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A Clinical Decision Tool for Selection of Patients With Symptomatic Cholelithiasis for Cholecystectomy Based on Reduction of Pain and a Pain-Free State Following Surgery

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IMPORTANCE There is currently no consensus on the indication for cholecystectomy in patients with uncomplicated gallstone disease.

OBJECTIVE To report on the development and validation of a multivariable prediction model to better select patients for surgery.

DESIGN, SETTING, AND PARTICIPANTS This study evaluates data from 2 multicenter prospective trials (the previously published Scrutinizing (In)efficient Use of Cholecystectomy: A Randomized Trial Concerning Variation in Practice [SECURE] and the Standardized Work-up for Symptomatic Cholecystolithiasis [Success] trial) collected from the outpatient clinics of 25 Dutch hospitals between April 2014 and June 2019 and including 1561 patients with symptomatic uncomplicated cholelithiasis, defined as gallstone disease without signs of complicated cholelithiasis (ie, biliary pancreatitis, cholangitis, common bile duct stones or cholecystitis). Data were analyzed from January 2020 to June 2020.

EXPOSURES Patient characteristics, comorbidity, surgical outcomes, pain, and symptoms measured at baseline and at 6 months' follow-up.

MAIN OUTCOMES AND MEASURES A multivariable regression model to predict a pain-free state or a clinically relevant reduction in pain after surgery. Model performance was evaluated using calibration and discrimination.

RESULTS A total of 1561 patients were included (494 patients in 7 hospitals in the development cohort and 1067 patients in 24 hospitals in the validation cohort; 6 hospitals included patients in both cohorts). In the development cohort, 395 patients (80.0%) underwent cholecystectomy. After surgery, 225 patients (57.0%) reported that they were pain free and 295 (74.7%) reported a clinically relevant reduction in pain. A multivariable prediction model showed that increased age, no history of abdominal surgery, increased visual analog scale pain score at baseline, pain radiation to the back, pain reduction with simple analgesics, nausea, and no heartburn were independent predictors of clinically relevant pain reduction after cholecystectomy. After internal validation, good discrimination was found (C statistic, 0.80; 95% CI, 0.74-0.84) between patients with and without clinically relevant pain reduction. The model had very good overall calibration and minimal underestimation of the probability. External validation indicated a good discrimination between patients with and without clinically relevant pain reduction (C statistic, 0.74; 95% CI, 0.70-0.78) and fair calibration with some overestimation of probability by the model.

CONCLUSIONS AND RELEVANCE The model validated in this study may help predict the probability of pain reduction after cholecystectomy and thus aid surgeons in deciding whether patients with uncomplicated cholelithiasis will benefit from cholecystectomy.

Invited Commentary

Supplemental content

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In Western society, the lifetime prevalence of gallstone disease is 10% to 20%, and this constitutes an important and growing health problem in an increasingly obese population.[1,2] Only 5% of patients develop gallstone-associated complications, such as cholecystitis, cholangitis, or biliary pancreatitis, while the remaining 95% remain free of biliary complications.[3] Cholecystectomy, the most commonly performed gastrointestinal surgical procedure worldwide, is indicated for complicated gallstone disease, while consensus among surgeons and gastroenterologists for the selection for cholecystectomy in uncomplicated gallstone disease is absent.[4,5] Consequently, cholecystectomy rates vary widely between practices, regions, and countries.[1,6]

Typically, symptomatic cholelithiasis (uncomplicated gallstone disease) presents with biliary colic, that is, acute severe pain attacks located in the right upper quadrant or epigastrium and lasting 15 to 30 minutes or longer.[7,8] The selection for laparoscopic cholecystectomy is generally based on application of these Rome III criteria. In the Scrutinizing (In) efficient Use of Cholecystectomy: A Randomized Trial Concerning Variation in Practice (SECURE) (NL3862)[9] including 1067 patients, we found that approximately 40% of patients experienced persistent abdominal pain regardless of a restrictive or regular policy for the indication for cholecystectomy. This trial showed that the Rome III criteria have a limited validity in the selection of patients for cholecystectomy. Additional selection criteria, including pain radiating to the back or positive pain response to simple analgesics, did not improve the percentage of patients with adequate outcome.[9]

A prediction model based on easily available patient characteristics and symptoms at presentation would be of considerable value for clinical decision-making. This study aimed to develop and validate a prediction model to select patients with uncomplicated symptomatic cholelithiasis for cholecystectomy in terms of a pain-free state and clinically relevant pain reduction. Two clinical trials were used, a previously published randomized clinical trial (SECURE trial[9]) and a nonrandomized clinical trial designed to validate the SECURE trial (the Standardized Work-up for Symptomatic Cholecystolithiasis [Success] trial [NL7069]).

