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A risk score model to predict incidental gallbladder cancer in patients scheduled for cholecystectomy

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ABSTRACT

Background: Gallbladder cancer (GBC) has a poor prognosis. The aim was to develop and validate a preoperative risk score for incidental gallbladder cancer (IGBC) in patients scheduled for cholecystectomy.

Methods: Data registered in the nationwide Swedish Registry for Gallstone Surgery (GallRiks) was analyzed, including the derivation cohort (n = 28915, 2007–2014) and the validation cohort (n = 7851, 2014–2016). An additive risk score model based on odds ratio was created.

Results: The scoring model to predict IGBC includes age, female gender, previous cholecystitis, and either jaundice or acute cholecystitis. The calibration by HL test and discrimination by AUROC was 8.27 ($P = 0.291$) and 0.76 in the derivation cohort (214 IGBC) and 14.28 ($P = 0.027$) and 0.79 in the validation cohort (35 IGBC). The scoring system was applied to three risk-groups, based on the risk of having IGBC, eg. the high-risk group (>8 points) included 7878 patients, with 154 observed and 148 expected IGBC cases.

Conclusion: We present the first risk score model to predict IGBC. The model estimates the expected risk for the individual patient and may help to optimize treatment strategies.

Introduction

Gallbladder cancer is a rare event.[1,2] It is usually discovered at an advanced stage[1,2] and 5-year overall survival rate is 5–13%.[1,3–6] If diagnosed at an early stage, the prognosis changes dramatically, with a 5-year survival rate up to 99% for T1aN0 cases and 70% for T2N0.[7,8] Most cases of gallbladder cancer (70%) are diagnosed incidentally in patients operated for benign gallbladder disease.[4,9] Surgery is still, despite advances in chemotherapy, the only potentially curative treatment option.[5,10]

In a previous study,[11] we identified five risk factors for incidental gallbladder cancer including; age ≥ 65 years, female gender, previous cholecystitis, and the combination of acute cholecystitis without jaundice or jaundice without acute cholecystitis. Several of these risk factors have also been identified in other publications[12,13,14] and Koshenkov et al.[15] formed a non-validated model based on three risk variables (age ≥65 years, dilated bile ducts and gallbladder wall thickening).

To our knowledge there is no previous risk score model to predict incidental gallbladder cancer. In the field of gallbladder surgery and gallbladder cancer a couple of risk score models have been published. Ethun et al.[16] has created a model to predict locoregional residual and distant disease at reoperation to estimate overall survival in incidental gallbladder cancer patients. Other risk score models have been developed for e.g. pancreatic cancer[17,18] and for prediction of prolonged operative time during cholecystectomy in patients with benign gallbladder disease.[19]

The aim of this study was to construct and validate a risk score model to predict incidental gallbladder cancer in patients scheduled for cholecystectomy for benign gallbladder disease.

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Material and methods

Data source

Data from cholecystectomies registered in GallRiks, the Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP)[20] was analyzed. A derivation cohort including patients that underwent surgery between January 1, 2007 and September 30, 2014, and a validation cohort including patients operated between October 1, 2014 and November 29, 2016 was created.

GallRiks is web-based, and the surgeon responsible for the procedure reports patient characteristics, indications for operation, surgical method, and intraoperative complications online. It is mandatory to respond to these questions in the registry. Also, 30-day follow-up is mandatory and performed by a non-physician coordinator at each participating hospital.[21] GallRiks consists of 466 pre-, intra-, and postoperative variables.

Study population

Inclusion criteria was age ≥40 years. Exclusion criteria were if the gallbladder had not been sent for histopathological analysis or the result was missing, if the cholecystectomy was performed for another indication than gallbladder disease, if the indication for cholecystectomy was secondary to another major procedure or performed on the preoperative suspicion of gallbladder cancer or gallbladder polyps, and if the patient had another rare malignancy in the gallbladder.

Finally, the derivation cohort consisted of 28915 patients and the validation cohort of 7851 patients. The derivation cohort, except patients <40 years of age that are excluded in the present study, are included in the study population of independent risk factors for incidental gallbladder cancer in a previous publication.[11]

Study design

The variables for the risk score model were identified in our previous publication using univariable and multivariable analysis.[11] The logistic regression method was used to test for possible interaction. For each identified interaction, we constructed a multiple dichotomous variable (a composite variable), representing the interaction, and recalibrated a separate model, including the multiple dichotomous variable and the same covariates as in the main effect model.

