Risk prediction in acute calculous cholecystitis: a systematic review and meta-analysis of prognostic factors and predictive models

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Abstract

Background

Laparoscopic cholecystectomy is the main treatment of acute cholecystitis. Although considered relatively safe, it carries 6-9% risk of major complications and 0.1-1% risk of mortality. There is no consensus regarding the evaluation of the preoperative risks, and the management of patients with acute cholecystitis is usually guided by surgeon's personal preferences. We assessed the best method to identify patients with acute cholecystitis who are at high risk of complications and mortality.

Methods

We performed a systematic review of studies which reported the pre-operative prediction of outcomes in people with acute cholecystitis. We searched the Cochrane Library, MEDLINE, EMBASE, WHO ICTRP, ClinicalTrials.gov and Science Citation Index Expanded until 27th April 2019. We performed a meta-analysis when possible.

Results

6827 people were included in one or more analyses in 12 studies. Tokyo guidelines 2013 (TG13) predicted mortality (two studies; Grade 3 vs Grade 1: OR 5.08, 95% CI 2.79 to 9.26). Gender predicted conversion to open cholecystectomy (two studies; OR 1.59, 95% CI 1.06 to 2.39). None of the factors reported in at least two studies had significant predictive ability of major or minor complications.

Conclusion

There is significant uncertainty in the ability of prognostic factors and risk prediction models in predicting outcomes in people with acute calculous cholecystitis. Based on studies of high risk of bias, TG13 Grade 3 severity may be associated with greater mortality than grade 1. Early referral of

such patients to high volume specialist centres should be considered. Further well-designed prospective studies are necessary.

Introduction

Acute cholecystitis is an acute inflammatory disease of the gallbladder. In United States of America (USA), there were about 213,000 hospital admissions related to acute cholecystitis in 2012[1]. The costs related to the management of these patients were about US$ 43,000 per patient[1]. Acute cholecystitis costs US$ 9.3 billion annually, accounting for 1.5% of total healthcare costs in USA[1]. Approximately 85% of acute cholecystitis are due to gallstones[2]. Approximately 0.3% to 0.4% of people with gallstones develop acute cholecystitis annually[3].

Laparoscopic cholecystectomy during the index admission is generally recommended in people with acute calculous cholecystitis, if they are fit to undergo surgery[3, 4]. However, laparoscopic cholecystectomy is a major surgical procedure and, although considered relatively safe, it is associated with about 0.1 to 1% mortality rate[5-7], approximately 0.2 to 1.5% risk of bile duct injury[6-8], and about 6–9% risk of major complications, such as myocardial infarction, heart failure, acute stroke, renal failure, pulmonary embolism, lung failure or postoperative shock[5].

Conservative management with fluids, analgesia and antibiotics is an alternative option for people with mildly symptomatic acute cholecystitis (i.e. in people without peritonitis or those who have worsening clinical condition). In a small randomised controlled trial (RCT) with high risk of bias including 64 participants, about 30% of people treated conservatively (33 participants) developed recurrent gallstone-related complications over a median follow-up of 14 years, and 60% of people had undergone cholecystectomy subsequently[9, 10]. Furthermore, the mean age of the participants in the trial of surgery versus conservative management in mildly symptomatic acute cholecystitis was about 55 years and the study excluded patients above 80 years or those with severe co-morbidities[10]. Therefore, the trial does not address the issue of whether surgery or conservative treatment is better in elderly people or those with severe comorbidities. Therefore, until new high-quality evidence becomes available, laparoscopic cholecystectomy can be considered the recommended treatment for people who are fit to undergo surgery.

Identification of patients with acute cholecystitis at high risk of complications and mortality, can help in optimising these patients prior to surgery or referral to high volume specialist centres, which may decrease the complications[11, 12]. This can also help in making informed decisions about surgery versus conservative management. However, there is no current consensus on how to measure the operative risk[4].

There are currently no systematic reviews of prognostic factors or risk prediction models in patients with acute calculous cholecystitis and the management of those patients is usually not evidence based.

The aim of our study is to assess the best method to predict the risk of death, complications, health-related quality of life, and conversion to open cholecystectomy in patients with acute cholecystitis. regardless of whether they underwent cholecystectomy.

Materials and methods

The protocol was registered with PROSPERO database registration number: CRD42019136890. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidance was followed[13, 14].

Criteria for considering studies for this review

Types of studies

We included prospective and retrospective studies which reported the prediction of outcomes in people with acute cholecystitis. There were no restrictions by publication status or language. We excluded studies in which the people received different treatments based on the prognostic characteristics or those that compared different treatments or timing of treatments.

Types of participants

We included studies where all participants had acute calculous cholecystitis or if prognostic information was available separately for participants who had acute calculous cholecystitis.

Type of interventions and outcomes

We included only studies in which any patient-related or disease-related prognostic factors or risk prediction models that could be applied pre-operatively to predict the short-term mortality, adverse events, conversion to open surgery (in people who underwent surgery), and health-related quality of life using a validated scale. For adverse events, we accepted the adverse events as defined by the authors and considered them serious if they caused deaths, or were life-threatening, required inpatient hospitalisation, resulted in a persistent or significant disability, or any important medical event which might have jeopardised the patient or required intervention to prevent it[15]. We also accepted Grade III or above in Clavien-Dindo complication classification system as serious adverse events[16, 17].

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, WHO ICTRP, ClinicalTrials.gov and Science Citation Index Expanded (including Conference Proceedings Citation Index) until 27th April 2019. We used the McMaster Health Information Research Unit search filters for MEDLINE and EMBASE databases[18, 19]. The detailed search strategy for each database is available in Supplementary Table S1.

Searching other resources

We also searched the references of the identified studies to identify further relevant studies.

Data collection and analysis

Two authors independently identified studies and extracted data from included studies in a pre-piloted data extraction form created using Microsoft Excel.

Selection of studies

We identified the studies for inclusion by screening the titles and abstracts of the studies retrieved during the searches and retrieved the full-texts of any articles identified by at least one of the review authors as being potentially eligible for inclusion. We selected studies for inclusion based on the assessment of the full-text articles (after translation, if required), and resolved any discrepancies arising regarding inclusion/exclusion through discussion.

Data extraction and management

Two authors independently extracted the following data.

1. Year and language of publication.
2. Country in which the participants were recruited.
3. Details of the settings such as primary care, secondary care, or tertiary care.
4. Year(s) in which the trial was conducted.
5. Inclusion and exclusion criteria.
6. Population characteristics such as age, sex, severity of acute cholecystitis.
7. Outcomes (mentioned above).
8. Risk of bias (described below).
9. Details of the prognostic factor(s) or risk prediction model(s) (including the threshold, the details of the variables included in the risk prediction model and whether this was a development study or a validation study: if the same study reported a development cohort and validation cohort, we considered these as two different cohorts).

We sought clarification of any unclear or missing information by contacting the authors of the individual trials. We resolved any differences in opinion through discussion.

Assessment of risk of bias in included studies

We independently assessed the risk of bias in the trials without masking the trial names. We used the PROBAST tool to assess the risk of bias[20]. The PROBAST tool has been mainly developed for risk prediction model. It includes the most relevant items from the QUIPS tool (developed for prognostic factor studies)[21]. The schema that we used to assess the risk of bias is available in Appendix 1. We considered studies to have a low risk of bias if we assessed all the risk of bias domains as being at low risk of bias. In all other cases, the studies were considered to have unclear or high risk of bias.

Data synthesis

We calculated the summary C-statistic with 95% confidence interval (CI) along with odds ratio and its 95% CI and planned to calculate the summary observed versus expected events ratio (O:E ratio) with 95% CI and prediction intervals (PI) to determine the ability of each scoring system to predict the outcomes. However, none of the studies reported observed versus expected events; therefore, we performed only the meta-analyses of C-statistic and odds ratio. We performed a meta-analysis only when this was meaningful (e.g. we combined only studies with identical thresholds used to define high and low levels of the prognostic score) using Stata 15. For meta-analysis of the C-statistic, we used the logit transformation; for odds ratio, we used log transformation. We used the random-effects model as default because of anticipated clinical heterogeneity among studies. We did not compare different thresholds of a specific prognostic scoring system against one another as planned because of the sparse data and the high risk of bias in the studies.

Subgroup analysis

We did not perform the planned subgroup analyses on elderly versus young patients because of the sparse data.

Reporting bias

We did not perform the planned exploration of reporting bias by funnel plots because of the few studies included for each prognostic factor or prognostic model. In some of the studies, the outcomes such as mortality and complications were not reported, although it is likely that they were measured. This indicates that there is possibility of reporting biases.

