite the fact that we faced more difficult cases. Laparoscopic cholecystectomy was safely used during the pandemic, as also demonstrated in a large number of cohorts [15].

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 [16]. A study examining elective cholecystectomies in the United Kingdom showed that in the pre-pandemic group a higher proportion of operations were performed for non-inflammatory pathology compared to the post-COVID recovery phase [17].

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 [18]. 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 [19]. In their meta-analysis, Loozen et al. studied 592 elderly patients (>70 years) and found a CR of 23% with a mortality rate of 3.5% [20]. In patients aged >65 years, do Amaral et al. found a higher CR but without a significant difference (CR: 10.3% vs 6.6%; $p = 0.49$) [21]. Although a patient's advanced age is not an absolute contraindication for acute early CCY, it may still be a determinant of complex AC treatment success [22]. 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). When analysing the clinical success rate of drainage, the higher number of adverse outcomes above the age of 65 years is also striking. 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

The age of the patient, although not an irrelevant factor, does not in itself provide information on the performance status of the patient. Of the ASA and CCI scores most commonly used to define PS, the ASA measures the risk of general anaesthesia, while the CCI estimates 10-year survival by taking into account the patient's age. 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 MORFOLOGICAL 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, but not always. 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%). In a prospective study by Eldar (1997), besides hydrops, and empyema, gangrenous cholecystitis was the most common cause of conversion [23]. A study of 373 patients by Terho (2016) yielded a similar result. They reported a CR of 22.5% and identified the following risk factors: elevated CRP levels, diabetes, age >65 years, and gangrenous gallbladder [24]. Several studies recommend percutaneous cholecystostomy in AAC [25], [26]. We should highlight that a mortality rate of almost 56% was observed after PTGBD among patients with AAC in our study. Due to the low number of cases, we have to interpret these results cautiously. However, a similar tendency was reported by Winbladh et al. In diagnostically uncertain cholecystitis, mortality is significantly higher mortality than in AC with a clear origin; where the rate of gallstones was lower, mortality was expected to be higher, even up to 40–60% [27]. The previous observation was supported by a population-based analysis by Schlottmann et al., where a significantly worse postoperative outcome was observed in AAC than in patients with ACC after 7,516 cholecystostomy tube placement interventions [28]. 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 [29]. Aledo et al. (2017) may have been referring to this when they suggested percutaneous drainage instead of cholecystectomy for acute acalculous cholecystitis, but also recommended cholecystectomy in the case of low surgical risk [30]. This is contradicted by our results, according to which an exceptionally high in-hospital mortality of 55.56% can be expected following PTGBD performed for AAC and that primary early cholecystectomy should perhaps be considered in such cases.

During the COVID pandemic, healthcare capacities dropped, with every level of the healthcare provision system from general practitioners to tertiary centres focusing on COVID. Patients frequently sought medical attention or accessed suitable healthcare providers after experiencing symptoms for several days and reaching an advanced stage of inflammation [31]. 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. A study conducted at a German tertiary centre yielded a similar result, though the elevated GP rate was characteristic of the older patients under investigation [32].

5. SEVERITY GRADING OF ACUTE CHOLECYSTITIS

Severity grading is the basis of TG18 and the starting point for choosing the therapeutic direction. In terms of surgical outcomes, the severity of AC was also found to be one of the most determinant factors in our studies. 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 [3], [22], 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 [33]. 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.

A) 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 [34]. Alore et al. (2019) recommended two days for the timing of surgery, although their recommendation was for the period after the date of hospitalisation [35]. Mora-Guzmán et al. (2021) studied CR, surgery time, bile duct injuries, other complications, reoperations, hospital stay, re-hospitalizations, and care costs in 381 patients [36]. Interestingly, they found no significant difference between those subjected to surgery within seven days and those beyond seven days. 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 [37], [38]. In a recent study, Ohya (2021) evaluated 327 cases of acute cholecystectomy and concluded that surgeries performed beyond 72 hours are expected to be more difficult and associated with greater blood loss and higher CR, as well as longer surgery time and hospital stay [39].

B) 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. A similar result was obtained by Ni et al. [40], who found a conversion rate of 19.2% in patients who had previously undergone PTGBD. 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 [41], [42], 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 [5], [6]. Needless to say, it is not always technically easy to perform. Whether the surgery is considered successful can be determined by LSR and CR, among others. Of the two, LSR is perhaps the more illustrative expression of success, as it takes the open surgery into account, but CR is perhaps more commonly used in the international literature.

