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CHAPTER 10

External validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model to predict operative risk in perihilar cholangiocarcinoma

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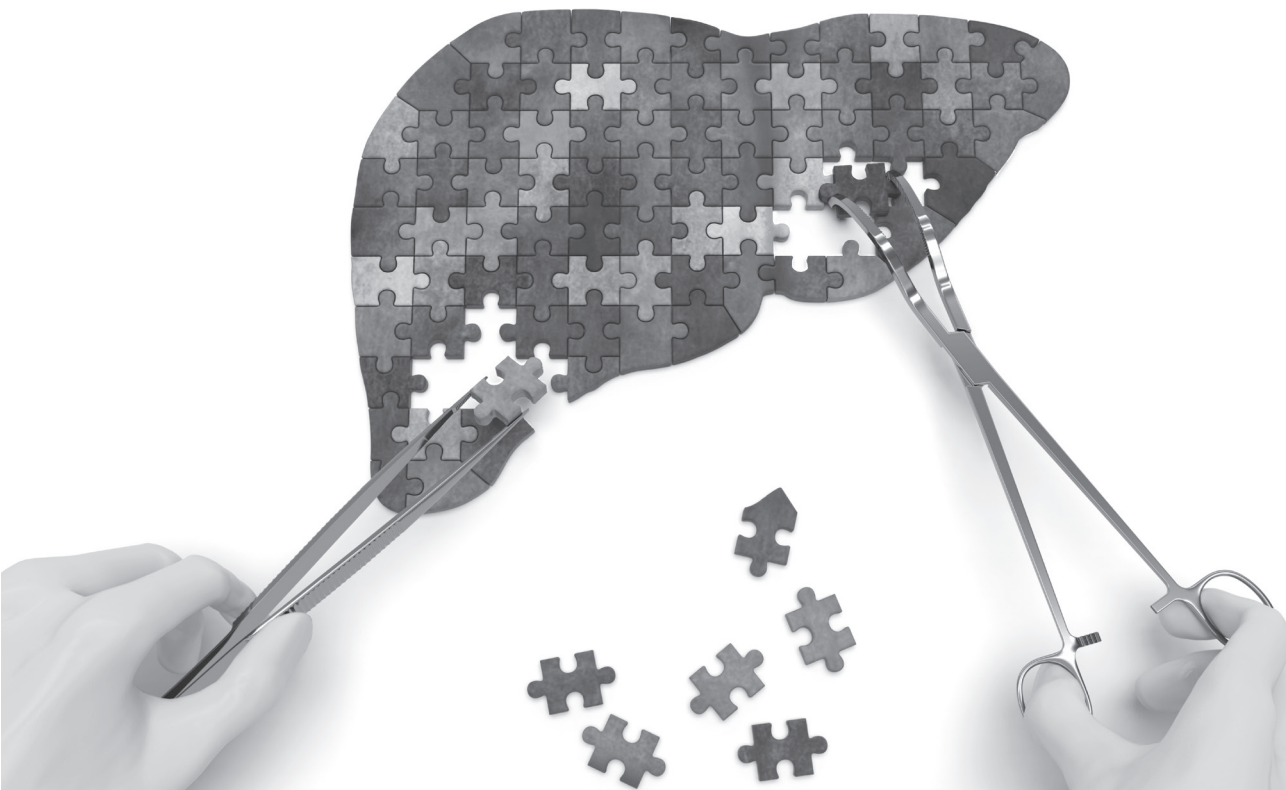

ABSTRACT

Importance: Resection of perihilar cholangiocarcinoma (PHC) is high-risk surgery, with reported operative mortality up to 17%. Therefore, preoperative risk assessment is needed to identify high-risk patients and anticipate postoperative adverse outcomes.

Objective: To provide external validation of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) risk model in a Western cohort of PHC.

Design, setting, and participants: E-PASS variables were collected from a database including 156 consecutive patients who underwent resection for suspected PHC between January 1, 2000, and December 31, 2015, at the Academic Medical Center, Amsterdam, the Netherlands. The accuracy of E-PASS using intra-operative variables and its modified form that can be used before surgery (mE-PASS) in predicting mortality was assessed by area under the curve (AUC) analysis (discrimination) and by the Hosmer-Lemeshow goodness-of-fit test (calibration).