Key Points

Question According to which criteria should patients with gallstones and abdominal pain be selected for cholecystectomy?

Findings In this analysis of 2 multicenter trials including 1561 patients, the development and validation of a multivariable prediction model showed that older patients and those with no history of abdominal surgery, an increased baseline visual analog scale pain score, pain radiation to the back, pain reduction with simple analgesics, nausea, or no heartburn had a higher chance for a clinically relevant pain reduction after cholecystectomy.

Meaning This internally and externally validated model may help surgeons decide whether patients with uncomplicated gallstone disease will benefit from cholecystectomy.

Methods

Patients and Data Sources

Patients were included from the outpatient clinics of 24 Dutch hospitals between February 2014 and April 2017 in the SECURE trial[9] and 7 Dutch hospitals between October 2017 and June 2019 in the Success trial. Six hospitals included patients in both cohorts at different times. Data were analyzed from January 2020 to June 2020. The Success trial was approved by the Medical Ethics Commission of the Radboud University Medical Center (METC 2017-3306). The SECURE trial[9] was approved by the Medical Ethics Commission of the Amsterdam University Medical Center (METC 2013-129). Both studies were also approved by the local ethical committees of the participating hospitals. All included patients provided written informed consent prior to participation. The authors had access to the study data and reviewed and approved the final manuscript. Research was performed in accordance with the ethical standards of the updated Helsinki Declaration of 2013. We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline.

In both studies, patients aged from 18 to 95 years were eligible for inclusion. All patients had ultrasonically confirmed gallstones or sludge, reported abdominal pain, and were referred to a surgical outpatient clinic. Exclusion criteria were identical in both studies: (1) history of complicated cholelithiasis (ie, biliary pancreatitis, cholangitis, common bile duct stones, or cholecystitis), (2) indication for primary open cholecystectomy, (3) history of current malignancy, (4) expected life span of less than 12 months, (5) American Society of Anesthesiologists physical status classification of III or IV, (6) known liver cirrhosis, (7) cognitive disorders that predispose unreliable questionnaire responses, (8) insufficient knowledge of the Dutch language, and (9) current pregnancy.[9,10]

In both studies, included patients received a study questionnaire after the first outpatient clinic visit (baseline) and at 3 and 6 months' follow-up. In both studies, the questionnaire focused on quality of life (EuroQol-5 Dimension-3 Level questionnaire), gastrointestinal symptoms (Gastrointestinal Quality of Life Index, Gallstone Symptom List, and Rome III criteria) and pain (integrated pain score, including visual analog scale [VAS] score). Details on the content of the questionnaires are described in the study protocol of the SECURE trial.[9,10]

From all patients, data were obtained from the medical records on health care consumption, gallstone-associated complications, treatment details, and surgical complications. The following complications were recorded: biliary pancreatitis, cholangitis, choledocholithiasis (gallstone in common hepatic duct), and cholecystitis. Postoperative surgical complications were classified according to the Clavien-Dindo classification system. A Clavien-Dindo score of 3 or higher was defined as a major complication.[11]

Development Cohort

Development data were obtained from the Success trial. Initially, the Success trial was set up as a validation cohort for the

Rome III–based triage tool for cholecystectomy as studied in the SECURE trial.[9] The sample size of the Success trial was similar to 1 arm of the SECURE trial[9]: 519 patients included for evaluation. However, the SECURE trial[9] found the triage tool to be of limited clinical value. Therefore, we decided to develop a new prediction model instead of validating the triage tool of the SECURE trial.[9] The Success trial data were used to improve and develop criteria to better select patients likely to benefit from cholecystectomy. The Success trial was a nonrandomized prospective study including patients in 7 Dutch hospitals between October 2017 and June 2019. During first consultation, the treating physician evaluated whether patients fulfilled the following 5 prespecified criteria for symptomatic cholelithiasis: (1) pain in attacks, (2) lasting 15 to 30 minutes or longer, (3) located in epigastrium or right upper quadrant, (4) pain radiating to the back, and (5) positive pain response to simple analgesics. Surgeons and patients were advised to select surgery only if at least 3 of the 5 prespecified criteria were present.