Logistic regression was used to recalibrate the results from our previous publication, since we in the present scoring model included patients ≥40 years of age, divided in 10-year age interval groups. An additive risk score model was created based on the odds ratio, achieved from the logistic regression modelling, using the predictors for incidental gallbladder cancer. This was performed in a similar statistic approach as in the EuroSCORE risk model.[22] The patients were divided, based on quartiles, into a low-risk group, intermediate-risk group and a high-risk group.

Statistical analysis

Data are presented as means with standard deviation, median with interquartile range (IQR) and frequency as appropriate. Unpaired Mann-Whitney U-tests were used to compare continuous variables and χ^2 tests were used to compare categorical variables among groups. Logistic regression was performed to recalibrate the model. The points in the scoring model were estimated from the odds ratio in the derivation cohort. The Hosmer-Lemeshow goodness-of-fit test, was used performed with six groups, to assess predictive accuracy and the area under the receiver-operating curve (AUROC) for the discriminatory power for incidental gallbladder cancer.

All statistical analysis and graphs were conducted using the Stata MP, version 15.1, 2018 statistical package for Mac OS X (StataCorp LP, College Station, TX).

Ethics were approved by the Regional Ethical Committee in Lund (2014/175).

Results

In the derivation cohort 214 (0.74%) patients were diagnosed with incidental gallbladder cancer compared to 35 (0.45%) patients in the validation cohort, $P = 0.039$. Distribution of the included variables for both groups are presented in Table 1.

From the recalibrated logistic regression model, odds ratio (OR) was calculated. Age>80 years resulted in the highest OR of 16 (CI: 8.9–30, P=<0.001). Female gender resulted in an OR of 3.7 (CI: 2.6–5.2, $P < 0.001$) and elevated bilirubin levels/no acute cholecystitis in an OR of 2.1 (CI:1.2–3.5, $P = 0.010$), Table 2.

An additive risk model was created, based on odds ratio, that was rounded up to a point system; <60 years: 0 points, 60–69 years: 3.5 points, 70–79 years: 6.5 points, ≥80 years: 16 points, female gender: 3.5 points, previous cholecystitis: 1.5 points, acute cholecystitis/no elevated bilirubin levels: 1.5 points and elevated bilirubin levels/no acute cholecystitis: 2.0 points (Fig. 1).

Further, three risk groups were created, based on quartiles; a low-risk group 0–3 points (n = 7149), an intermediate-risk group 3.5–8 points (n = 21739) and a high-risk group >8 points (n = 7878). In the low-risk group 8 IGBC patients were observed, whereas 18 IGBC patients were expected, in the intermediate-risk group 87 were observed and 108 were expected, and in the high-risk group 154 were observed and 148 were expected.

A high score group based on the ROC curve was created, including patients with >12 points (e.g. a 71-year old woman with previous cholecystitis and elevated bilirubin level). The group consisted of a total of 2080 patients, 67 with IGBC and 87 were expected, meaning a predicted incidence for IGBC of 4.2%.

The AUROC for predicting incidental gallbladder cancer using the scoring model was 0.76 (95% CI 0.725–0.79) in the derivation cohort and 0.79 (95% CI 0.73–0.85), $P = 0.363$ in the validation cohort (Fig. 2). The corresponding calibration (HL-test) was 8.27, $P = 0.219$ and 14.28, $P = 0.027$, respectively.

Discussion

In this paper, we present a risk score model to predict gallbladder cancer in patients scheduled for cholecystectomy on benign indications. The model is based on five, easily registered clinical variables. It is easy to use and can be applied in everyday work at a surgical department to assist in predicting the risk of gallbladder cancer.

Table 1
Patient characteristics in the derivation and validation cohort.

