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Unraveling factors associated with textbook outcome after cholecystectomy in patients with uncomplicated cholecystolithiasis: A posthoc analysis of individual data of 1,124 patients

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ABSTRACT

Background: A textbook outcome for the management of uncomplicated cholecystolithiasis is the targeted clinical scenario and is characterized by no recurrent biliary colic, absence of surgical and biliary complications, and absence or relief of abdominal pain. The aim of this study was to assess the incidence of textbook outcomes after cholecystectomy and identify associated baseline factors.

Methods: Patients from 2 Dutch multicenter prospective trials between 2014 and 2019 (SECURE and SUCCESS trial) were included. The primary outcome was the proportion of patients with textbook outcomes after cholecystectomy at 6-month follow-up. Regression analysis was used to identify which factors before surgery were associated with textbook outcomes.

Results: A total of 1,124 patients underwent cholecystectomy. A textbook outcome at 6-month follow-up was reached in 67.9% of patients. Persistent abdominal pain was the main reason for the failure to achieve textbook outcome. Patients who did achieve textbook outcomes more often reported severe pain attacks (89.4% vs 81.7%, $P < .001$) and/or biliary colic (78.6% vs 68.4%, $P < .001$) at baseline compared with patients without textbook outcomes. The presence of biliary colic at baseline (odds ratio = 1.56, 95% confidence interval: 1.16–2.09, $P = .003$) and nausea/vomiting at baseline (odds ratio = 1.33, 95% confidence interval: 1.01–1.74, $P = .039$) were associated with textbook outcome. The use of non-opioid analgesics (odds ratio = 0.76, 95% confidence interval: 0.58–0.99, $P = .043$) and pain frequency ≥1/month (odds ratio = 0.56, 95% confidence interval: 0.43–0.73, $P < .001$) were negatively associated with textbook outcome.

Conclusion: Textbook outcome is achieved in two-thirds of patients who undergo cholecystectomy for uncomplicated cholecystolithiasis. Intensity and frequency of pain, presence of biliary colic, and nausea/vomiting at baseline are independently associated with achieving textbook outcomes. A more stringent selection of patients may optimize the textbook outcome rate in patients with uncomplicated cholecystolithiasis.

Introduction

Laparoscopic cholecystectomy (LC) is the recommended treatment for patients with either symptomatic or complicated cholecystolithiasis (ie, choledocholithiasis, cholecystitis, biliary pancreatitis).[1,2] As such, LC is the most performed abdominal

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surgical procedure worldwide, accounting for over 700.000 operations in the USA each year.[3] Despite increasing awareness among surgeons that not all patients with abdominal pain and the presence of gallstones will benefit from LC and improved patient selection, still one-third of patients who underwent LC because of gallstones and abdominal pain report persistent pain.[4] Different randomized and nonrandomized trials investigated the optimal selection for cholecystectomy in patients with uncomplicated cholecystolithiasis.[4,5]

First, several groups reported the uncertain outcome of LC.[4,6,7] Second, a prospective analysis of 401 patients with gallstones found that 35% of patients also fulfilled the criteria for a functional gastrointestinal disorder (FGID), which hamper the outcomes after surgery. These poor outcomes were the rationale for developing a model to predict pain relief after LC.[5,8] The model included age, history of abdominal surgery, VAS pain score, positive response to simple analgesics, nausea during pain attacks, and absence of heartburn. The factors highlight the importance of assessing patient characteristics, including FGID-related symptoms, preoperatively before deciding on LC in patients with abdominal pain and gallstones. Recently, a textbook outcome (TO) for the treatment of patients with uncomplicated cholecystolithiasis was defined in a mixed-methods study involving clinical experts from 81 countries and Dutch patients with a history of cholecystolithiasis.[9,10] A TO is a composite outcome and includes all decisive parameters that define an ideal result instead of using single indicators, such as incidence of surgical complications or reintervention rates.[11,12] TO was defined as no recurrent biliary colic with hospitalization, absence of biliary and surgical complications, and absence or reduction of upper abdominal pain (UAP) after treatment. [9,10]

To make an informed decision for surgical treatment of uncomplicated cholecystolithiasis, it is valuable to acquire insights into factors associated with TO after cholecystectomy. In contrast with the previous randomized and nonrandomized trials, in which the focus was on persistent pain after surgery, this study is focused on the more comprehensive TO. The aim of this posthoc study is to identify baseline factors associated with achieving TO six months after cholecystectomy in patients with uncomplicated cholecystolithiasis.