Validation Cohort

External validation data were obtained from the SECURE trial.[9] The trial protocol (Supplements 1, 2, and 3),[12] the statistical analysis plan,[13] and the primary results[14] of the SECURE trial have been published. The sample size for the SECURE trial[9] is explained in the trial protocol and in the statistical analysis plan, and included a total of 1038 patients for evaluation.[12,13]

Outcomes for Prediction Modeling

Prediction models were developed for 2 distinct outcomes of cholecystectomy: being pain free and experiencing a clinically relevant reduction in pain at 6 months' follow-up. A pain-free state was defined as an Izbicki pain score of 10 or lower and a VAS pain score of 4 or less, according to the definition used in the SECURE trial.[9] Clinically relevant pain reduction was defined as a reduction of at least 4 points on the VAS pain score after 6 months (baseline VAS pain score minus 6-month VAS pain score, or ΔVAS). The absolute 4-point relief on an 11-point VAS score is more than the minimum of 30% pain relief required by the US Food and Drug Administration[14] or the European Medicines Agency for pain medication.

Predictors

For the development of a new prediction model, preoperatively available variables were assessed based on expert opinion and previous literature. The predictors were based on data assessed from patient surveys and clinical data in the hospital medical files. Two abstractors (S.Z.W., SECURE trial,[9] and C.S.S.L., SECURE trial[9] and Success trial), collected the data according to a standardized predefined case-record form. Abstractors were not blinded to the study objectives. The presence of predictors and the outcome (pain-free state and pain reduction) were based on patient questionnaires and were not influenced by the abstractors of the data.

The following predictors were included: patient characteristics (age [continuous], sex [dichotomous], body mass index [calculated as weight in kilograms divided by height in meters squared; categorical, including less than 25, 25 to 30, and greater than 30], history of abdominal surgery [dichotomous], VAS pain score at baseline [continuous; 11-point scale]); biliary symptoms (pain in attacks, lasting 15 to 30 minutes or longer, location in epigastrium or right upper quadrant, pain radiating to the back, use of analgesics, positive pain response to analgesics, frequency of pain attacks, urge to move during pain attacks, and nausea during pain attacks [all dichotomous]); and functional gastrointestinal symptoms (difficult defecation, diarrhea, heartburn, and abdominal bloating [all dichotomous]). Collinearity was considered and did not appear to be an issue. Because of sample size restrictions, no interaction terms were considered.

Statistical Analysis

Missing Data and Imputation

The following patients were excluded from analysis. In the development cohort, included patients with missing pain scores at baseline or missing data regarding treatment were excluded from analyses. In the validation cohort, randomized patients with missing pain scores at baseline, or who withdrew their informed consent or were wrongfully included were excluded from analyses. Hence, missing data of baseline characteristics were not imputed. Missing data concerning the pain scores (Izbicki pain score, VAS pain score) at 6 months' follow-up were imputed. We performed a multiple imputation strategy using predictive mean matching, similar to the imputation strategies of the SECURE trial.[9,13] Analyses were performed using SPSS statistics version 25.0 (IBM) and R version 3.6.3 with package rms (the R Foundation).