Main outcomes and measures: In-hospital mortality, severe morbidity (Clavien-Dindo Grade ≥III) and high Comprehensive Complication Index.

Results: Among 156 patients included in the study, the median age was 63 years, and 62.8% (n = 98) were male. Of them, 85.3% (n = 133) underwent major liver resection. Severe morbidity occurred in 51.3% (n = 80), and in-hospital mortality was 13.5% (n = 21). Both E-PASS and mE-PASS had adequate discriminative performance, with areas under the curve of 0.78 (95% CI, 0.67-0.88) and 0.79 (95% CI, 0.70-0.89), respectively, while E-PASS showed better calibration (P = 0.33 vs P = 0.02, Hosmer-Lemeshow goodness-of-fit test). The ratios of observed to expected mortality were 1.31 for E-PASS and 1.24 for mE-PASS. Both models were able to distinguish groups with low risk, intermediate risk, and high risk, with observed mortality rates of 0.0% to 3.6%, 8.3% to 9.0%, and 25.0% to 28.3%, respectively. Severe morbidity and a high Comprehensive Complication Index were more frequently observed among high-risk patients.

Conclusions and relevance: Both E-PASS models accurately identify patients at high risk of postoperative in-hospital mortality after resection for PHC. The mE-PASS model can be used before surgery in outpatient settings and allows for risk assessment and shared decision making.

INTRODUCTION

Resection of perihilar cholangiocarcinoma (PHC) offers the only chance for long-term survival. The procedure typically consists of a combined extrahepatic bile duct and liver resection, and often requires an extended hemihepatectomy or vascular reconstruction to obtain a radical resection.[1, 2] This technically challenging and aggressive approach in mostly post-cholestatic livers contributes to a high postoperative mortality rate, ranging from 5% to 17% even in experienced centres.[1, 3-6]

Both patient-related factors and surgical parameters are important contributors to substantial operative risk, resulting in high morbidity and mortality. Factors that have been associated with adverse postoperative outcomes in PHC include advanced age[6], preoperative cholangitis[3], small future liver remnant (FLR) volume[7], portal vein reconstruction[5] and intraoperative blood loss.[4] However, several of these factors can only be determined at the time of surgery. Ideally, a PHC-specific risk model would aid the clinician in the phase of preoperative risk assessment and shared decision making by identifying high-risk patients. Although much needed, no such model specifically addressing PHC is available to date.

More than a decade ago, Japanese colleagues developed a scoring system to predict postoperative outcome after elective gastrointestinal surgery.[8, 9] That model is based on the hypothesis that postoperative complications result from a disruption of homeostasis due to overwhelming surgical stress exceeding a patient's reserve capacity, thus addressing both preoperative- and surgical variables. The Estimation of Physiologic Ability and Surgical Stress (E-PASS) model has proved effective in predicting postoperative morbidity and mortality after various gastrointestinal surgical procedures, although it has mainly been studied in Asian populations.[10] This model was modified (mE-PASS) by reducing the number of surgical variables and allocating fixed stress scores (median values) to specific procedures.[11] The risk score thereby is clinically valuable at the time of surgical planning.

Both E-PASS models were recently shown to accurately predict postoperative outcome in PHC at two Asian institutions[12, 13] Therefore, the present study aimed to provide external validation of these models in a Western PHC cohort.