	Derivation cohort (n = 28915)	Validation cohort (n = 7851)
Age (years)	59 ± 12	61 ± 12
Female gender	16 482 (57)	4259 (54)
Previous cholecystitis	5845 (20)	1496 (19)
Acute cholecystitis	8443 (29)	2739 (35)
Elevated bilirubin level[a]	2829 (10)	966 (12)

[a] P-Bilirubin elevation (>50 mmol/L) and/or bile duct stones. Values in parentheses are percentages.

Table 2
Multivariable risk factors for incidental gallbladder cancer, including 28915 patients.

Risk variable	Odds ratio (95% confidence interval)	*P*-value
40–49 years	1	
50–59 years	1.6 (0.9–3.2)	0.138
60–69 years	3.6 (2.0–6.4)	<0.001
70–79 years	6.5 (3.6–12)	<0.001
>80 years	16 (8.8–30)	<0.001
Female gender	3.6 (2.6–5.1)	<0.001
Previous cholecystitis	1.5 (1.1–2.0)	0.023
No elevated bilirubin level/no acute cholecystitis	1	
No elevated bilirubin level/acute cholecystitis	1.4 (1.0–1.9)	0.037
Elevated bilirubin level[a]/no acute cholecystitis	2.1 (1.2–3.5)	0.006
Elevated bilirubin level/acute cholecystitis	1.5 (0.88–2.5)	0.143

[a] P-Bilirubin elevation (>50 mmol/L) and/or bile duct stones.

The GallRiks registry that was used to develop this model is unique in many ways. It is a registry for gallstone intervention. Important parameters, besides more usual ones, are registered, such as suspicion of malignancy preoperatively, making it possible to study real incidental cases of gallbladder cancer, and the result of the surgeon's inspection of the gallbladder during or directly after surgery. It provides data from more than 90% of the centers in Sweden, the coverage is reported annually and the validation is good.[21] Cholecystectomy is a common surgical procedure and most patients have a benign diagnosis.[23] Previously known risk factors for gallbladder cancer such as porcelain gallbladder and polyps ≥10 mm are indications for prophylactic cholecystectomy.[24,25] It is of great clinical importance to predict the risk for gallbladder cancer in the large population of patients scheduled for cholecystectomy on benign indications.

The present risk model is highly dependent on the patients age, and the highest points are achieved if the patient is over 80 years old. The model starts at a patient age of 40 years, since the aim is to present a clinical applicable model and gallbladder cancer is uncommon in young people. Age has in previous studies been shown to be a risk factor.[11,26] Female gender is the second most significant factor followed by elevated bilirubin level without concomitant acute cholecystitis. Female gender has in previous single center reports also been described as a risk factor.[12] Elevated bilirubin has not been presented as a risk factor except in our previous study[11] but e.g. dilated bile ducts which can support our findings.[15,26] The last two risk factors in our model were acute cholecystitis without elevated bilirubin and chronic cholecystitis. Whereas acute cholecystitis has been presented as a risk factor[13] chronic cholecystitis has not. However, some studies present gallbladder wall thickening as a risk factor,[15,27] which can be seen both in acute and chronic inflammation.

To more easily assess the scoring points to an individual patient the risk score was grouped. By separating the patients into three risk categories, the surgeon can estimate the risk of gallbladder cancer in a patient scheduled for a cholecystectomy on benign gallstone related pain or complications. The incidence of gallbladder cancer is low, which makes it difficult for a scoring model to identify these patients.[1,2] However, the odds ratio in the high-risk group was 18 and the AUROC of 0.79 in the validation cohort. This implies information that can be of value in the clinical situation. Especially since the prognosis of gallbladder cancer changes dramatically when diagnosed at an early stage.[7,8]

If a patient proves to have a high risk of gallbladder cancer some actions can be made, including additional preoperative imaging with e.g. contrast-enhanced ultrasound (CEUS),[28] computed