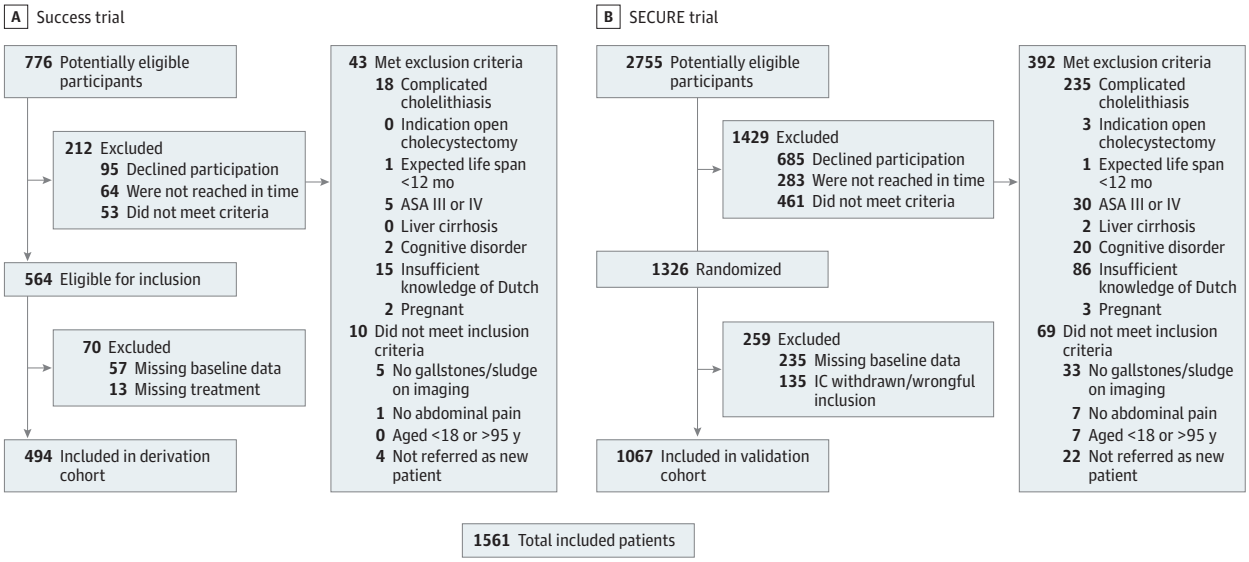
Model Development

Logistic regression analyses were performed with outcomes pain-free and clinically relevant pain reduction, using the prespecified predictors. Multivariable logistic regression with a backward selection procedure was used to achieve the most informative and parsimonious combination of predictors. The Wald χ^2 test of individual factors was used. Tests were 2-tailed, and $P < .05$ was considered significant. The threshold for variable selection was .157. The number of predictors for the sample size was in accordance with the minimum 10 events per parameter estimated rule of thumb and sample size requirements for prediction models reported elsewhere.[15,16]

Prediction Model Performance

The performance of the model was assessed by discrimination ability to differentiate between patients with and without a pain-free state or clinically relevant pain reduction after cholecystectomy and by calibration, which measures the agreement between observed and predicted risk. Discrimination was quantified by the C statistic. Values of C statistic close to 1.0 indicated good discriminative ability, while values close to 0.5 indicated poor discriminative ability (less than 0.6 was defined as poor, 0.6 to 0.7 as fair, 0.7 to 0.8 as good, 0.8 to 0.9 as very good, and 0.9 or greater as excellent). Calibration was assessed by calibration-in-the-large and slope statistic. Calibration-in-the-large lower or higher

Figure 1. Flowchart of Development and Validation Cohorts



Inclusion criteria for both trials: patients aged 18 to 95 years referred to a surgical outpatient clinic with abdominal pain and ultrasonically confirmed gallstones. ASA indicates American Society of Anesthesiologists; IC, informed consent.

than 0 indicates that prediction is systematically too high or low, respectively. A slope of 1.0 indicates perfect overall calibration (1.0 to 1.10 was defined as very good, 1.10 to 1.20 as good; 1.20 to 1.30 as fair, greater than 1.30 as poor, 0.9 to 1.0 as very good, 0.8 to 0.9 as good, 0.7 to 0.8 as fair, and less than 0.7 as poor); slopes below 1.0 indicated overestimation of the probability of the outcome by the model, and slopes above 1.0 indicated underestimation.

Internal and External Validation

As prediction models produced with multivariable regression analyses are known for overfitting, the model was validated internally using bootstrapping techniques, for which 500 samples were drawn with replacement from the development cohort. After internal validation, the model performance was reevaluated. The prediction model was externally validated in the validation cohort and model performance was evaluated. Six hospitals in the validation cohort were similar to the hospitals in the development cohort; however, all patients were included in different time periods. If needed, predictions were recalibrated, and model performance was assessed again.

Nomogram and an Online Decision Tool

To make the present model clinically applicable a nomogram and online decision tool were created. Additionally, a nomogram was created based on the predictors of the model to easily calculate the probability of achieving clinically relevant pain reduction or a pain-free state after cholecystectomy. An applicable online calculator to estimate both outcomes after cholecystectomy was made and is available at https://gallbladderresearch.shinyapps.io/SUCCESS/.