Results

Results of the search

We identified a total of 4697 references through electronic searches of The Cochrane Hepato-Biliary Group Controlled Trials Register and the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (n = 72), MEDLINE (n = 595), EMBASE (n = 3269), and Science Citation Index Expanded (n = 740), ClinicalTrials.gov (n = 14), WHO trial register (n= 7). We excluded 500 duplicates and 4167 clearly irrelevant references through reading abstracts. The remaining 30 references were retrieved as full text for further assessment. No references were identified through scanning reference lists of the identified studies. We excluded 18 references for the reasons listed under the 'Characteristics of excluded studies'. In total, 12 studies fulfilled the inclusion criteria and provided data for the systematic review. The reference flow is shown in Figure 1.

Characteristics of included studies

Of the 12 included studies, only one study was a prospective study [22]; nine studies were retrospective studies[23-31]; it was not clear whether the remaining two studies were prospective or retrospective studies[32, 33].

A total of 7978 people were eligible for this review in the 12 studies and 6827 people were included in one or more analyses in the 12 studies[22-33]. A total of 1151 participants (14.4%) were excluded from the analysis by the authors due to missing data or because they did not undergo surgery. Eleven studies included only patients who underwent cholecystectomy[22-30, 32, 33]. In the remaining

study, 76.3% of people underwent cholecystectomy and the remaining patients were treated conservatively. Seven studies included only people who underwent laparoscopic cholecystectomy[22, 23, 25, 29, 30, 32, 33]. In the remaining five studies, cholecystectomy was started as open procedure in 4.4% to 45.9% of patients[24, 26-28, 31]. The proportion of people who required conversion from laparoscopic to open procedure was 5.4% to 23.8% in the 11 studies that reported this information[22-26, 28-33]. In seven studies, the cholecystectomy was performed early[22, 23, 27, 28, 30, 32, 33]; in two studies, the timing of cholecystectomy was not stated[26, 31]. The timing of surgery in the remaining three studies are as follows: in one study, 240 participants (89%) had early surgery[24]; in a second study, 41 participants (77.4%) had surgery within 72 hours of admission[29]; in the last study, the median time to cholecystectomy was 7 days[25].

Eleven studies included adults of different age groups[22-26, 28-33], while one study included only elderly patients (> 65 years)[27]. All studies included patients with and without comorbidities. It was difficult to estimate the proportion of patients with comorbidities in the studies as the comorbidities were defined in different ways in different studies.

The prognostic factors studied included individual prognostic factors such as age, gender, presence of diabetes, previous abdominal surgery, existing risk prediction scores such as ASA, Charlson Comorbidity Index, P-Possum, and Frailty index, and new predictive models based on regression, discriminant analysis, and artificial neural network.

The outcomes reported in the studies included all-cause mortality, major complications, minor complications, all complications, and conversion to open cholecystectomy. All the outcomes were reported until discharge or until 30 days of surgery. None of the studies reported predictors of health-related quality of life.

The characteristics of included studies are summarised in Supplementary Table S2. The prognostic factors or predictive models and the outcomes reported in each study is summarised in Table 1.

Characteristics of excluded studies

Eighteen studies were excluded for the following reasons: not a primary research study[34, 35], data on prognostic factors not available:[36-40], prognostic accuracy data not available:[41-43], study not including all acute cholecystitis but only a subgroup of patients based on severity (for example, only those had severe acute cholecystitis) or patients who had one of the outcomes (for example, only those who underwent conversion from laparoscopic cholecystectomy to open cholecystectomy rather than a cohort of patients who underwent laparoscopic cholecystectomy for acute cholecystitis)[44-50], and full text not available to make a sufficient assessment[51].

Risk of bias and applicability concerns

The risk of bias and applicability concerns in the studies are summarised in Supplementary Table S3. All the studies were at high risk of bias for one or more domains. The major reasons were that most studies were retrospective studies, the predictor or outcome measurements were not defined clearly for most predictors and outcomes, and blinding of predictor or outcome measurement was not reported. The number of participants with outcomes was less than 100 or the threshold was determined by optimal threshold for all the outcomes.

There were no concerns about whether the included participants were different from the usual type of patients with acute cholecystitis. However, it was not clear whether predictors or outcomes were measured in the same way as they would be measured in clinical practice, for example, it was not clear whether the predictors were measured on arrival or just after admission into the hospital or the complications included all the complications that would be routinely measured in clinical practice.

Discrimination results

A summary of the results from each study is presented in Supplement Tables S4 and S5. The OR and the 95% CI are presented as forest plots in Figures 2 to 4 when there were at least two studies

reporting the prognostic factor or predictive model, and in Supplementary figures SF1 to SF4 for other factors or predictive models with only one study.

All-cause mortality

Five studies (5655 participants) reported the ability of five prognostic factors or models (age, Charlson Comorbidity Index, Tokyo guidelines 2013 (TG13), number of dysfunctioning organs, and Body Mass Index (BMI)) in predicting all-cause mortality[23, 24, 26, 28, 31]. The median (IQR) risk of all-cause mortality was 1.3% (0.8%, 1.5%). TG13: Grade 3 (severe acute cholecystitis) vs Grade 1 (mild acute cholecystitis) was reported in two studies and had significant predictive ability (OR 5.08, 95% CI 2.79 to 9.26). The remaining factors were reported either in only one study or did not have significant predictive ability.

Major complications

Three studies (884 participants) reported the predictive ability of three prognostic factors or predictive models (Charlson Comorbidity Index, TG13, and BMI) in predicting major complications[23, 24, 26]. One study reported major complications as organ failure, bleeding, bile duct injury, and bile leak[23]; another study reported major complications as intrahepatic abscess, bleeding, bile leakage, biliary tract injury, and post-operative pancreatitis[24]; and the last study reported major complications as Clavien-Dindo grades III or IV)[26]. The median (IQR) risk of major complications was 3.3% (2.0%, 3.9%). None of the factors reported in at least two studies had significant predictive ability.

Minor complications

Two studies (735 participants) reported the predictive ability of two prognostic factors or predictive models (Charlson Comorbidity Index, and BMI) in predicting minor complications[24, 26]. The median (IQR) risk of minor complications was 6.1% (5.4%, 6.7%). None of the factors reported in at least two studies had significant predictive ability.

All complications

Six studies (1807 participants)[24, 26-28, 30, 32] reported the predictive ability of 24 prognostic factors or predictive models (male, previous upper abdominal surgery, age, albumin, alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, Charlson Comorbidity Index, chronic liver disease, chronic obstructive airway disease, chronic renal failure, diabetes, glucocorticosteroid use, Haemoglobin, hypotension, ischaemic heart disease, platelets, P-Possum physiology score, previous biliary colic, Simplified Acute Physiology Score (SAPS-II), temperature, white blood count (WBC), Frailty score, and BMI) in predicting all complications. The median (IQR) risk of all complications was 10.0% (6.3%, 15.0%). Male gender was reported in two studies and had significant predictive ability (OR 1.59, 95% CI 1.06 to 2.39). The remaining factors were reported either in only one study or did not have significant predictive ability.

Conversion to open cholecystectomy

Ten studies (6331 participants) reported the predictive ability of 40 prognostic factors or predictive models (male, previous upper abdominal surgery, age, diabetes, hypertension, adhesion to the adjacent organs (on preoperative scan), alkaline phosphatase, ALT, angle of the gallbladder, antiplatelet or anticoagulant use for cardiovascular disease, artificial neural network, associated organ dysfunction, AST, Bilirubin, BMI, bulging of the abdominal muscle, Charlson Comorbidity Index, C-reactive protein (CRP), discriminant analysis, hyperattenuation of adjacent parenchyma, location of gallstone, logistic regression, Mirizzi syndrome, mucosal disruption, perforation, pericholecystic fluid, preoperative biliary intervention, short-axis diameter, wall thickening (on preoperative scan), WBC, and TG13) in predicting conversion to open cholecystectomy[22-26, 29-33]. The median (IQR) probability of conversion to open cholecystectomy was 16.0% (11.1%, 19.3%). The following factors were reported in at least two studies and had significant predictive ability:

- Male (OR 4.95, 95% CI 1.99 to 12.27)
- Previous upper abdominal surgery (OR 2.69, 95% CI 1.42 to 5.12)
- Age (OR 1.03, 95% CI 1.00 to 1.05 per year increase in age).

The remaining factors were reported either in only one study or did not have significant predictive ability.