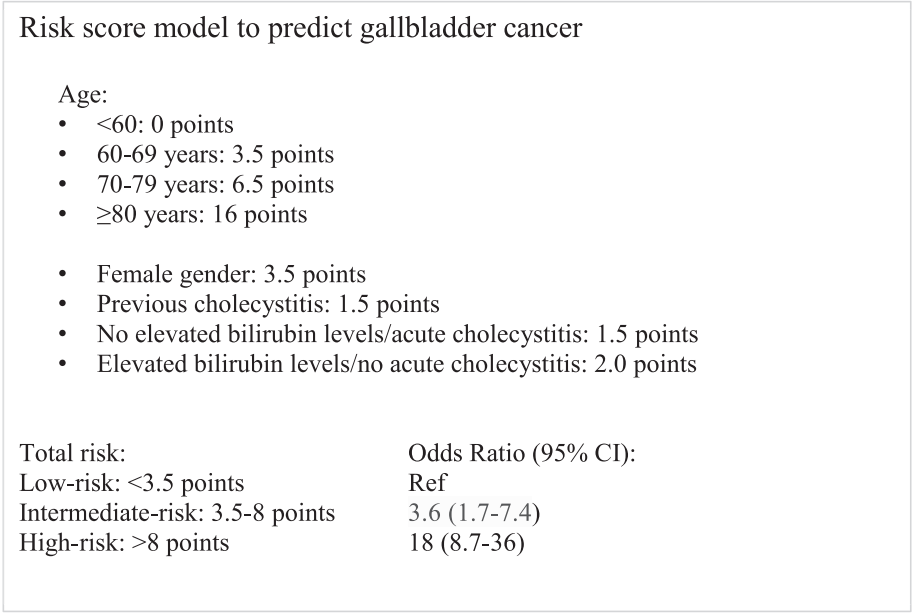

Fig. 1. Risk score model for incidental gallbladder cancer. The values for each factor are added to a total risk score, ranging from <3.5 points to >8 points. The patients are separated into either low-, intermediate-or high-risk group based on their total risk score.

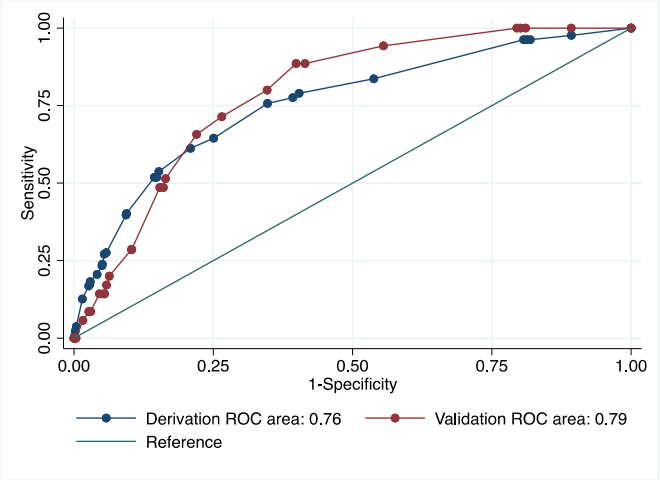

Fig. 2. The risk score model's receiver operation curve (ROC) for the derivation (blue line) and validation (red line) cohort, with no difference between the area under curve for the two groups, $P = 0.363$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tomography (CT) scan or magnetic resonance imaging (MRI). Furthermore, the physician in charge can ensure that the cholecystectomy is performed during daytime by an experienced surgeon. It is also important to avoid perforation of the gallbladder, since intraoperative bile spillage is known to significantly worsen the prognosis.[26] Also, the postoperative gross exam of the gallbladder done by the surgeon, should be more carefully performed in high risk patients.

The results of this study carry limitations associated with the retrospective analysis of a registry database, the quality of the source data, the number of missing data, and the lack of standardization associated with multicenter studies (such as sending the gallbladder to histopathological evaluation). Further, some interesting data is not entered in the register including tumor markers, gallbladder wall thickening and the results of ultrasonography. Also, the incidence of IGBC was lower in the validation cohort, which explains why the model was less calibrated according to the HL test.

The strengths of the study include the high-quality register data. The patient characteristics are similar in both cohorts, making the validation reliable. The validation cohort is an external group of patients that is close in time to the derivation cohort.

Conclusions

We introduce the first risk score model to predict gallbladder cancer in patients that are planned for cholecystectomy for a benign indication. The model was validated through a separate cohort and has an ability to predict incidental gallbladder cancer in adult patients before surgery. It can be used to distinguish patients with greater risk for cancer, making it possible to optimize the preoperative investigations and the treatment strategies.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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