Results

Patients

In 7 hospitals, 776 patients were approached for participation in the SUCCESS trial and 494 patients were included in the development cohort (**Figure 1**). Missing data for the Izbicki pain score and VAS were imputed in 66 patients (13.3%). The external validation cohort consisted of patients included in the SECURE trial[9] (2755 were approached and 1067 included from 24 hospitals). Missing data were imputed in 49 patients (4.6%). In total, 1561 patients were included for analyses in this study.

Baseline Characteristics

Baseline patient characteristics, pain scores, biliary symptoms, and functional symptoms of the development and validation cohorts are summarized in **Table 1**. Patients in the development cohort had a mean (SD) age of 51.6 (14.5) years, and 357 of 494 (72.3%) were female. At baseline, the median (interquartile range) Izbicki pain score was 35.8 (28.4-43.1) and the median (interquartile range) VAS pain score was 8.0 (6.5-9.5). Cholecystectomy was performed in 395 patients (80.0%) (**Table 2**).

Patient-Reported Outcomes After Surgery

In the development cohort, a pain-free state was reported in 225 of 395 patients (57.0%), and clinically relevant pain reduction was reported in 295 patients (74.7%). Resolution of biliary colic was reported in 356 patients (95.2%). Patient-reported outcomes of the validation cohort are summarized in Table 2. Gallstone and surgery-related complications are described in Table 2 and eResults 1 in Supplement 4.

Table 1. Baseline Characteristics of Patients Included in the Development and Validation Cohorts

Characteristic	No. (%)		
	Total (N = 1561)	Development cohort (n = 494)	Validation cohort (n = 1067)
Age, mean (SD), y	49.9 (14.2)	51.6 (14.5)	48.5 (13.9)
Female	1143 (73.2)	357 (72.3)	786 (73.7)
Male	419 (26.8)	137 (27.7)	281 (26.3)
BMI, median (IQR)[a]	27.5 (24.2-30.9)	27.8 (24.1-31.4)	27.5 (24.2-30.8)
Consumes alcohol	797 (51.5)	302 (61.1)	495 (46.4)
Currently smokes	295 (18.9)	86 (17.4)	209 (19.6)
History of abdominal surgery	590 (37.9)	189 (38.3)	401 (37.6)
Abdominal pain, median (IQR)			
Izbicki pain score[b]	35.3 (28.3-42.3)	35.8 (28.4-43.1)	35.0 (28.4-41.6)
VAS pain score[b]	8.0 (6.3-9.7)	8.0 (6.5-9.5)	7.6 (5.7-9.4)
Biliary symptoms			
Pain in attacks	1239 (79.4)	388 (78.5)	851 (79.8)
Pain located in right upper quadrant or epigastric region	1408 (90.2)	433 (87.7)	975 (91.4)
Duration of pain longer than 15-30 min	1324 (84.8)	441 (89.3)	883 (82.8)
All 3 Rome III criteria/biliary colic	1046 (67.0)	329 (66.6)	717 (67.2)
Pain radiating to the back	1072 (68.7)	348 (70.4)	724 (67.9)
Pain responds to simple analgesics	793 (50.8))	220 (44.5)	573 (53.7)
Use of pain medication	841 (53.9)	313 (63.4)	528 (49.5)
Pain attacks more than twice/mo[c]	1029 (66.0)	344 (70.1)	685 (64.2)
Urge to move during pain attack[c]	1081 (69.3)	347 (70.5)	734 (68.8)
Nausea during pain attack	828 (53.0)	193 (39.1)	635 (59.5)
Functional symptoms[d]			
Difficulty defecating	284 (18.2)	85 (17.2)	199 (18.7)
Diarrhea	257 (16.5)	68 (13.8)	189 (17.7)
Heartburn	410 (26.3)	78 (15.8)	332 (31.1)
Abdominal bloating	702 (45.0)	163 (33.0)	539 (50.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; VAS, visual analog scale.

[a] Assessed in 1560 patients.

[b] Assessed in 1453 patients (489 in development cohort and 964 in validation cohort).

[c] Assessed in 1558 patients.

[d] The baseline patient characteristics between the development cohort and validation cohort are quite similar, except that the validation cohort had a smaller proportion that of individuals who consume alcohol and a larger proportion of individuals who have nausea during attacks, heartburn, and abdominal bloating.