METHODS

Study population and preoperative work-up

A waiver was granted from the Institutional Review Board of the Academic Medical Center, Amsterdam, the Netherlands, for approval of this retrospective study. The need for written or oral informed consent was waived. Data were retrospectively obtained from a prospective database that included all consecutive patients who underwent resection for suspected PHC between January 1, 2000, and December 31, 2015, at the Academic Medical Center. Perihilar cholangiocarcinoma was defined as a tumor mass or seemingly malignant stricture at or near the biliary confluence, arising between the origin of the cystic duct and the segmental bile ducts.[14]

Preoperative optimization included endoscopic or percutaneous biliary drainage of at least the FLR in the presence of obstructive cholestasis with jaundice. Portal vein embolization was performed for a small FLR volume (computed tomography volumetry <35%) or when hepatobiliary scintigraphy indicated poor FLR function.[15] Any episode of preoperative cholangitis induced by biliary decompression was treated with antibiotics and, when indicated, additional drainage or drain revision. Patients underwent surgery not earlier than they had fully recovered from drainage-related complications and cholestasis.

Surgical procedures

Patients underwent radical resection of the tumor encompassing hilar resection with en bloc (extended) hemihepatectomy including the caudate lobe in most cases. Excision and reconstruction of the left or right portal vein or its bifurcation was performed when involved by the tumor. Complete lymphadenectomy of the hepatoduodenal ligament was routinely performed. For biliary reconstruction, end-to-side anastomoses of the segmental ducts and a Roux- en-Y jejunal loop were constructed.[2] In selected patients with Bismuth type I or II tumors, only an extrahepatic bile duct resection without liver resection was performed. Frozen section of the proximal and distal bile duct margins was routinely performed to ensure tumor-free margins. All resections were performed by staff surgeons with extensive hepatobiliary expertise.

E-PASS models

Both the E-PASS and mE-PASS scoring systems are regression models that have previously been described in detail by Haga *et al*.[11, 13] Briefly, a Comprehensive Risk Score (CRS) is calculated by combining a Preoperative Risk Score (PRS) consisting of 6 preoperative variables and a Surgical Stress Score (SSS) consisting of 3 surgical variables.

The PRS is calculated using the following formula:
PRS = - 0.0686 + 0.00345 X_1 + 0.323 X_2 + 0.205 X_3 + 0.153 X_4 + 0.148 X_5 + 0.0666 X_6, where X_1 is age, X_2 is the presence (1 point) or absence (0 points) of severe heart disease (New York Heart Association class III-IV or severe arrhythmia requiring mechanical support), X_3 is the presence (1 point) or absence (0 points) of severe pulmonary disease (vital capacity <60% or forced expiratory volume in 1 second <50%), X_4 is the presence (1 point) or absence (0 points) of type 1 or 2 diabetes (World Health Organization [WHO] criteria), X_5 is the WHO performance status index (range, 0-4 points), and X_6 is the American Society of Anesthesiologists physiological status classification (range, 1-5 points). The WHO status was checked at first presentation in our center.

The SSS is calculated using the following formula:
SSS = - 0.342 + 0.0139 X_1 + 0.0392 X_2 + 0.352 X_3
where X_1 is blood loss (in grams) divided by body weight (in kilograms), X_2 is the operative time (in hours), and X_3 is the extent of the skin incision (0 points for a minor incision or laparoscopic or thoracoscopic surgical procedure, 1 points for laparotomy or thoracotomy alone, and 2 points for laparotomy and thoracotomy). Because all patients in the study cohort underwent laparotomy alone, the value for extent of skin incision consistently was 1.

The CRS is calculated using the following formula:
CRS = - 0.328 + (0.936 × PRS) + (0.976 × SSS)

For the modified model (mE-PASS), a fixed CRS (CRSf) was computed by combining the PRS and a fixed SSS (SSSf). Predefined values for different resection types were 0.401 for extrahepatic bile duct resection only, 0.453 for liver segmentectomy, 0.663 for hemihepatectomy and 1.025 for extended hemihepatectomy.[11]

The CRSf is calculated using the following formula:
CRSf = 0.052 + (0.58 × PRS) + (0.83 × SSSf)

The predicted in-hospital mortality rate (Y) for both E-PASS models was then calculated with the following predefined equations:

CRS < 0.159	Y ≈ 0
0.159 ≤ CRS < 2.98	Y = - 0.465 + 1.192 (CRS) + 10.91 $(CRS)^2$
CRS≥ 2.98	Y = 100

CRSf < 0.326	Y ≈ 0
CRSf ≥ 0.326	Y = – 0.0541(CRSf) + 0.197$(CRSf)^2$ – 0.00328

All variables needed for calculating the CRS and CRSf were collected from our PHC database. Total scores and predicted in-hospital mortality were then calculated for each individual patient.