Health-related quality of life

None of the studies reported the ability of any of the prognostic factors or risk prediction models in predicting health-related quality of life.

Calibration results

None of the studies reported results in a format from which calibration results could be calculated, i.e. none of the studies presented the expected events based on the prognostic factor or prediction model, from which calibration could be calculated.

Discussion

Summary

In this systematic review and meta-analysis, we included 12 studies and 6827 people with acute cholecystitis in one or more analysis. Only few factors were reported in a format similar enough to combine for a meta-analysis. The remaining factors were analysed in single studies or used different thresholds: therefore, there is no information on their reproducibility and the results may be unreliable. This is of significant concern since the predictive ability of the factors which were measured in two or more studies differed considerably.

Among the prognostic factors reported in at least two studies, TG13 grade 3 had increased risk of all-cause mortality compared to grade 1. However, the timing of surgery in those who underwent cholecystectomy was not reported in this study and might have influenced the outcome. The studies were also at high risk of bias.

Furthermore, most studies included only people who underwent surgery and excluded participants who did not undergo surgery. There have been no randomised controlled trials of surgery versus

conservative treatment in people with severe acute calculous cholecystitis. The role of percutaneous cholecystostomy either as a bridging treatment to cholecystectomy or a definitive treatment in patients at high surgical risk is unclear, as indicated by a Cochrane systematic review[52]. A RCT published since the Cochrane review showed that in patients with acute cholecystitis and high physiological risk but considered eligible for surgery (acute physiology assessment and chronic health evaluation II/APACHE II scores of between 7 and 15), laparoscopic cholecystectomy performed by experienced surgeons had lower major complication rates than percutaneous cholecystostomy with no planned cholecystectomy[53]. Although the study was not powered to measure differences in mortality[53], it is extremely unlikely that conservative treatment without surgery is an effective way of treating people with severe acute cholecystitis who are fit to undergo surgery. Therefore, it appears that despite the increased risk of mortality in TG13 grade 3 compared to TG13 grade I, early surgery seems to be the preferred option when possible. However, early referral to high volume specialist centres, where patients can be optimised using integrated medical care and undergo early cholecystectomy may decrease the complications[11, 12] and resulting mortality, and should be considered in people with TG13 grade 3 acute cholecystitis.

None of the factors reported in at least two studies had significant predictive ability for major and minor complications analysed separately. The definition used for major complications were also different across studies. Male gender was associated with increased risk of 'all complications' and increased proportion of conversion to open cholecystectomy. The possible factors for poorer outcomes in males include increased skeletal muscle mass[54], particularly, in the trunk [55] and increased visceral abdominal fat in males[54, 56, 57] (which could make laparoscopic surgery more difficult) and delay in seeking medical help in males due to misguided perception of masculinity[58, 59] (which could mean that the males had more severe disease than females at the time of presentation to hospital). Another potential reason for delay in seeking medical help in males could be gender differences in pain perception between gender. In a systematic review, there was no evidence of difference in visceral pain threshold or intensity between males and females[60]. However, this

information is based on two studies including just 38 participants. Therefore, the reasons for the difference in the complications and conversion between males and females are not clear but may be due to a combination of the above factors. Again, referral to high volume specialist centres is an option, particularly because the gallstone incidence and operations are twice as frequent in females as males, i.e. fewer patients need referral to specialist services[61, 62]. However, this may need reorganisation of services if one-third of patients with acute cholecystitis have to be referred to a high volume or specialist centre.

Previous upper abdominal surgery is a risk factor for conversion to open cholecystectomy. This is expected because of the intra-abdominal adhesions related to previous upper abdominal surgery. In a data linkage study in Scotland conducted in the era of open surgery, of 8717 patients who underwent upper abdominal surgery, 321 patients (3.7%) had hospital readmissions directly related to intra-abdominal adhesions and another 1962 patients (24.8%) had hospital readmissions possibly related to intra-abdominal adhesions[63]. Therefore, referral of patients with previous upper abdominal surgery to specialists centres can be considered, as the risk of complications and proportion of patients requiring conversion from laparoscopic to open cholecystectomy is lower when performed by specialists[11, 12].

Older age had a minor increase in the conversion to open cholecystectomy. However, the increase is cumulative, i.e. elderly patients may have a clinically important increase in conversion to open cholecystectomy compared to young people. Various confounding factors such as comorbidities and higher incidence of upper abdominal surgery may contribute to the increased probability of conversion to open cholecystectomy.

Applicability of the evidence

We restricted our selection to studies that included only patients with acute calculous cholecystitis. Most studies included only patients undergoing cholecystectomy for acute cholecystitis. Therefore, the findings of this review are applicable only in patients undergoing cholecystectomy for acute

cholecystitis. We included only preoperative factors or risk models based on preoperative factors. Therefore, the findings of the review are applicable only before surgery is performed and does not include intraoperative or post-operative findings. There are likely to be other intraoperative or post-operative factors such as bile duct injury during surgery or severe adhesions found intraoperatively or post-operative bile leak that affect the clinical outcomes.

The Tokyo guidelines 2018 severity grading criteria adopted the Tokyo guidelines 2013 severity grading criteria in predicting outcomes in people with acute calculous cholecystitis[64]. Therefore, the results of TG13 severity grading criteria are applicable to TG18 severity grading criteria as well, although the management algorithms of TG13 and TG18 based on the severity grading criteria were different.

Quality of evidence

The risk of bias in the studies was high because of one or more reasons described in the result section. There was significant heterogeneity in the thresholds used for measurement. Most of the prognostic factors at a particular threshold were reported in only one study. Many of these factors are routinely measured such as age, BMI, coexisting diabetes, and hypertension. Furthermore, most of the outcomes are routinely measured outcomes such as mortality, major complications, and minor complications; yet, only a few studies reported these outcomes. This raises the possibility of publication bias. Therefore, there is significant uncertainty in the ability of the prognostic factors or risk prediction models in predicting outcomes in patients with acute cholecystitis. This uncertainty can impede shared decision making.

Strengths and weaknesses

Two people selected studies and extracted data independently. We did not apply any language restrictions and searched a wide range of medical databases. We assessed the risk of bias in the studies using PROBAST, the tool currently recommended for assessing the risk of bias in prognostic studies.

The major weakness of the review is that we had to use search filters for identifying the studies. There may be other clinical studies which looked at the prediction of different factors without mentioning terms related to risk prediction or prognosis in the title, abstract, or keywords. These studies would have been missed by using the filter. These may be related to the predictive ability of the outcomes, contributing to reporting bias. However, one has to be pragmatic and choose between performing a systematic review using these filters versus attempting to seek information from an unmanageable number of full texts, making the review impossible to complete.

We have limited the prognostic factors to preoperative factors. This is because our main objective was to determine the best method to predict the risk of death, complications, health-related quality of life, and conversion to open cholecystectomy preoperatively in patients with acute cholecystitis. We acknowledge that there are several intraoperative factors that could influence these outcomes; however, such intraoperative factors will not be available at the time of informed decision making about the treatment. Future studies should consider adjusting for surgeon-level or centre-level average levels of intraoperative factors while developing the prognostic models that can be used preoperatively.

Conclusions

There is significant uncertainty in the ability of prognostic factors and risk prediction models in predicting outcomes in people with acute calculous cholecystitis. Based on data from studies of high risk of bias, Tokyo guidelines 2013 - Grade 3 severity may be associated with greater mortality than grade 1 severity of acute cholecystitis. Referral of such patients to high volume or specialist centres should be considered. High quality studies are necessary to provide better information on prognostic information in people with acute cholecystitis and improve shared decision making. Such studies should be prospective, of adequately large sample size to ensure that there are at least 100 events for the outcome measured and should use blinded collection of prognostic factors and outcomes

when possible. They should also consider adjusting for surgeon-level or centre-level average levels of intraoperative factors.