Table 2. Treatment, Complications, and Patient-Reported Outcome

Variable	No. (%)[a]		
	Total (N = 1561)	Development cohort (n = 494)	Validation cohort (n = 1067)
Treatment			
Randomization	NA	No	Yes
Usual care	537 (34.4)	NA	537 (50.3)
Restrictive care	1024 (65.6)	494 (100.0)	530 (49.7)
Cholecystectomy	1124 (72.0)	395 (80.0)	729 (68.3)
Complications			
Gallstones[b]	106 (7.3)	28 (7.4)	78 (7.3)
Surgical[c]	152 (13.5)	43 (10.9)	109 (15.0)
Surgical complication CDC ≥ 3	26 (2.3)	6 (1.5)	20 (2.7)
Patient-reported outcome after surgery (N = 1124)			
Pain free (IPS ≤ 10, VAS ≤ 4)[d]	670 (59.6)	225 (57.0)	445 (61.0)
Clinically relevant pain reduction[e]	817 (72.7)	295 (74.7)	522 (71.6)
Absence of biliary colic[f]	356 (95.2)	356 (95.2)	NA

Abbreviations: CDC, Clavien-Dindo classification; IPS, Izbicki pain score; NA, not applicable; VAS, visual analog scale.

[a] Missing data were imputed in 66 patients (13.3%) in the development cohort, and in 49 patients (4.6%) in the validation cohort.

[b] Assessed in 1446 patients.

[c] Assessed in 1124 patients (395 in the development cohort and 729 in the validation cohort).

[d] Pain free was defined as an Izbicki pain score ≤ 10 and VAS ≤ 4. Reduction in VAS pain score ≥4 points = VAS pain score at baseline − VAS pain score at 6 months' follow-up.

[e] Clinically relevant pain reduction was defined as a reduction in VAS ≥ 4 points.

[f] Assessed in 374 patients after cholecystectomy.

Table 3. Predictors for Clinically Relevant Pain Reduction After Cholecystectomy

Predictor	Regression coefficient (β) after internal validation[a]	Odds ratio (95% CI)
Intercept	−5.03	
Age, y	0.02	1.02 (1.00-1.05)
History of abdominal surgery		
No	Reference	1 [Reference]
Yes	−0.57	0.54 (0.31-0.94)
VAS pain score at baseline	0.57	
Pain radiating to the back		
No	Reference	1 [Reference]
Yes	0.62	1.87 (1.60-2.23)
Positive response to simple analgesics		
No	Reference	1 [Reference]
Yes	0.47	1.69 (0.87-3.25)
Did not use analgesics	1.21	3.81 (1.70-8.90)
Nausea during pain attacks		
No	Reference	1 [Reference]
Yes	0.48	1.69 (0.93-3.13)
Heartburn		
No	Reference	1 [Reference]
Yes	−0.79	0.42 (0.19-0.91)

Abbreviation: VAS, visual analog scale.

[a] Logistic backward regression analyses in the development cohort with clinically relevant pain reduction as outcome; a *P* value ≥0.1 was used to remove predictors. Model development was based on 395 patients.

Model for a Pain-Free State

The model to predict a pain-free state after surgery showed that older patients and those without a history of abdominal surgery, with a low VAS baseline score, with pain in attacks, without the use of pain medication, or without heartburn had a higher chance of a pain-free state after cholecystectomy (eTable in Supplement 4). The performance of this model is described in eResults 2 and eFigure 1 in Supplement 4.

Model for Clinically Relevant Pain Reduction

The model to predict clinically relevant pain reduction after surgery revealed that older patients and those without a history of abdominal surgery, with a high VAS baseline score, with pain radiation to the back, a positive pain response to simple analgesics, nausea during pain attacks, or no heartburn had a higher chance for pain reduction after cholecystectomy (**Table 3**).

A shrinkage factor of 0.91 was estimated through bootstrapping in internal validation. After internal validation, the C statistic was 0.80 (95% CI, 0.74-0.84), indicating a very good discrimination between patients with and without clinically relevant pain reduction. A very good overall calibration was found, with minimal underestimation of the probability by the model (**Figure 2**). External validation resulted in a C statistic of 0.74 (95% CI, 0.70-0.78), indicating a good discrimination between patients with and without clinically relevant pain reduction. A fair calibration was found, with some overestimation of probability by the model. Recalibration of the intercept did not result in an improved model.