Endpoints

Study endpoints were in-hospital mortality and postoperative morbidity. All complications occurring within 30 days after surgery or in the hospital were scored according to the Clavien-Dindo grading system (range, I-V).[16] Severe morbidity was defined as Clavien-Dindo Grade III-V. Also, the Comprehensive Complication Index (CCI) (range, 0 to 100), which summarizes all postoperative complications, was calculated for each patient according to the incidence and consequence of postoperative events.[17] Complications such as post-hepatectomy liver failure, biliary leakage, and hemorrhage, were scored and graded according to the International Study Group of Liver Surgery (ISGLS) criteria, with grade B and C considered as clinically relevant and severe morbidity.[18-20]

Statistical analysis

Continuous variables are presented as the mean (SD) or median (range) for non-normal distributed data. Categorical variables are expressed as counts and percentages. The CCI was transformed into a categorical variable using a CCI greater than the third quartile as the cut-off for low and high CCI.[21]

The predictive performance of the E-PASS models was analyzed in terms of discrimination and calibration. Discrimination, the ability to distinguish patients who died after surgery from those who did not, was assessed by area under the receiver operating characteristic curve (AUC) analysis with 95% confidence intervals (CIs). Areas under the curve exceeding 0.70 and 0.80 were considered acceptable and excellent discrimination, respectively. Calibration, the agreement between predicted mortality and observed mortality, was assessed by the Hosmer-Lemeshow goodness-of-fit test, with a significant outcome (P <0.05) indicating poor calibration.

Observed in-hospital mortality rates were then compared between three risk categories (low, intermediate, and high) based on the total CRS and CRSf scores. Furthermore, the incidence of severe complications among these groups was observed and compared using the Pearson chi-squared test. The association between CRS and severe morbidity (CCI above third quartile) was also assessed in multivariable analysis by logistic regression, which was adjusted for sex, preoperative biliary drainage, preoperative cholangitis, preoperative bilirubin, FLR volume, and vascular reconstruction.

Two variables needed for CRS calculation had missing data, namely, intraoperative blood loss (10.9% [17 of 156] missing data) and body weight (1.9% [3 of 156] missing data). To avoid bias, multiple imputation with 10 imputed datasets was performed for these missing data before calculating the CRS.[22] A regression model was used with baseline values, E-PASS, and outcome variables. Data were subsequently pooled using the rule by Rubin.[23] There were no missing data for CRSf calculation.

Analyses were performed using statistical software (SPSS Statistics for Windows, version 23.0; IBM and R, version 3.1.2; R Foundation for Statistical Computing). Two-tailed P <0.05 was considered statistically significant.

RESULTS

Patient demographics and operative characteristics

A total of 156 consecutive patients (98 [62.8%] male) underwent resection for presumed PHC during the study period. Demographics and operative characteristics are listed in **Table 1**. Most patients (139 [89.1%]) had undergone preoperative biliary drainage, and a high incidence (59 [37.8%]) of preoperative cholangitis was noted. A combined extrahepatic bile duct resection and liver resection was performed in 137 (87.8%) patients, with 133 (85.3%) undergoing a major hepatectomy (i.e., three or more Couinaud segments). Portal vein reconstruction was performed in 36 (23.1%) patients. Observed median SSS for patients undergoing formal hemihepatectomy and extended hemihepatectomy were 0.790 and 0.995, respectively.

Pathological examination confirmed PHC in 129 patients (82.7%) and revealed other disease in 27 patients. Intraductal papillary neoplasm of the bile duct without invasive component was found in 7 patients (4.5%), other malignant neoplasms in 4 patients (2.6%), and benign lesions in 16 patients (10.3%).