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Table S5 Ordinal predictors

Study name	Outcome	Prognostic factor	Baseline	Level compared	Ln OR	SE Ln OR	Logit C	SE Logit C	OR (95% CI)	C (95% CI)
Amirthalingam 2017[23]	All-cause mortality	TG13	Grade 1	Grade 3	1.633391153	2.018028835	1.099355661	1.432746013	5.08 (2.79-9.26)	0.75 (0.66- 0.82)
Yokoe 2017[31]	All-cause mortality	TG13	Grade 1	Grade 3	1.625135724	0.30984543	1.093697922	0.212521788	5.08 (2.79-9.26)	0.75 (0.66-0.82)
Amirthalingam 2017[23]	All-cause mortality	TG13	Grade 1	Grade 2	1.653800025	1.642899736	1.113348973	1.15436858	1.01 (0.21-4.89)	0.49 (0.26- 0.72)
Yokoe 2017[31]	All-cause mortality	TG13	Grade 1	Grade 2	-0.386580024	0.380706051	-0.25786241	0.254735031	1.01 (0.21-4.89)	0.49 (0.26- 0.72)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	6 organs failed	3.57987474	1.170204903	2.484782835	0.869106716	35.87 (3.62-355.47)	0.92 (0.69- 0.99)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	5 organs failed	3.069049117	1.111776138	2.110177984	0.809178133	21.52 (2.44-190.20)	0.89 (0.63- 0.98)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	4 organs failed	3.069049117	0.797525035	2.110177984	0.579377704	21.52 (4.51-102.74)	0.89 (0.73- 0.96)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	3 organs failed	3.174409632	0.434538788	2.186753502	0.316694657	23.91 (10.20-56.04)	0.90 (0.83- 0.94)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	2 organs failed	2.201948629	0.380065181	1.492884038	0.266078553	9.04 (4.29-19.05)	0.82 (0.73- 0.88)
Yokoe 2017[31]	All-cause mortality	Number of organs dysfunctioning	No organ failure	1 organ failed	1.233804535	0.323790838	0.827091219	0.219669903	3.43 (1.82-6.48)	0.70 (0.60- 0.78)
Lauro 2018[26]	All-cause mortality	BMI	<25	25-30	-1.533644073	1.552454677	-1.031093112	1.085327067	0.22 (0.01-4.52)	0.26 (0.04- 0.75)
Lauro 2018[26]	All-cause mortality	BMI	<25	>=30	0.440208057	1.23289479	0.293682182	0.839953055	1.55 (0.14-17.40)	0.57 (0.21- 0.87)

Amirthalingam 2017[23]	Major complications	TG13	Grade 1	Grade 3	1.633391153	2.018028835	1.099355661	1.432746013	5.12 (0.10-267.38)	0.75 (0.15- 0.98)
Amirthalingam 2017[23]	Major complications	TG13	Grade 1	Grade 2	1.653800025	1.642899736	1.113348973	1.15436858	5.23 (0.21-130.82)	0.75 (0.24-0.97)
Lauro 2018[26]	Major complications	BMI	<25	25-30	-1.755201873	0.770571663	-1.183012618	0.533155559	0.17 (0.04-0.78)	0.23 (0.10- 0.47)
Lauro 2018[26]	Major complications	BMI	<25	>=30	0.639658496	0.497981273	0.427082097	0.334587937	1.90 (0.71-5.03)	0.61 (0.44- 0.75)
Lauro 2018[26]	Minor complications	BMI	<25	25-30	-1.897119985	0.627716911	-1.280911227	0.435540344	0.15 (0.04-0.51)	0.22 (0.11- 0.39)
Lauro 2018[26]	Minor complications	BMI	<25	>=30	0.607919925	0.405109649	0.405832253	0.271772991	1.84 (0.83-4.06)	0.60 (0.47- 0.72)
Lorenzon 2017[27]	All complications	Frailty_score	Robust	Severe frailty	2.369074834	0.715839996	1.610150715	0.505546963	10.69 (2.63-43.47)	0.83 (0.65- 0.93)
Lorenzon 2017[27]	All complications	Frailty_score	Robust	Intermediate	0.816207273	0.723833432	0.545470212	0.489328366	2.26 (0.55-9.35)	0.63 (0.40- 0.82)
Lauro 2018[26]	All complications	BMI	<25	25-30	-1.911867842	0.492310564	-1.291112398	0.341323218	0.15 (0.06-0.39)	0.22 (0.12-0.35)
Lauro 2018[26]	All complications	BMI	<25	>=30	0.697601531	0.336047622	0.465901095	0.225569379	2.01 (1.04-3.88)	0.61 (0.51- 0.71)
Amirthalingam 2017[23]	Conversion to open cholecystectomy	TG13	Grade 1	Grade 3	0	1.572490786			1.06 (0.70-1.60)	0.51 (0.44- 0.58)
Yokoe 2017[31]	Conversion to open cholecystectomy	TG13	Grade 1	Grade 3	0.059473337	0.212231264	0.039649411	0.14158352	1.06 (0.70-1.60)	0.51 (0.44- 0.58)
Amirthalingam 2017[23]	Conversion to open cholecystectomy	TG13	Grade 1	Grade 2	1.74413142	0.83792458	1.175395822	0.580123775	2.38 (0.87-6.49)	0.64 (0.48- 0.78)
Yokoe 2017[31]	Conversion to open cholecystectomy	TG13	Grade 1	Grade 2	0.569870695	0.152480652	0.380368992	0.102050531	2.38 (0.87-6.49)	0.64 (0.48- 0.78)

Wevers 2013[30]	Conversion to open cholecystectomy	Regression_model	Low risk	Intermediate	1.06877714	0.343167781	0.715492055	0.231949461	2.91 (1.49- 5.71)	0.67 (0.56- 0.76)
Wevers 2013[30]	Conversion to open cholecystectomy	Regression_model	Low risk	High risk	2.646962509	0.479683477	1.806893915	0.341952506	14.11 (5.51- 36.13)	0.86 (0.76- 0.92)
Lauro 2018[26]	Conversion to open cholecystectomy	BMI	<25	25-30	- 0.092878356	0.330320827	- 0.061920882	0.220574816	0.91 (0.48- 1.74)	0.48 (0.38- 0.59)
Lauro 2018[26]	Conversion to open cholecystectomy	BMI	<25	>=30	- 0.052056362	0.443785063	-0.03470459	0.296686988	0.95 (0.40- 2.27)	0.49 (0.35- 0.63)
Wevers 2013[30]	Conversion to open cholecystectomy	ASA	Grade 1	Grade 4	2.739967804	1.652631818	1.873251075	1.196081938	15.49 (0.61- 395.07)	0.87 (0.38- 0.99)
Wevers 2013[30]	Conversion to open cholecystectomy	ASA	Grade 1	Grade 3	1.167068247	0.425427671	0.781907754	0.288410914	3.21 (1.40- 7.40)	0.69 (0.55- 0.79)
Wevers 2013[30]	Conversion to open cholecystectomy	ASA	Grade 1	Grade 2	0.636351809	0.336021292	0.424867749	0.25355194	1.89 (0.98- 3.65)	0.60 (0.50- 0.70)

Table S4 Binary, dichotomised, and continuous predictors

Study name	Outcome	Prognostic factor	Threshold	Ln OR	SE Ln OR	Logit C	SE Logit C	OR (95% CI)	C (95% CI)
Nikfarjam 2014[28]	All-cause mortality	Age	80	2.009003298	0.922495418	1.358436261	0.644814568	7.46 (1.22-45.47)	0.80 (0.52-0.93)
Bonaventura 2018[24]	All-cause mortality	Charlson Comorbidity Index	5	3.982469366	1.500850941	2.786016883	1.132779109	53.65 (2.83-1016.46)	0.94 (0.64-0.99)
Bonaventura 2018[24]	Major complications	Charlson Comorbidity Index	5	0.461034959	0.819976614	0.30759799	0.552886253	1.59 (0.32-7.91)	0.58 (0.32-0.80)
Bonaventura 2018[24]	Minor complications	Charlson Comorbidity Index	5	0.94511117	0.626076956	0.632136627	0.423510462	2.57 (0.75-8.78)	0.65 (0.45- 0.81)
Botaitis 2012[32]	All complications	Male		0.642	0.327	0.428650165	0.219304428	1.59 (1.06-2.39)	0.58 (0.51- 0.64)
Nikfarjam 2014[28]	All complications	Male		0.339164028	0.269771687	0.226205553	0.180260226	1.59 (1.06-2.39)	0.58 (0.51- 0.64)
Botaitis 2012[32]	All complications	Previous upper abdominal surgery		1.775	0.675	1.196641358	0.466740643	2.78 (0.72-10.63)	0.66 (0.44- 0.83)
Nikfarjam 2014[28]	All complications	Previous upper abdominal surgery		0.398152461	0.524411196	0.265590526	0.351547246	2.78 (0.72-10.63)	0.66 (0.44- 0.83)
Botaitis 2012[32]	All complications	Age	65	0.833	0.337	0.556748818	0.226707486	2.30 (1.19-4.45)	0.64 (0.53- 0.73)
Nikfarjam 2014[28]	All complications	Age	80	1.105391976	0.303262856	0.740215109	0.205081828	3.02 (1.67-5.47)	0.68 (0.58- 0.76)
Wevers 2013[30]	All complications	Age	Continuous	0.03	0.012	0.020000067	0.008000096	1.03 (1.01-1.05)	0.50 (0.50- 0.51)
Nikfarjam 2014[28]	All complications	Albumin	30 g/L	0.968280899	0.353700762	0.647737392	0.238584565	2.63 (1.32-5.27)	0.66 (0.54-0.75)
Botaitis 2012[32]	All complications	ALT	60 units/L	0.833	0.343	0.556748818	0.23075591	2.30 (1.17-4.51)	0.64 (0.53- 0.73)