Materials and Methods

Data source and study population

For this post-hoc analysis, data were obtained from a Dutch randomized controlled trial (SECURE trial, METC 2013-129/NTR4022) and a Dutch prospective cohort (SUCCESS trial, METC 2017-3306/NTR7069).[4,5] Both studies were approved by the medical ethical committees from the participating hospitals. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). SUCCESS-trial was approved by the Medical Ethics Commission of the Radboud University Medical Center (METC 2017−3306). The SECURE trial was approved by the Medical Ethics Commission of the Amsterdam University Medical Center (METC 2013−129). Informed consent was taken from all individual participants. In both trials, eligible patients aged between 18 to 95 years with suspected symptomatic uncomplicated cholecystolithiasis were referred to a surgical outpatient clinic to discuss cholecystectomy. The current study included only consecutive patients who were treated by LC (Figure 1).

In both trials, patients filled out questionnaires at baseline and at 6-month follow-up. The questionnaires assessed gastrointestinal symptoms (biliary colic in accordance with ROME III criteria and other abdominal symptoms including heartburn, difficulty defecating, bloating, nausea/vomitus, and diarrhea), intensity of pain based on a Visual Analog Scale (VAS) score (0 = no pain and 10 = the worst imaginable pain), pain frequency, and use of pain medication. The SECURE trial followed the Consolidation Standard of Reporting Trials, and the SUCCESS trial followed the Strengthening of the Reporting of Observational Studies in Epidemiology.[13,14]

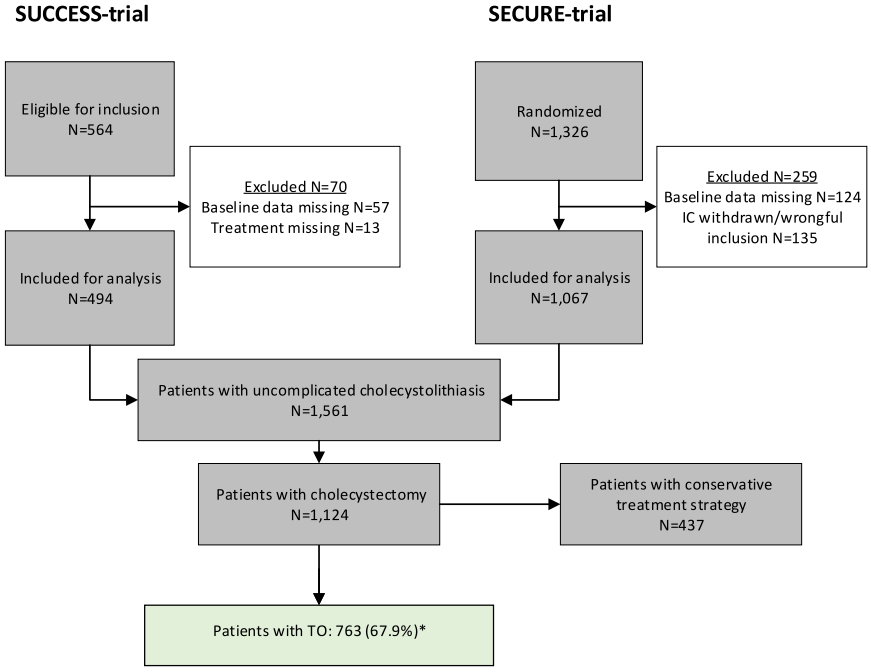

Figure. Flowchart of included patients. *For the textbook outcome, the following criteria were selected: no recurrent biliary colic with hospitalization, absence of biliary complications, absence of surgical complications, and free or relief of upper abdominal pain at 6 months of follow-up. Textbook outcomes were achieved in 763 of 1,124 patients (67.9%) after cholecystectomy as a treatment strategy. Out of 1,561 patients, 437 patients (28%) received a conservative treatment strategy. *TO,* textbook outcome.

Outcomes

The primary outcome of this study was the proportion of patients that reached TO after LC at 6-month follow-up. Secondary endpoints were differences between characteristics of patients with and without TO.[9] The following patient characteristics were assessed at baseline before surgery and were analyzed to determine their association with TO: demographics (sex, age, body mass index [BMI]), pain characteristics (frequency of pain, use of simple anesthetics, intensity of pain [VAS] score), and abdominal symptoms (nausea/vomiting, heartburn, abdominal bloating, diarrhea, difficult defecation). A logistic regression analysis was performed to identify associated factors to reach TO after LC.