Postoperative events

Twenty-one patients (13.5%) died in the hospital after surgery. All of these patients had undergone a major hepatectomy. There was a suggestion of higher mortality after extended hemihepatectomy compared with standard hemihepatectomy (24.0% [12 of 50] vs. 11.3% [9 of 80], P = 0.06). Causes of death were liver failure (13 [61.9%] patients), sepsis with multi-organ failure (7 [33.3%] patients), or myocardial infarction (1 [4.8%] patient). Liver remnant volume below 30% was significantly associated with either sepsis or liver failure-related death (odds ratio, 3.18; 95%CI, 1.15-8.80; P=0.03).

A total of 122 (78.2%) patients developed one or more postoperative complications of any grade. The total number of complications among all patients was 341 (median, 2 per patient), and the median CCI was 29.6. The incidence of complications with Clavien-Dindo Grade III or higher was 80 of 156 (51.3%). An overview of postoperative complications is summarized in **Table 2**. Biliary leakage was the most frequent complication, occurring in 53 patients (34.0%), and 47 (30.1%) of these events were classified as ISGLS grade B or C. The median hospital stay was 13 days (range, 4-95 days), including the day of admission.

Table 1. Demographics and operative characteristics of the study cohort

Characteristic	Patients (N=156)
Age, years, median (range)	63 (36-81)
Male sex, n (%)	98 (62.8)
Jaundice at presentation, n (%)	120 (76.9)
Total bilirubin, mmol/L, median (range)	
Before drainage	119 (3-698)
Before surgery	13 (3-91)
Preoperative biliary drainage, n (%)	
None	17 (10.9)
Endoscopic biliary drainage	79 (50.6)
Percutaneous transhepatic biliary drainage	17 (17.9)
Both	43 (27.6)
Preoperative cholangitis, n (%)	59 (37.8)
ASA classification, n (%)	
1	35 (22.4)
2	98 (62.8)
3	23 (14.7)
WHO performance score, n (%)	
0	100 (64.1)
1	44 (28.2)
2	9 (5.8)
3	3 (1.9)
Bismuth-Corlette stage, n (%)	
I	6 (3.8)
II	22 (14.1)
IIIa	57 (36.5)
IIIb	28 (17.9)
IV	27 (17.3)
Left or right duct	16 (10.3)
FLR volume, % of total, median (range)	49 (16-92)
FLR < 30%, n (%)	24 (15.4)
Portal vein embolization, n (%)	8 (5.1)
Surgical procedure, n (%)	
Extrahepatic bile duct resection only	19 (12.2)
Segmentectomy	4 (2.6)
Central liver resection	3 (1.9)
Left hemihepatectomy	55 (35.3)
Left extended hemihepatectomy	7 (4.5)
Right hemihepatectomy	25 (16.0)
Right extended hemihepatectomy	43 (27.6)
Portal vein reconstruction, n (%)	36 (23.1)
Operation time, minutes, median (range)	467 (170-1011)
Intra-operative blood loss, mL, median (range)	2200 (136-13500)
Final pathology	
Perihilar cholangiocarcinoma	129 (82.7)
Intraductal papillary neoplasm of the bile duct	7 (4.5)
Other malignancy	4 (2.6)
Benign	16 (10.3)

ASA, American Society of Anesthesiologists; WHO, World Health Organization; FLR, future liver remant

Table 2. Postoperative outcomes and events

	Patients (N=156)
Mortality, in-hospital, n (%)	21 (13.5)
Morbidity, n (%)	
Any complication	122 (78.2)
Grade I	37 (23.7)
Grade II	69 (44.2)
Grade III	80 (51.3)
Grade IIIa	66 (42.3)
Grade IIIb	19 (12.2)
Grade IV	36 (23.1)
Grade IVa	25 (16.0)
Grade IVb	14 (9.0)
Morbidity specified*, n (%)	
Liver failure	
Grade A	13 (8.3)
Grade B/C	29 (18.6)
Biliary leakage	
Grade A	6 (3.8)
Grade B/C	47 (30.1)
Hemorrhage	
Grade A	-
Grade B/C	13 (8.3)
Sepsis	19 (12.2)
Intra-abdominal abscess	22 (14.1)
Ascites	11 (7.1)
Enteric anastomotic leakage	3 (1.9)
Chylous leakage	4 (2.6)
Enteral/parenteral nutrition	12 (7.7)
Abdominal compartment syndrome	1 (0.6)
Abdominal wall dehiscence	6 (3.8)
Wound infection	13 (8.3)
Cholangitis	5 (3.2)
Ileus/delayed gastric emptying	5 (3.2)
Stenosis/occlusion reconstructed portal vein	7 (4.5)
Thromboembolic events	6 (3.8)
Myocardial infarction	4 (2.6)
Atrial fibrillation	5 (3.2)
Pleural effusion	6 (3.8)
Pneumonia	14 (9.0)
Renal insufficiency	6 (3.8)
Delirium	8 (5.1)