Botaitis 2012[32]	All complications	AST	60 units/L	1.335	0.327	0.895752528	0.222433431	3.80 (2.00- 7.21)	0.71 (0.61- 0.79)
Nikfarjam 2014[28]	All complications	Bilirubin	60 µmol/L	0.755219609	0.439257153	0.50453613	0.29541749	2.13 (0.90- 5.03)	0.62 (0.48- 0.75)
Bonaventura 2018[24]	All complications	Charlson Comorbidity Index	5	0.796943974	0.511506872	0.532536365	0.344543904	2.22 (0.81- 6.05)	0.63 (0.46- 0.77)
Lorenzon 2017[27]	All complications	Charlson Comorbidity Index	Not stated	1.236104083	0.550567354	0.828649461	0.374388898	3.44 (1.17- 10.13)	0.70 (0.52- 0.83)
Nikfarjam 2014[28]	All complications	Chronic liver disease		-0.85115143	1.049628959	- 0.568943789	0.714911238	0.43 (0.05- 3.34)	0.36 (0.12- 0.70)
Nikfarjam 2014[28]	All complications	Chronic obstructive airway disease		0.963843272	0.407930954	0.644748856	0.275281464	2.62 (1.18- 5.83)	0.66 (0.53- 0.77)
Nikfarjam 2014[28]	All complications	Chronic renal failure		1.003219392	0.355108601	0.671276449	0.239708338	2.73 (1.36- 5.47)	0.66 (0.55- 0.76)
Nikfarjam 2014[28]	All complications	Diabetes		1.18708685	0.310496928	0.795453417	0.210388335	3.28 (1.78- 6.02)	0.69 (0.59- 0.77)
Nikfarjam 2014[28]	All complications	Glucocorticosteroid use		1.704748092	0.720459287	1.148321628	0.497376003	5.50 (1.34- 22.57)	0.76 (0.54- 0.89)
Nikfarjam 2014[28]	All complications	Haemoglobin	10 g/L	1.944152164	0.685073714	1.313462315	0.476384623	6.99 (1.82- 26.76)	0.79 (0.59- 0.90)
Nikfarjam 2014[28]	All complications	Hypotension	100 mm Hg	1.176821815	0.42008428	0.788506716	0.284839122	3.24 (1.42- 7.39)	0.69 (0.56- 0.79)
Nikfarjam 2014[28]	All complications	Ischaemic heart disease		0.659104873	0.326016168	0.440106592	0.218694758	1.93 (1.02- 3.66)	0.61 (0.50- 0.70)
Nikfarjam 2014[28]	All complications	Platelets	100 x 10^9/L	0.561811178	1.162601361	0.374976987	0.791312366	1.75 (0.18- 17.12)	0.59 (0.24- 0.87)
Lorenzon 2017[27]	All complications	P-Possum physiology score	21	2.662587827	0.792100045	1.818024023	0.566103128	14.33 (3.03- 67.70)	0.86 (0.67- 0.95)

Nikfarjam 2014[28]	All complications	Previous biliary colic		-0.299584532	0.27133812	-0.19978934	0.181259002	0.74 (0.44- 1.26)	0.45 (0.36- 0.54)
Lorenzon 2017[27]	All complications	SAPS-II	Not stated	1.078809661	0.548676363	0.722264165	0.37175049	2.94 (1.00- 8.62)	0.67 (0.50- 0.81)
Botaitis 2012[32]	All complications	Temperature	37 deg	0.916	0.344	0.612545603	0.231783345	2.50 (1.27- 4.90)	0.65 (0.54- 0.74)
Nikfarjam 2014[28]	All complications	Temperature	38 degree Centigrade	0.955511445	0.285617717	0.639138488	0.192506109	2.60 (1.49- 4.55)	0.65 (0.57- 0.73)
Nikfarjam 2014[28]	All complications	WBC	15 x 10^9/L	0.122892994	0.308812646	0.081933245	0.206187269	1.13 (0.62- 2.07)	0.52 (0.42- 0.62)
Kim 2014[25]	Conversion to open cholecystectomy	Male		1.609	0.683	1.082643802	0.469934066	4.95 (1.99- 12.27)	0.74 (0.61- 0.84)
Teckchandani 2010[22]	Conversion to open cholecystectomy	Male		2.816263786	1.225492351	1.92788262	0.884411157	4.95 (1.99- 12.27)	0.74 (0.61- 0.84)
Utsumi 2017[29]	Conversion to open cholecystectomy	Male		1.147402453	0.736249613	0.768607214	0.500985456	4.95 (1.99- 12.27)	0.74 (0.61- 0.84)
Botaitis 2012[32]	Conversion to open cholecystectomy	Previous upper abdominal surgery		1.224	0.491	0.820448392	0.333549536	2.69 (1.42- 5.12)	0.66 (0.56- 0.75)
Kim 2014[25]	Conversion to open cholecystectomy	Previous upper abdominal surgery		0.551176919	0.43345858	0.367863235	0.29068073	2.69 (1.42- 5.12)	0.66 (0.56- 0.75)
Utsumi 2017[29]	Conversion to open cholecystectomy	Previous upper abdominal surgery		1.84582669	0.85711675	1.245472532	0.595436864	2.69 (1.42- 5.12)	0.66 (0.56- 0.75)
Kim 2014[25]	Conversion to open cholecystectomy	Age	Continuous	0.049	0.022	0.032666957	0.014667159	1.03 (1.00- 1.05)	0.50 (0.50- 0.51)
Wevers 2013[30]	Conversion to open cholecystectomy	Age	Continuous	0.02	0.01	0.013333353	0.006666706	1.03 (1.00- 1.05)	0.50 (0.50- 0.51)
Kim 2014[25]	Conversion to open cholecystectomy	CRP	Continuous	0.086	0.028	0.057334904	0.018668408	1.04 (0.97- 1.12)	0.51 (0.49- 0.52)

Wevers 2013[30]	Conversion to open cholecystectomy	CRP	Continuous	0.01	0.003	0.006666669	0.002000002	1.04 (0.97- 1.12)	0.51 (0.49- 0.52)
Kim 2014[25]	Conversion to open cholecystectomy	Diabetes		0.122602322	0.539602232	0.081739431	0.361263002	0.97 (0.41- 2.28)	0.49 (0.36- 0.63)
Utsumi 2017[29]	Conversion to open cholecystectomy	Diabetes		-0.331357136	0.746379131	-0.220994473	0.501988807	0.97 (0.41- 2.28)	0.49 (0.36- 0.63)
Kim 2014[25]	Conversion to open cholecystectomy	Hypertension		-0.418816441	0.575333654	-0.279391974	0.386043784	0.67 (0.28- 1.56)	0.43 (0.30- 0.57)
Utsumi 2017[29]	Conversion to open cholecystectomy	Hypertension		-0.385262401	0.663683803	-0.256982545	0.445854693	0.67 (0.28- 1.56)	0.43 (0.30- 0.57)
Kim 2014[25]	Conversion to open cholecystectomy	Adhesion to the adjacent organs		2.038619547	0.432089561	1.379010398	0.30077363	7.68 (3.29- 17.91)	0.80 (0.69- 0.88)
Kim 2014[25]	Conversion to open cholecystectomy	Alkaline phosphatase	Continuous	0	0.005			1.00 (0.99- 1.01)	
Kim 2014[25]	Conversion to open cholecystectomy	ALT	Continuous	0	0.005			1.00 (0.99- 1.01)	
Kim 2014[25]	Conversion to open cholecystectomy	Angle of the gallbladder	Continuous	-0.02	0.016	-0.013333353	0.010666753	0.98 (0.95- 1.01)	0.50 (0.49- 0.50)
Utsumi 2017[29]	Conversion to open cholecystectomy	Antiplatelet or anticoagulant use for cardiovascular disease		1.41706602	0.699025295	0.951572514	0.478495124	4.13 (1.05- 16.23)	0.72 (0.50- 0.87)
Eldar 2002[33]	Conversion to open cholecystectomy	Artificial neural network (training data)		7.643589381	1.503300325	5.74571509	1.274311155	2087.22 (109.64- 39735.65)	1.00 (0.96- 1.00)
Eldar 2002[33]	Conversion to open cholecystectomy	Artificial neural network (validation data)		3.526360525	1.014599312	2.445141843	0.751583805	34.00 (4.65- 248.37)	0.92 (0.73- 0.98)
Kim 2014[25]	Conversion to open cholecystectomy	Associated organ dysfunction		1.714798428	0.842834723	1.155227417	0.583054135	5.56 (1.06- 28.98)	0.76 (0.50- 0.91)
Kim 2014[25]	Conversion to open cholecystectomy	AST	Continuous	0	0.008			1.00 (0.98- 1.02)	