Data collection

Information on demographic characteristics was collected from the baseline survey. Clinical outcome data from all included patients were obtained after 6 months of follow-up. Medical records were evaluated for information on cholecystectomy (yes/no), recurrent biliary colic with hospitalization, biliary complications, and surgical complications. The following biliary complications were recorded and included biliary pancreatitis, development of cholecystitis before cholecystectomy, choledocholithiasis, and cholangitis. The following surgical complications were recorded: wound infections, postoperative pain with a prolonged hospital stay, bile spillage or bleeding that led to drain placement and/or prolonged hospital stay, and bile duct injury. Bile duct injuries were recorded and classified according to Bergman et al.[15] The authors have completed the Strengthening of the Reporting of Observational Studies in Epidemiology reporting checklist. Original studies completed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guidelines.

Textbook outcome

TO for the treatment of uncomplicated symptomatic cholecystolithiasis was defined in an international mixed-method study.[9] TO was finally defined as no recurrent biliary colic with hospitalization, absence of biliary complications, absence of surgical complications, and absence or reduction of upper abdominal pain. Hospitalization was defined as a visit to the emergency department with admission due to unresponsiveness to analgesics. Pain-free was defined as a VAS $\leq$4 and reduction of pain as a reduction of $\geq$4 points on the VAS pain score.[9] Achieving a 4-point decrease on an 11-point VAS scale represents more than the minimum 30% pain relief required by regulatory bodies such as the US Food and Drug Administration or the European Medicines Agency for pain medications.[16]

Statistical analysis

We used TO after 6-month follow-up as a dichotomous outcome variable.[4,5] TO was achieved when patients met all selected criteria for TO at 6-month follow-up.[17] Baseline characteristics (age, BMI) and information from the survey (pain scores) were presented as mean (SD) or median (IQR) depending on the distribution. Dichotomous variables were summarized by frequencies and proportions (pain characteristics, fulfillment of the ROME-III criteria, and abdominal symptoms). Differences between patients with and without TO were analyzed using chi-squared tests, Fisher exact tests, independent *t* tests, or Mann–Whitney *U* tests, depending on the type of data.

Variables associated with achieving TO were assessed using univariable and multivariable logistic regression analysis. TO state served as the dependent binary variable in this analysis. In order to ensure sufficient power, a minimum of 10 outcome events per selected predictor variable was applied as a rule of thumb.[18] Continuous variables were tested for linear assumption by adding quadric and tertiary terms. Collinearity of the individual variables was tested and no correlation between individual variables was found. A multivariable logistic regression with Wald backward elimination was performed to explore which factors were associated with TO. Odds ratios (OR) and their 95% CIs were reported. Data analysis was performed using SPSS, version 27 (IBM SPSS, Inc, Armonk, NY).

Results

Patients and characteristics

Patients were included between 2014 and 2017 in the SECURE trial (N = 1,067) and between October 2017 and June 2019 in the SUCCESS trial (N = 494). A total of 1,124 patients underwent LC (N = 729 in the SECURE trial; N = 395 in the SUCCESS trial) and were included for analysis (Figure 1).

Table I shows an overview of patient characteristics. A total of 75% (848/1,124) of the patients are female, with a mean age of 48.0 years (SD 20) at the study baseline and a median BMI of 27.7 kg/m^2 (IQR 24.7–31.6). Biliary colic was reported in 75.4% of patients (n = 847 out of 1,124). Median VAS pain score at baseline was 8.0 (IQR 6.5–9.0).

Textbook outcome after cholecystectomy

At 6-month follow-up, TO was achieved by 763 of 1,124 patients (67.9%). As shown in Table II, the main reason for not achieving TO (32.1%, n = 361) was persistent upper abdominal pain (15.4%, n = 173). Other reasons for failing TO included surgical complications (13.7%, n = 154), of whom 12 patients were treated for bile duct injury, with 4 patients with a major bile duct injury (0.4%). Other surgical complications were wound infections (n = 54), bile spillage during surgery (n = 36), prolonged admission due to pain or malaise (n = 17), or bleeding (n = 10). Biliary complications (ie, development of cholecystitis before cholecystectomy, biliary pancreatitis) were reported in 4.9% of patients (n = 55/361). Recurrent biliary colic with hospitalization occurred in 3.7% of patients (n = 42/361).