*Most frequently observed and severe complications are listed. Other complications that are not listed include edema, circulatory overload, urinary tract infection, COPD exacerbation, antibiotics for raised infectious parameters, opioid intoxication, electrolyte dysfunction, blood transfusion, and pancreatitis.

E-PASS model performance

Discriminative power of the E-PASS models to predict in-hospital mortality is shown in **Figure 1**. Areas under the curve for CRS and CRSf were 0.78 (95%CI, 0.67-0.88) and 0.79 (95%CI, 0.70-0.89), respectively, indicating acceptable discrimination. Agreement between predicted mortality and observed mortality was best for E-PASS as shown by a pooled *P*=0.33 for the Hosmer-Lemeshow goodness-of-fit test for 10 imputed datasets. The mE-PASS model showed poor fit between the predicted and observed mortality (*P*=0.02). Subgroup analysis revealed that mE-PASS calibration was poor for patients undergoing formal hemihepatectomy (*P*=0.002) but was acceptable for those undergoing extended hemihepatectomy (*P*=0.14). The ratios of observed to predicted mortality for the present cohort were 1.31 for E-PASS and 1.24 for mE-PASS (**Table 3**). When the risk of formal hemihepatectomy was reweighted using the observed median SSS of 0.790 for this procedure in the study cohort, mE-PASS calibration for patients undergoing this type of liver resection remained poor (*P*=0.02).

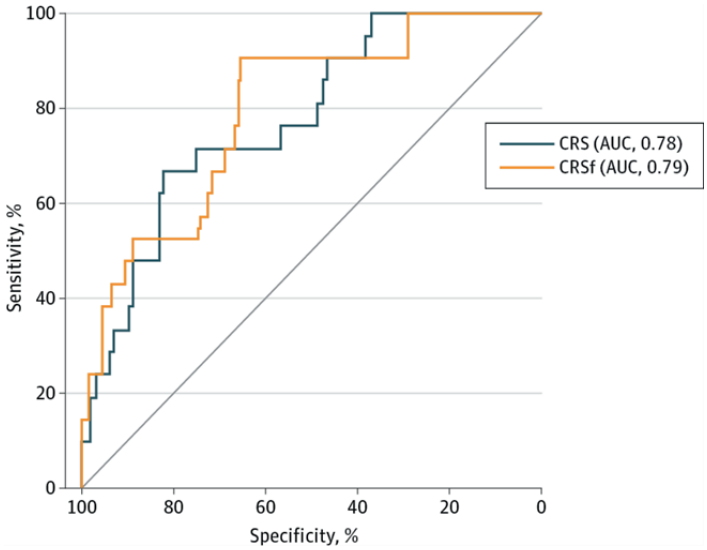

Figure 1. Receiver operative characteristic curve analysis for E-PASS models (CRS and CRSf) as a discriminant of postoperative in-hospital mortality.