Kim 2014[25]	Conversion to open cholecystectomy	Bilirubin	Continuous	-0.186	0.364	-0.124015882	0.243212736	0.83 (0.41-1.69)	0.47 (0.35- 0.59)
Kim 2014[25]	Conversion to open cholecystectomy	BMI		-0.094	0.07	-0.062668717	0.046674497	0.91 (0.79-1.04)	0.48 (0.46- 0.51)
Kim 2014[25]	Conversion to open cholecystectomy	Bulging of the abdominal muscle		1.025490024	0.648350284	0.68628987	0.439417297	2.79 (0.78-9.94)	0.67 (0.46- 0.82)
Bonaventura 2018[24]	Conversion to open cholecystectomy	Charlson Comorbidity Index	5	0.804699666	0.513146695	0.537743206	0.345700147	2.24 (0.82-6.11)	0.63 (0.47- 0.77)
Eldar 2002[33]	Conversion to open cholecystectomy	Discriminant analysis (training data)		0.78845736	0.378822509	0.526839607	0.254746995	2.20 (1.05-4.62)	0.63 (0.51- 0.74)
Eldar 2002[33]	Conversion to open cholecystectomy	Discriminant analysis (validation data)		0.893817876	0.803401858	0.597625124	0.544630187	2.44 (0.51-11.80)	0.65 (0.38- 0.84)
Kim 2014[25]	Conversion to open cholecystectomy	Hyperattenuation of adjacent parenchyma (multivariate model)		-0.479220284	0.470331106	-0.319751187	0.31530131	0.62 (0.25-1.56)	0.42 (0.28- 0.57)
Kim 2014[25]	Conversion to open cholecystectomy	Location of gallstone (cystic duct)		0.779	0.752	0.52049219	0.50833449	2.18 (0.50-9.52)	0.63 (0.38- 0.82)
Kim 2014[25]	Conversion to open cholecystectomy	Location of gallstone (fundus or body)		0.489	0.501	0.326287897	0.336029573	1.63 (0.61-4.35)	0.58 (0.42- 0.73)
Kim 2014[25]	Conversion to open cholecystectomy	Location of gallstone (neck)		0.982	0.554	0.656978297	0.374632929	2.67 (0.90-7.91)	0.66 (0.48- 0.80)
Eldar 2002[33]	Conversion to open cholecystectomy	logistic regression (training data)		1.375967247	2.008561096	0.923601863	1.419408888	3.96 (0.08-202.89)	0.72 (0.13- 0.98)
Eldar 2002[33]	Conversion to open cholecystectomy	logistic regression (validation data)		1.484274769	2.035758759	0.997383826	1.442402874	4.41 (0.08-238.48)	0.73 (0.14- 0.98)
Kim 2014[25]	Conversion to open cholecystectomy	Mirrizi syndrome		1.025490024	0.648350284	0.68628987	0.439417297	2.79 (0.78-9.94)	0.67 (0.46- 0.82)
Kim 2014[25]	Conversion to open cholecystectomy	Mucosal disruption		1.143732724	0.40893531	0.766125965	0.277034387	3.14 (1.41-7.00)	0.68 (0.56- 0.79)

Kim 2014[25]	Conversion to open cholecystectomy	Perforation		0.700067623	0.708707924	0.467553992	0.478135601	2.01 (0.50- 8.08)	0.61 (0.38- 0.80)
Kim 2014[25]	Conversion to open cholecystectomy	Pericholecystic fluid (multivariate model)		2.846	0.701	1.949223526	0.504379057	17.22 (4.36- 68.03)	0.88 (0.72- 0.95)
Kim 2014[25]	Conversion to open cholecystectomy	Preoperative biliary intervention		1.171182982	0.517126053	0.784691465	0.35096246	3.23 (1.17- 8.89)	0.69 (0.52- 0.81)
Kim 2014[25]	Conversion to open cholecystectomy	Short-axis diameter	Continuous	0.737	0.268	0.492315414	0.179903934	2.09 (1.24- 3.53)	0.62 (0.53- 0.70)
Kim 2014[25]	Conversion to open cholecystectomy	Wall thickening	Continuous	0.104	0.071	0.06933611	0.04734241	1.11 (0.97- 1.28)	0.52 (0.49- 0.54)
Kim 2014[25]	Conversion to open cholecystectomy	WBC	Continuous	0.049	0.041	0.032666957	0.027334716	1.05 (0.97- 1.14)	0.51 (0.49- 0.52)

Table S3 Risk of bias and applicability concerns in included studies

Study name	Participants	Risk of bias				Applicability	
		Predictors	Outcomes	Analysis	Participants	Predictors	Outcomes
Amirthalingam 2017[23]	-	?	?	-	+	?	?
Bonaventura 2018[24]	-	?	?	-	+	?	+
Botaitis 2012[32]	?	?	?	-	+	?	?
Eldar 2002[33]	?	?	?	-	+	?	+
Kim 2014[25]	-	?	?	-	+	?	+
Lauro 2018[26]	-	?	?	-	+	?	+
Lorenzon 2017[27]	-	?	?	-	+	?	+
Nikfarjam 2014[28]	-	?	?	-	+	?	?
Teckchandani 2010[22]	+	?	?	-	+	+	+
Utsumi 2017[29]	-	?	?	-	+	?	+
Wevers 2013[30]	-	?	?	-	+	?	?
Yokoe 2017[31]	-	?	?	-	+	?	+

Main reasons

Participants: retrospective study

Predictors: predictor measurement was not defined clearly for most predictors and blinding of predictor measurement was not reported

Outcomes: outcome measurement was not defined clearly for most outcomes and blinding of outcome measurement was not reported

Analysis: the number of participants with outcomes was less than 100 or the threshold was determined by optimal threshold

Participants: there were no concerns about whether the included participants were different from the clinical setting

Predictors: it was not clear whether predictors were measured in the same way as they would be measured in clinical practice, for example, on admission

Outcomes: it was not clear whether outcomes were measured in the same way as they would be measured in clinical practice, for example, the complications.

Table S2 Characteristics of included studies

Study name	Country	Prospective or retrospective	Number of patients who met inclusion criteria	Number of patients excluded (%) and reasons for exclusion	Number included for analysis	Mean age (years)	Females (%)	Cholecystectomy (%)	Started as open (%)	Conversion to open cholecystectomy (%)	Timing
Amirthalingam 2017[23]	Singapore	Retrospective	149	0	149	58	67 (45.0%)	149 (100.0%)	0 (0.0%)	8 (5.4%)	Early
Bonaventura 2018[24]	Italy	Retrospective	271	Not reported	271	67	169 (62.4%)	271 (100.0%)	41 (15.1%)	27 (11.7%)	240 (89%) had early surgery
Botaitis 2012[32]	Greece	Not stated	315	Not reported	315	53	214 (67.9%)	315 (100.0%)	0 (0.0%)	60 (19.0%)	Early
Eldar 2002[33]	Israel	Not stated	225	0	225	56	128 (56.9%)	225 (100.0%)	0 (0.0%)	44 (19.6%)	Early
Kim 2014[25]	South Korea	Retrospective	195	12 (06%) Reasons: lack of adequate CT scan imaging	183	60	71 (38.8%)	183 (100.0%)	0 (0.0%)	30 (16.4%)	Median interval between CT scan and surgery was 7 days
Lauro 2018[26]	Italy	Retrospective	464	Not reported	464	59	196 (42.2%)	464 (100.0%)	59 (12.7%)	51 (12.6%)	Not stated
Lorenzon 2017[27]	Italy	Retrospective	93	8 (09%) Reasons: did not undergo gallbadder removal	85	75	36 (42.4%)	85 (100.0%)	39 (45.9%)	Not reported	Early
Nikfarjam 2014[28]	Australia	Retrospective	443	32 (07%) Reasons: did not undergo gallbadder removal	411	Not reported	216 (52.6%)	411 (100.0%)	18 (4.4%)	38 (9.7%)	Early
Teckchandani 2010[22]	India	Prospective	50	Not reported	50	38	46 (92.0%)	50 (100.0%)	0 (0.0%)	8 (16.0%)	Early
Utsumi 2017[29]	Japan	Retrospective	53	Not reported	53	74	24 (45.3%)	53 (100.0%)	0 (0.0%)	12 (22.6%)	41 (77.4%) had surgery within 72 hours of admission
Wevers 2013[30]	Netherlands	Retrospective	261	Not reported	261	56	155 (59.4%)	261 (100.0%)	0 (0.0%)	62 (23.8%)	Early