A Nomogram and Online Decision Tool

A nomogram was created based on the predictors of the model to calculate the probability of an individual achieving clinically relevant pain reduction (eFigure 2 in Supplement 4) or a pain-free state (eFigure 3 in Supplement 4) after cholecystectomy. An applicable online decision tool was made to estimate both outcomes after cholecystectomy. The decision tool is available at https://gallbladderresearch.shinyapps.io/SUCCESS/.

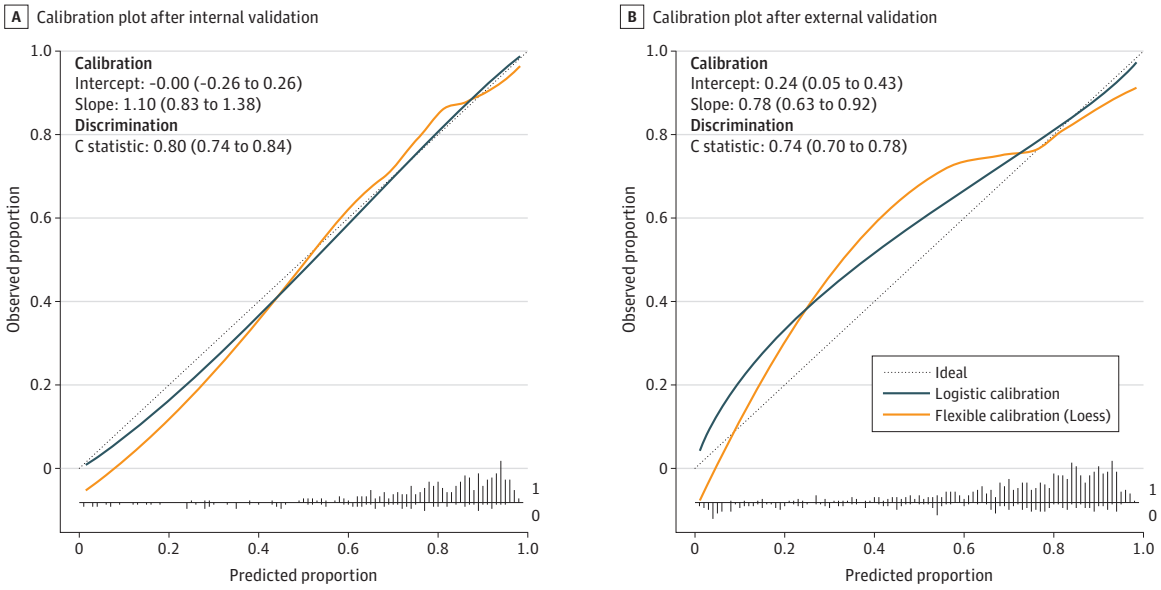
Discussion

We developed and validated a model to predict the symptomatic response following a cholecystectomy in patients with gallstones and abdominal pain. Older patients and those without a history of abdominal surgery, with a high baseline pain score, pain with radiation to the back, a positive pain response to simple analgesics, nausea during pain attacks, or who did not report heartburn had a higher chance of achieving clinically relevant pain reduction after cholecystectomy. Knowledge of the value of these criteria is pivotal for general physicians, gastroenterologists, and surgeons who make daily treatment decisions with patients with abdominal pain and gallstones. These findings may provide evidence to improve future patient selection for cholecystectomy.

Rome III criteria are consensus based and result from a 1988 observational study, which assessed symptoms and presence of gallstones in a cohort of 2325 Italian administrative employees.[7,8] The SECURE trial[9] illustrated that these criteria are insufficient to predict a pain-free state after cholecystectomy. A previous cohort study including 1008 patients who received cholecystectomy for gallstones and upper abdominal pain focused on identifying symptoms associated with pain relief.[12] The study found that features of abdominal pain and concomitant functional gastrointestinal disorders determine the odds of pain relief after cholecystectomy. An important shortcoming of this study is that baseline sampling was immediately before or within 4 weeks after cholecystectomy which may introduce relevant recall bias because of poor patient recollection of upper abdominal pain severity and characteristics. Our findings corroborate the results from this study reinforcing the concept that patient selection on the basis of reported features of upper abdominal pain may aid in decision-making regarding who is most likely to benefit from cholecystectomy.