Differences at baseline between patients with and without TO

Individual baseline characteristics of patients with and without TO were compared (Table I). Sex and BMI were evenly distributed within groups. Patients who achieved TO reported more frequent severe pain attacks at baseline (89.4% vs 81.7%, P < .001). Patients who achieved TO reported more often the presence of a biliary colic at baseline (78.6% vs 68.4%, P < .001). The VAS pain score was statistically significantly different (8.0 IQR 6.6–9.0 vs 8.0 IQR 6.4–9.0, P = .044), although the median and IQR were comparable. Patients without TO were more likely to use non-opioid analgesics (56.4% vs. 62.6%, P = .047) and reported more frequent episodes of pain (>1x/month) (37.1% vs. 52.0%, P < .001).

Factors associated with TO

The following variables were included in the regression analyses to assess independent predictive factors: age, sex, BMI, history of abdominal surgery, biliary colic, use of simple anesthetics, pain radiating to the back, urge to move during pain attack,

Table I
Baseline characteristics and a comparison of patients with and without TO after cholecystectomy

	Total $N = 1,124$	Patients with TO $N = 763$ (67.9%)	Patients without TO $N = 361$ (32.1%)	*P* value
Baseline characteristics				
Age, mean (SD)	48.0 (20)	48.0 (20)	48.0 (14)	.884[†]
Sex, Female *n* (%)	848 (75.4)	576 (75.5)	272 (75.3)	.958[†]
BMI, median (IQR)	27.7 (24.7–31.6)	27.5 (24.7–31.2)	28.3 (24.8–32.1)	.125[†]
Abdominal surgery in history, *n* (%)	426 (37.9)	278 (36.4)	148 (41.0)	.141[†]
Baseline–Abdominal pain				
VAS pain score, median (IQR)	8.0 (6.5–9.0)	8.0 (6.6–9.0)	8.0 (6.4–9.0)	.044[†]
Pain frequency >1/mo, *n* (%)	444 (42.0)	264 (37.1)	180 (52.0)	.001[†]
Baseline–Biliary symptoms				
Severe pain in attacks (%)[*]	977 (86.9)	682 (89.4)	295 (81.7)	.001[†]
Located in right upper quadrant or epigastric region (%)[*]	1,059 (94.2)	721 (94.5)	338 (93.6)	.561[†]
Duration of pain longer than 15–30 min (%)[*]	1,002 (89.1)	695 (91.1)	307 (85.0)	.002[†]
Biliary colic by ROME III-criteria[†], *n* (%)	847 (75.4)	600 (78.6)	247 (68.4)	.001[†]
Pain radiating to the back, *n* (%)	852 (75.8)	572 (75.0)	280 (77.6)	.343[†]
Use of non-opioid analgesics, *n* (%)	656 (58.4)	430 (56.4)	226 (62.6)	.047[†]
Urge to move during pain attack, *n* (%)	871 (77.6)	602 (79.0)	269 (74.5)	.092[†]
Baseline–Functional symptoms				
Nausea/vomiting, *n* (%)	630 (56.0)	445 (58.3)	185 (51.2)	.026[†]
Heartburn, *n* (%)	276 (24.6)	182 (23.9)	94 (26.0)	.427[†]
Abdominal bloating, *n* (%)	510 (45.4)	348 (45.6)	162 (44.9)	.379[†]
Diarrhea, *n* (%)	184 (16.4)	130 (17.0)	54 (15.0)	.817[†]
Difficult defecation, *n* (%)	200 (17.8)	129 (16.9)	71 (19.7)	.258[†]

BMI, body mass index; *TO,* textbook outcome; *VAS,* visual analog scale.
[*] ROME criteria.
[†] Fulfilment for biliary colic by Rome III criteria.

frequency of pain more than once a month, nausea and/or vomiting, heartburn, abdominal bloating, diarrhea, and difficult defecation.

Independent predictive factors for achieving TO after cholecystectomy were investigated (Table III). Multivariable analysis showed that the presence of biliary colic (OR 1.56, 95% CI 1.16–2.10, $P = .003$) and nausea and/or vomiting (OR 1.33, 95% CI 1.1–1.74, $P = .039$) was independently associated with achieving TO. Use of nonopioid analgesics (OR 0.76, 95% CI 0.57–0.99, $P = .043$) and frequency of pain more than once a month (OR 0.56, 95% CI 0.53–0.73, $P < .001$) were negatively associated with achieving TO.