Yokoe 2017[31]	Japan and Taiwan	Retrospective	5459	1099 (20%) Reasons: missing data	4360	68	Not reported	3325 (76.3%)	969 (29.1%)	248 (10.5%)	Not stated

CT = computed tomography

Only one trial Lorenzon 2017[27] included solely patients about 65 years. The remaining trials included adult patients of all age groups and did not report the proportion of patients above 65 years.

Comorbidities were reported differently in different trials; therefore, it is not possible to estimate the proportion of patients with comorbidities in the trials

Teckchandani 2010[22]: cholecystectomy had to be abandoned because of phlegmon formation in two patients

Table S1. Search strategies for identification of studies

Database	Timespan	Search strategy
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library (Wiley)	Issues 1, April 2019	#1 MeSH descriptor: [Frail Elderly] explode all trees #2 MeSH descriptor: [Frailty] explode all trees #3 frail* #4 MeSH descriptor: [Prognosis] explode all trees #5 MeSH descriptor: [Models, Statistical] explode all trees #6 diagnosed or cohort or predictor or death #7 #1 or #2 or #3 or #4 or #5 or #6 #8 laparoscop* or celioscop* or coelioscop* or abdominoscop* or peritoneoscop* #9 cholecystecto* or colecystecto* #10 #8 and #9 #11 MeSH descriptor: [Cholecystectomy, Laparoscopic] explode all trees #12 #10 or #11 #13 cholecystitis or colecystitis or colecistitis*

		#14 MeSH descriptor: [Cholecystitis, Acute] explode all trees #15 MeSH descriptor: [Cholecystitis] explode all trees #16 #13 or #14 or #15 #17 #12 and #16 #18 #7 AND #17
Medline (PubMed)	Until 27th April 2019	1. exp Frail Elderly/ or exp Frailty/ 2. frail*.ti,ab. 3. prognosis.sh. or diagnosed.tw. or cohort:.mp. or predictor:.tw. or death.tw. or exp models, statistical/ 4. 1 or 2 or 3 5. (laparoscop* or celioscop* or coelioscop* or abdominoscop* or peritoneoscop*).ti,ab. 6. (cholecystecto* or colecystecto*).ti,ab. 7. 5 and 6 8. exp Cholecystectomy, Laparoscopic/ 9. 7 or 8 10. (cholecystitis or colecystitis or colecistitis*).ti,ab.

		11. exp Cholecystitis/ or exp Cholecystitis, Acute/ 12. 10 or 11 13. 9 and 12 14. 4 and 13
EMBASE (OvidSP)	Until 27th April 2019	1. exp frailty/ 2. frail*.ti,ab. 3. follow-up.mp. or prognos:.tw. or ep.fs. 4. 1 or 2 or 3 5. (laparoscop* or celioscop* or coelioscop* or abdominoscop* or peritoneoscop*).ti,ab. 6. exp laparoscopic surgery/ 7. 5 or 6 8. (cholecystecto* or colecystecto*).ti,ab. 9. exp cholecystectomy/ 10. 8 or 9 11. 7 and 10 12. (cholecystitis or colecystitis or colecistitis*).ti,ab. 13. exp acute cholecystitis/ 14. 12 or 13 15. 4 and 14
WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx)	Until 27th April 2019	Condition: Acute cholecystitis

		Title: frail* OR diagnosed OR cohort OR predictor OR death
ClinicalTrials.gov	Until 27th April 2019	frail* OR diagnosed OR cohort OR predictor OR death | Acute Cholecystitis
Science Citation Index Expanded (SCI Expanded) (ISI Web of Knowledge)	Until 27th April 2019	#1 TS=(frail* OR diagnosed or cohort or predictor or death) #2 TS=(laparoscop* or celioscop* or coelioscop* or abdominoscop* or peritoneoscop*) #3 TS=(cholecystecto* OR colecystecto*) #4 TS=(cholecystitis OR colecystitis OR colecistitis*) #5 #4 AND #3 AND #2 AND #1

Supplementary figures

Figure SF1 Mortality, major, and minor complications (binary predictors)

The figure shows the odds ratio and 95% confidence intervals (CI) for binary predictors or predictors that have been dichotomised. If the confidence intervals do not overlap 1, then the factor has significant predictive ability. The thresholds used are indicated at the end of the prognostic factor or predictive model.

Figure SF2 All complications (binary and continuous predictors)

The figures shows the odds ratio and 95% confidence intervals (CI) for binary predictors, predictors that have been dichotomised, and continuous predictors. If the confidence intervals do not overlap 1, then the factor has significant predictive ability. The thresholds used are indicated at the end of the prognostic factor or predictive model. The figures have been split for better readability of text.

Figure SF3 Conversion to open cholecystectomy (binary and continuous predictors)

The figures shows the odds ratio and 95% confidence intervals (CI) for binary predictors, predictors that have been dichotomised, and continuous predictors. If the confidence intervals do not overlap 1, then the factor has significant predictive ability. The thresholds used are indicated at the end of the prognostic factor or predictive model. The figures have been split for better readability of text.

Figure SF4 Ordinal predictors

The figures shows the odds ratio and 95% confidence intervals (CI) for ordinal predictors that were reported in only one study. If the confidence intervals do not overlap 1, then the factor has significant predictive ability. The thresholds used are indicated at the end of the prognostic factor or predictive model. The figures have been split for better readability of text.

Appendices

Appendix 1. Schema used to assess the risk of bias

Participants (risk of bias)

- Low risk of bias (all conditions should be met): the study was prospective cohort study; the study included only acute cholecystitis; no inappropriate exclusion of participants (for example, based on severity); no inappropriate inclusion of participants in whom the outcome is already present.
- High risk of bias (at least one of the following criteria are met): the study was a retrospective cohort study, registry data, case-control studies; the study included other people in addition to acute cholecystitis; participants were excluded based on severity.
- Moderate risk of bias (at least one of the following criteria are met but the criteria for high risk of bias are not met): the study design was not clear; it was not clear if other people in addition to acute cholecystitis were included; it was not clear whether participants were excluded based on the severity of acute cholecystitis.

Participants (applicability concerns)

- Low risk of bias: there were no concerns that the participants or setting in the study did not match the review question.
- High risk of bias: there were concerns that the participants or setting in the study did not match the review question.
- Unclear risk of bias: it was unclear if the participants or setting in the study matched the review question.

Predictors (risk of bias)

- Low risk of bias (all criteria are met): the components of the prognostic scoring system/prognostic factors were measured using appropriate methods in all participants; the components of the prognostic scoring system/prognostic factors were measured in the same way in all the participants; the components of the prognostic scoring system/prognostic factors were measured blinded to the outcome; the predictors were measured at < 72 hours of admission.
- High risk of bias (at least one of the following criteria are met): there are concerns in the way components of the prognostic scoring system were measured; the components of the prognostic scoring system were not measured in the same way in all the participants; the components of the prognostic scoring system were measured without any blinding to the outcome; the predictors were measured at the appropriate time.
- Moderate risk of bias (at least one of the following criteria are met but the criteria for high risk of bias are not met): the method of measurement of the components of the prognostic scoring system was not reported; it was not clear whether the components of the prognostic scoring system were measured in the same way in all the participants; it was not clear whether the components of the prognostic scoring system were measured blinded to the outcome; timing of measurement was not clear or highly variable.

Predictors (applicability concerns)

- Low risk of bias: there were no concerns that the predictors were measured in a way that would not routinely used in clinical practice.
- High risk of bias: there were concerns that the predictors were measured in a way that would not routinely used in clinical practice.