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. Previous upper abdominal surgery is a well-known risk factor for both elective and acute CCYs [39], [43]. 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. In some cases, the patient's general condition does not allow for subsequent surgery, whereas in others, the patient chooses not to have delayed CCY. Our data show that in almost half of the cases with PTGBD, there was no subsequent CCY (46.94%). Harai et al. reported a similar trend: no CCY surgery was performed in almost 40% of the cases after PTGBD [44]. Moreover, in a systematic review study of 1,925 patients by Winbladh et al., the proportion of patients who did not undergo surgery after percutaneous cholecystostomy was 62% [27]. Further investigations are needed to clarify the exact causes of subsequent CCYs.

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%). A similar result was published by Ni et al. who found a CR of 19.2% when analysing CCYs after PTGBD [40]. In a systematic review by Winbladh et al., the frequency of emergency CCY after percutaneous cholecystostomy was found to be between 2 and 20%[1], [27]. In our study, 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 [1]. The aim of introducing PTGBD was both to improve the surgical management of subsequent CCY and to improve the mortality data measured in the context of AC. 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 [27]. 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. This mortality figure is already in line with Winbladh's systematic review and meta-analysis of 1918 patients and 53 publications (mortality: 4.5%) [27]. 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. An adverse surgical situation in AC or after PTGBD makes it difficult to identify Calot's triangle, thus increasing the chance of biliary tract injury.

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%) [45], [46]. A study of 781 patients by Törnqvist (2016) also found that acute cholecystectomy in itself is a risk factor for BDI (OR: 1.97); in grade I cases, there was no increase in the risk of bile duct injuries (OR: 0.96), but grade II and III cases were associated with a considerably higher risk of BDI (OR: 2.41 and 8.43, respectively) [47].

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. According to Altieri, elective CCYs occurred in approximately 30% of patients after 9,738 PTGBDs, with a BDI rate of approximately 1.6% [48].

Due to the small number of cases, no major conclusions can be drawn and further studies are needed to analyse BDIs in more detail.

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. LIMITATIONS

Some limitations of these studies should be acknowledged. The retrospective study design may have introduced an element of bias. Moreover, data pertaining to body mass index and detailed ultrasound findings (e.g., gallbladder wall thickness) could not be obtained during data collection. The lack of precise distinction between mortality during and after hospital stay was also a limitation. Because of the low mortality and low incidence of BDI, the relevant risk factors could not be identified. Larger multicentre studies can provide more definitive evidence in this regard. After PTGBD we were unable to identify the direct causes of the absence of elective CCY, so we can only infer them.

VII. 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 (CR, LSR, mortality, BDI), 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 (ASA, CCI) and previous upper abdominal surgery. The role of PTGBD in the care of AC is becoming increasingly prominent. In practised hands, it is an easy procedure to perform with good TRS and CSR. In elderly, comorbid patients or in advanced inflammation (Grade II-III), 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.

VIII. 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.

IX. ACKNOWLEDGEMENTS

I would like to thank everyone who helped me with my research and the preparation of this thesis! First of all, to the Head of the Department of Surgery, Professor György Lázár, who has continuously supported and helped me in my work and in my scientific activities from the beginning. No less am I indebted to my thesis supervisor, Dr. Szabolcs Ábrahám, who introduced me to the mysteries of scientific work, helped me a lot in writing articles and thesis, and always motivated and supported me when I needed it.

I would like to thank all the employees of the Department of Surgery who helped my work in one way or another.

Thanks to my co-authors for their work, which allowed us to publish in high quality journals, Professor András Petri, Dr. Attila Paszt, Dr. Zsolt Simonka, Dr. Aurél Ottlakán, Dr. László Andrási, Dr. János Tajti jr., Dr. Dániel Váczi, Dr. Emil Terhes, Dr. András Négyessy, Dr. László Libor, Dr. József Pieler, Dr. Gabriella Kovács, Dr. Zita Morvay, Dr. András Nagy, Professor Zoltán Szepes, Dr. Dóra Illés, Dr. Emese Ivány, Dr. Máté Tajti, Zain Karamya, Bálint Czakó! Special thanks to Professor László Czakó, who helped me a lot in writing and successfully publishing the COVID-related article!

Thanks to Dr. Ria Benkő and Dr. Mária Matuz, pharmacist colleagues, for their great help in setting up the basis of the articles and statistical analysis of the data!

Thanks to Dr. Tamás Csarnai for his help in translating the articles and proofreading the articles and the thesis!

Thanks to Ágnes Kovács, librarian of the Department of Surgery, for her help in editing and uploading the articles!

And last but not least, thanks to my family for their encouragement, endless patience, understanding and support, which helped me overcome the deadlocks and get to this point!

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XI. ANNEX

Co-author certification

I, myself as a corresponding author of the following publication declare that the authors have no conflict of interest, and Illés Tóth Ph.D. candidate had significant contribution to the jointly published research. The results discussed in is thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

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10.01.2025. Szabolcs Ábrahám MD, PhD, med.habil.

The publication(s) relevant to the applicant's thesis:

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.