Discussion

The present study assessed TO as a posthoc analysis in patients in 2 multicenter Dutch trials. TO is achieved in two-thirds of patients who underwent LC for uncomplicated symptomatic cholecystolithiasis. Considering the large number of cholecystectomies performed annually, this outcome highlights the need for improvement in patient selection. Selection should focus on the prevention of persistent pain, as this is the main factor contributing to a low TO rate. This posthoc analysis in patients included in 2 multicenter Dutch trials shows that the presence of biliary colics and nausea/vomiting as complaints at baseline are independent predictors for achieving TO after LC. In contrast, the use of nonopioid analgesics and pain frequency >1 event/month are independently associated with precluding TO.

LC is not a one-size-fits-all procedure, and well-defined selection criteria are crucial for optimal patient-reported outcomes. In the majority of patients, typical biliary colic is effectively resolved after surgery.[5] The current study shows nausea and/or vomiting are associated with reaching TO after cholecystectomy, which is often reported as a part of biliary colic.[19] One-third of patients with uncomplicated cholecystolithiasis report persistent UAP after cholecystectomy.[4] The literature suggests that several gastrointestinal symptoms deriving from disease etiologies other than gallstones are responsible for the development of persisting UAP. FGID has a prevalence of 20% to 30% among patients with uncomplicated cholecystolithiasis. [20,21] Symptomatic cholecystolithiasis and FGID may be very similar in presentation and pain characteristics.[3,22] These similarities complicate diagnosing the condition responsible for a patient's complaints and, as a result, possibly lead to abdominal pain being improperly attributed to gallstones and may influence the choice for cholecystectomy.

The clinical workup for patients with abdominal pain and suspected gallstones generally starts with an abdominal ultrasound (US). In many care systems, a US is requested by the general practitioner, and if gallstones are present, the patient is subsequently referred to the surgical outpatient clinic. Although ultrasound is non-invasive and relatively inexpensive, a recent study reported a diagnostic yield of 36% for the detection of gallstones by a US in patients with abdominal pain and clinical suspicion of gallstones, according to the general practitioner.[23] To aid general practitioners in selecting patients for abdominal US, a model to predict the presence of gallstones was developed.[23] Predictors for the presence of gallstones were increased pain, frequency of pain less than weekly, the presence of biliary colic, and the absence of heartburn. Subsequently, selection for surgery during shared decision-making at the surgical outpatient clinic requires another tool to aid patients and surgeons. Therefore, another online decision tool was recently developed to predict the probability that a patient will have significant pain reduction after cholecystectomy.[5] This model considers patient characteristics, pain scores, surgical history, and absence of heartburn. It is relevant to emphasize that both the decision tools for the general practitioner and the surgeon include patient characteristics, pain, and the presence of FGID.

Adequate treatment for patients with nontypical biliary symptoms is challenging. A recent study showed worse outcomes of surgery in 401 patients with abdominal pain and gallstones if a FGID was present.[8] Treatment for FGID is not as straightforward as cholecystectomy and includes physical and psychological factors. However, there is a lack of understanding of the role of conservative

Table II
Patient outcomes in terms of the Textbook Outcome criteria

	Total ($N = 1,124$)
Selected criteria*	
No recurrent biliary colic with hospitalization,† *n* (%)	1,082 (96.3)
Absence of biliary complications after 6 mo, *n* (%)	1,069 (95.1)
Biliary complication, *n* (%)	55 (4.9)
Development of cholecystitis before cholecystectomy, *n* (%)	19 (1.7)
Choledocholithiasis, *n* (%)	30 (2.7)
Cholangitis, *n* (%)	0
Biliary pancreatitis, n (%)	6 (0.5)
Absence of surgical complication after treatment,‡ n (%)	970/1124 (86.3)
Surgical complications, *n* (%)	154 (13.7)
Postoperative pain with prolonged hospital stay, *n* (%)	17 (11.5)
Wound infections, *n* (%)	54 (35.1)
Bile spillage with drain placement and/or prolonged hospital stay, *n* (%)	36 (23.4)
Bleeding during surgery, *n* (%)	10 (6.5)
Bile duct injury§	
Minor injury, *n* (%)	8 (0.5)
Major injury, *n* (%)	4 (0.3)
Pain-free or relief of abdominal pain after 6 mo follow-up‖, *n* (%)	951 (84.6)
Composite Textbook Outcome rate, *n* (%)	763 (67.9)

TO, textbook outcome; *VAS,* visual analog scale.

* For the TO, the following criteria were selected: no recurrent of biliary colic with hospitalization; absence of biliary complications; and absence of surgical complications; and free or relief of Upper Abdominal Pain at 6 months of follow-up. TO was achieved in 763 of 1,124 patients (67.9%).

† Hospitalization was reported as visit of the emergency department or clinical admission for simple anesthetics.