- Unclear risk of bias: it was unclear if the predictors were measured in a way that would not routinely used in clinical practice.

Outcomes (risk of bias)

- Low risk of bias (all criteria are met): the outcome was defined appropriately in all participants; the outcome was defined using prespecified or standard definition; the predictors were not included in the outcome definition; the same definition of the outcome was used in all the participants; the outcome assessment was blinded to the level of the prognostic scoring system; the time interval between the predictor measurement and outcome measurement was appropriate.
- High risk of bias (any criteria are met): there are concerns in the way the outcome was defined; the predictors were included in the outcome definition; different definitions of the outcome was used in different participants; the outcome assessors were aware of the level of the prognostic scoring system; the time interval between the predictor measurement and outcome measurement was inappropriate.
- Moderate risk of bias (at least one of the following criteria are met but the criteria for high risk of bias are not met): the definition of the outcome was not reported; it was not clear whether the predictors were included in the definition of the outcomes; it was not clear whether the outcome was measured in the same way in all the participants; it was not clear whether the outcome assessors were blinded to the level of the prognostic scoring system.

Outcomes (applicability concerns)

- Low risk of bias: there were no concerns that the outcomes were measured in a way that would not routinely used in clinical practice.
- High risk of bias: there were concerns that the outcomes were measured in a way that would not routinely used in clinical practice.

- Unclear risk of bias: it was unclear if the outcomes were measured in a way that would not routinely used in clinical practice.

Analysis (risk of bias)

- Low risk of bias (all criteria are met): the number of participants with outcome was more than 100; the continuous predictors were not converted into two or more categories (applicable only for prognostic modelling studies); all participants were included in the analysis or appropriate methods such as multiple imputation were used to handle missing data; predictors were not selected into model based on univariate analysis (applicable only for model development studies); modelling was performed appropriately (for example, Cox regression for time-to-event outcomes and adjustment for sample fraction in studies where only a fraction of the sample is included in the analysis); information on model performance i.e. calibration (how well the actual and predicted risks compare) and discrimination (how well the model distinguishes people with and without outcome) were available; the choice of threshold was prespecified.
- High risk of bias (any criteria are met): the number of participants with outcome was <= 100; some participants were excluded from the analysis (for example, because the predictors or outcomes were unclear or not available) and multiple imputation was not performed; predictors were selected into model based on univariate analysis (applicable only for model development studies); model was performed inappropriately (see above examples for appropriate modelling); no information was available on model performance (either calibration or discrimination); the choice of the threshold was not prespecified and based on optimal threshold.
- Moderate risk of bias (at least one of the following criteria are met but the criteria for high risk of bias are not met): it was not clear whether continuous variables were converted into categorical variables; it was not clear whether all participants were included in the analysis;

the selection of predictors into model was not clear (applicable only for model development studies); the reason for the choice of threshold was not reported.

Figures

Figure 1 Study flow diagram

The figure shows the reference flow.

Figure 2 Ordinal predictors

Meta-analysis showing the odds ratio and 95% confidence intervals for ordinal prognostic factors with at least two studies reporting the outcome. Tokyo Guidelines 2013 (TG13) grading was the only ordinal prognostic factor which had at least two studies. TG13 Grade 3 increased the risk of all-cause mortality compared to grade 1. There was no evidence of significant discriminatory ability for TG13 grade 2 versus grade 1 for either all-cause mortality or conversion to open cholecystectomy or TG13 grade 2 versus grade 1 for all-cause mortality.

Figure 3 All complications (binary predictors)

Meta-analysis of all complications showing the odds ratio and 95% confidence intervals for binary prognostic factors with at least two studies reporting the outcome. Male gender had good discriminatory ability to predict 'all complications', but there was no evidence of significant discriminatory ability for previous upper abdominal surgery to predict 'all complications'.

Figure 4 Conversion to open cholecystectomy (binary and continuous predictors)

Meta-analysis of conversion to open cholecystectomy showing the odds ratio and 95% confidence intervals for binary and continuous prognostic factors with at least two studies reporting the outcome. Male gender, previous upper abdominal surgery, and age had good discriminatory ability to predict conversion, but there was no evidence of significant discriminatory ability for diabetes or hypertension to predict conversion.

Tables

Table 1 Prognostic factors or risk prediction models and outcomes in included studies

Study name	Prognostic factor or prediction model studied	Outcomes reported	Number of participants	Deaths	Major complications	Minor complications	All complications	Laparoscopic cholecystectomy
Amirthalingam 2017[23]	TG13	All-cause mortality; conversion to open cholecystectomy; major complications	149	1/149 (0.7%)	1/149 (0.7%)	Not reported	8/149 (5.4%)	8/149 (5.4%)
Bonaventura 2018[24]	Charlson Co-morbidity Index	All complications; all-cause mortality; conversion to open cholecystectomy; major complications; minor complications	271	4/271 (1.5%)	9/271 (3.3%)	13/271 (4.8%)	22/271 (8.1%)	27/230 (11.7%)
Botaitis 2012[32]	Age; ALT; AST; male; previous upper abdominal surgery; temperature; previous upper abdominal surgery	All complications; conversion to open cholecystectomy	315	Not reported	Not reported	Not reported	18/315 (5.7%)	60/315 (19.0%)
Eldar 2002[33]	Artificial neural network; discriminant analysis; logistic regression	Conversion to open cholecystectomy	225	Not reported	Not reported	Not reported	Not reported	44/225 (19.6%)
Kim 2014[25]	Adhesion to the adjacent organs; age; alkaline phosphatase; ALT; angle of the gallbladder; associated organ dysfunction; AST; bilirubin; BMI; bulging of the abdominal muscle; CRP;	Conversion to open cholecystectomy	183	Not reported	Not reported	Not reported	Not reported	30/183 (16.4%)

	diabetes; hyperattenuation of adjacent parenchyma; hypertension; location of gallstone (cystic duct); location of gallstone (fundus or body); location of gallstone (neck); male; Mirizzi syndrome; mucosal disruption; perforation; pericholecystic fluid; preoperative biliary intervention; previous upper abdominal surgery; short-axis diameter; wall thickening; WBC							
Lauro 2018[26]	BMI	All complications; all-cause mortality; conversion to open cholecystectomy; major complications; minor complications	464	3/464 (0.6%)	21/464 (4.5%)	34/464 (7.3%)	55/464 (11.9%)	51/405 (12.6%)
Lorenzon 2017[27]	Charlson Co-morbidity Index; frailty score; P-Possum physiology score; SAPS-II	All complications	85	Not reported	Not reported	Not reported	18/85 (21.2%)	Not stated/46 ()
Nikfarjam 2014[28]	Age; albumin; bilirubin; chronic liver disease; chronic obstructive airway disease; chronic renal failure; diabetes; Glucocorticosteroid use; haemoglobin; hypotension; ischaemic heart disease; male; platelets; previous biliary colic; previous upper abdominal surgery; temperature; WBC; age	All complications; all-cause mortality	411	5/411 (1.2%)	Not reported	Not reported	66/411 (16.1%)	38/393 (9.7%)
Teckchandani 2010[22]	Male	Conversion to open cholecystectomy	50	Not reported	Not reported	Not reported	Not reported	8/50 (16.0%)
Utsumi 2017[29]	Antiplatelet or anticoagulant use for cardiovascular disease; diabetes; hypertension; male; previous upper abdominal surgery	Conversion to open cholecystectomy	53	Not reported	Not reported	Not reported	Not reported	12/53 (22.6%)
Wevers 2013[30]	Age; ASA; CRP; regression model	All complications; conversion to open	261	31/261 (11.9%)	Not reported	Not reported	Not reported	62/261 (23.8%)

		cholecystectomy						
Yokoe 2017[31]	Number of organs dysfunctioning; TG13	All-cause mortality; conversion to open cholecystectomy	4360	65/4360 (1.5%)	Not reported	Not reported	Not reported	248/2356 (10.5%)
Median and quartiles			**243 (133-339)**	**1.3% (0.8%-1.5%)**	**3.3% (2.0%-3.9%)**	**6.1% (5.4%-6.7%)**	**10.0% (6.3%-15.0%)**	**16.0% (11.1%-19.3%)**
Abbreviations: **TG 13 = Tokyo Guidelines 2013** **ALT = Alanine Aminotransferase** **AST = Aspartate Aminotransferase** **BM = Body Mass Index** **CRP = C-Reactive Protein** **WBC = White Blood Count** **SAPS-II = Simplified Acute Physiology Score II** **ASA = The American Society of Anesthesiologists**								