Selecting patients for cholecystectomy and solely relying on pain features seems inadequate. Patient characteristics, pain scores, surgical history, and signs of functional gastrointestinal disorders are relevant factors during decision-making in patients with gallstones and abdominal pain. A cholecystectomy in patients with a low pain score should be avoided. In general, women more often report accompanying symptoms associated with irritable bowel syndrome or functional dyspepsia. Underlying gastrointestinal disorders hamper the

Figure 2. Calibration Plot of the Prediction Model for Clinically Relevant Pain Reduction After Internal and External Validation



A, Calibration plot of the prediction model for a clinically relevant pain reduction after internal validation represents the observed proportion vs the predicted probabilities. The broom plot shows the distribution of predicted probabilities for patients with (1) and without (0) clinically relevant pain reduction. B, Calibration plot of the prediction model for a clinically relevant pain reduction after external validation before recalibration of the intercept, which did not result in an improved model, represents the observed proportion vs the predicted probabilities. The broom plot shows the distribution of predicted probabilities for patients with (1) and without (0) clinically relevant pain reduction.

outcome of cholecystectomy to achieve a satisfying outcome.[17-21] During initial consultations, doctors need to address these specific disorders and rule them out as potential causes of abdominal pain. A wait-and-see policy and a second thorough history taking after an interval of a few weeks are justified. We advise this policy, as it generally discriminates more adequately between biliary and nonbiliary pain relative to additional diagnostic tests or an invasive gastrointestinal endoscopy. Nevertheless, we are aware that functional disorders as obstipation, dyspepsia, or heartburn are sometimes difficult to differentiate from biliary pain.[22-24]

Based on our work, we advise clinicians to implement shared decision-making with patients with gallstones and abdominal pain, especially when nonbiliary pain is present. For shared decision-making, clinicians need to provide patients with high-quality and complete information. The present model, simplified in an online tool, can quickly assess the probability of clinically relevant pain reduction or a pain-free state after surgery for the individual patient. Results from this study can be used to address the risk of gallstone-associated complications and can adequately guide doctors and patients to a surgical or more conservative approach.

Although the criteria of the Success study may already improve indications for cholecystectomy in current practice, there is still room for further improvement in discriminatory capacity of the selection tool. Future researchers are cordially invited to replicate the findings reported here to further build confidence that holding the status quo is suboptimal and may not be in the best interest of patients.

The C-GALL trial[25] is currently randomizing 430 patients with symptomatic cholelithiasis in a surgical or conservative study arm, to test the hypothesis that "there is no difference between medical management and cholecystectomy in terms of generic quality of life (36-Item Short Form Survey) after 18 months' follow-up."[26] This study design is exclusively focused on the effect of surgery, while the target population is not strictly defined. All patients with ultrasound-confirmed gallstones are eligible for inclusion regardless of the severity of symptoms. This design does not reflect the practice of optimizing patient selection before excluding patients from surgery.

Determining successful outcome after cholecystectomy is difficult, and several studies use different outcomes. The C-GALL trial[25] uses the pain domain of the 36-Item Short Form Survey questionnaire. The SECURE trial[9] used a pain-free state according to the Izbicki pain score as primary outcome; however, our results showed that a prediction model for the pain-free outcome after cholecystectomy is not sufficient after internal and external validation. Achieving a pain-free state after cholecystectomy appears only feasible in 60% of patients. Therefore, we set the goal of predicting clinically relevant pain relief after surgery.

Strengths and Limitations

This study has strengths and limitations. More than 45% of patients screened for inclusion were excluded based on predefined exclusion criteria. We excluded patients with American Society of Anesthesiologists physical status classi-

fication of III or IV, which limits the generalizability of the results. Six hospitals in the validation cohort were similar to the hospitals in the development cohort; however, all patients were included in different time periods. Moreover, we only included patients in the Netherlands, which warrants external validation elsewhere. The sample size restricted the number of predictors included in our analysis, and statistical significance to include predictors has its limitations. The wide confidence intervals limit the clinical utility of the tool. Despite this considerable uncertainty, this information about prognostic certainty and uncertainty may still support transparent shared decision-making between patient and physician, as it is the best evidence currently available to our knowledge. The strengths of this study are the 2 independent multicenter cohorts with prospectively sampled data, the use of validated questionnaires, and a well-characterized design, as well as the above-mentioned internal and external validation and the online decision tool which is ready to use and applicable in daily clinical practice.

Conclusions

The model validated in this study may help predict the probability of pain reduction after cholecystectomy and thus aid surgeons in deciding whether patients with uncomplicated cholelithiasis will benefit from cholecystectomy.

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