‡ Surgical complications (included wound infection, bile spillage, bile duct injury, hematoma, pain postoperative or malaise during same admission, hernia cicatricalis hospital bacterial infection, gastrointestinal perforations) and cardiovascular complications (pneumonia, pulmonary embolism, cardial complications) and were classified in accordance of the CDC classification (Dindo et al).[26]

§ Bile duct injury is classified in minor or major injury.[16]

‖ Pain-free was defined as VAS ≤4. Pain relief was defined as reduction VAS pain score ≥4 points.[5]

treatment, which typically consists of a multifactorial approach, including informing and educating patients on the relief of symptoms. The recent TRIODe trial (NCT03205319) in patients with unaffirmed dyspepsia showed that a personalized education tool is effective in reassuring patients about symptoms and reducing the number of gastroscopies by 40%.[24] A personalized self-help guide for patients with UAP with an absence of typical symptoms of gallstone disease may help patients make better-informed decisions and improve patient-reported outcomes. A randomized controlled trial (NCT06002516) is currently underway for patients with UAP due to functional dyspepsia, irritable bowel syndrome, and gallstone disease. The intervention arm will consist of a self-help guide combined with a lifestyle clinic visit. The hypothesis tested in this trial is that providing education on symptoms and lifestyle assessment to patients may lead to a reduction in unnecessary treatment and diagnostics interventions (ie, cholecystectomy, gastroscopy, colonoscopy) while also improving patient-reported outcomes in terms of abdominal symptoms and satisfaction. TO will be an important outcome parameter in both arms of this trial.

We acknowledge that this study comes with some limitations. First, the definition of TO was determined after both trials were conducted, and with the posthoc design of the present study this may introduce bias. Secondly, defining a successful outcome after surgery for the treatment of uncomplicated cholecystolithiasis remains a subject of ongoing debate. In our questionnaires, we evaluate the presence of abdominal pain by use of the VAS; however, the type of persisting pain and the impact on the patient's overall quality of life were not evaluated.[25] Third, participants were enrolled in 2 prospective trials, which may introduce a risk of bias. However, both studies applied identical inclusion criteria, and hospitals included patients in both cohorts but at different time intervals.

In conclusion, the consensus-based TO may be a future tool to assess quality outcomes for the treatment of patients with symptomatic uncomplicated cholecystolithiasis. The present study illustrates a relatively low success rate in achieving TO, endorsing a more optimized selection for cholecystectomy. TO after cholecystectomy is associated with biliary colic and nausea/vomiting at baseline, but surgery should be reconsidered in patients with more frequent pain and the use of nonopioid analgesics that could be related to cholecystolithiasis. The low incidence of biliary complications displays the possibility of treating patients with atypical symptoms conservatively and postponing surgery.

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Table III
Univariable and multivariable analysis of the associated factors achieving TO after cholecystectomy

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Regression coefficient
Baseline characteristics					
Age	0.999–1.009	.906	0.994–1.014	.460	1.004
Sex (female)	0.754–1.348	.958	0.816–1.545	.477	1.123
BMI	0.959–1.007	.156	0.959–1.010	.227	0.984
History of abdominal surgery	0.638–1.066	.141	0.666–1.144	.326	0.873
Abdominal pain					
VAS Pain score	0.970–1.082	.392	0.932–1.054	.757	0.990
Biliary colic by ROME III-criteria*	1.282–2.251	< .001	1.158–2.096	.003	1.558
Use of non-opioid analgesics	0.597–0.997	.047	0.574–0.992	.043	0.755
Pain radiating to the back	0.644–1.165	.343	0.703–1.374	.869	0.973
Urge to move during pain attack	0.959–1.727	.093	0.818–1.539	.476	1.122
Pain frequency >1/mo	0.419–0.705	< .001	0.427–0.731	< .001	0.559
Functional symptoms					
Nausea and/or vomiting	1.035–1.712	.026	1.014–1.735	.039	1.326
Heartburn	0.676–1.187	.427	0.676–1.286	.676	0.934
Abdominal bloating	0.801–1.325	.817	0.800–1.437	.639	1.073
Diarrhea	0.827–1.649	.379	0.892–1.874	.174	1.293
Difficult defecation	0.603–1.146	.259	0.609–1.218	.399	0.862

BMI, body mass index; *OR,* odds ratio; *TO,* textbook outcome.

* All 3 ROME criteria included: severe pain in attacks, located in right upper quadrant or epigastric region and duration of pain longer than 15 to 30 minutes.

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