Table 3. In-hospital mortality risk as predicted by E-PASS models and actual number of deaths

	E-PASS	mE-PASS	E-PASS	mE-PASS	E-PASS	mE-PASS	E-PASS	mE-PASS
Predicted risk of hospital death (%)	**No. of patients**		**Observed no. of deaths**		**Predicted no. of deaths**		**Observed:Predicted ratio**	
0-10	99	91	6	3	4	6	1.50	0.50
10-20	35	52	7	11	5	8	1.40	1.38
20-30	20	12	6	6	5	3	1.20	2.00
30-40	0	1	0	1	0	0	-	-
40-50	0	0	0	0	0	0	-	-
50-60	1	0	1	0	1	0	1.00	-
60-70	0	0	-	-	-	-	-	-
70-80	1	0	1	0	1	0	1.00	-
Total	156	156	21	21	16	17	1.31	1.24

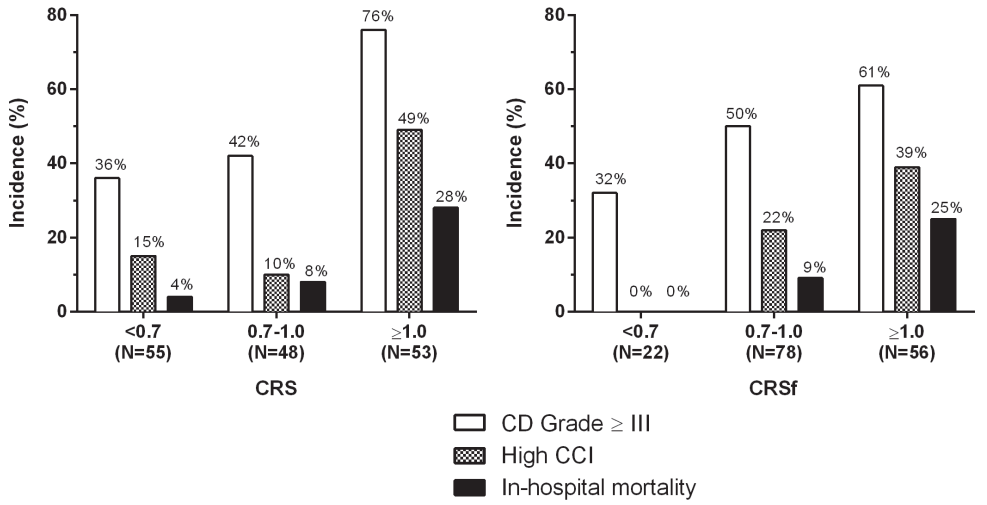

Figure 2. Morbidity and mortality rates among risk groups of E-PASS models. Left: CRS risk categories (E-PASS model), right: CRSf risk categories (mE-PASS) model).

Observed mortality and morbidity among the CRS and CRSf risk groups are shown in **Figure 2**. Observed mortality rates ranged from 3.6% (2 of 55) in the low-risk group to 8.3% (4 of 48) in the intermediate-risk group and to 28.3% (15 of 53) in the high-risk group (P<0.001) for CRS. For the mE-PASS model, observed mortality rates were 0% (0 of 22) in the low-risk group, 9.0% (7 of 78) in the intermediate-risk group, and 25.0% (14 of 56) in the high-risk group (P=0.004) for CRSf. A significant higher incidence of severe complications (Clavien-Dindo grade ≥III) was observed in the high-risk group compared with the low-risk and intermediate-risk groups (75.5% [40 of 53] vs. 36.4% [20 of 55] vs. 41.7% [20 of 48], respectively; P<0.001) for CRS. Even so, high CCI was comparable in the low-risk and intermediate-risk groups for CRS, but more frequent in the high-risk group (14.5% [8 of 55] vs. 10.4% [5 of 48] vs. 49.1%

[26 of 53], respectively; *P*<0.001). For the mE-PASS model, a higher complication rate was observed in the highest-risk group for CRSf, but it was only significantly higher compared with the lowest-risk group (60.7% [34 of 56] vs. 31.8% [7 of 22], respectively; *P*=0.02). High CCI was significantly increased in both the intermediate-risk and high-risk CRSf groups (0 vs. 21.8% [17 of 78] and 40.0% [22 of 55], respectively; *P*=0.001).

Multivariable logistic regression analysis revealed that CRS (adjusted odds ratio, 13.57; 95%CI, 3.34-55.22) and preoperative cholangitis (adjusted odds ratio, 10.57; 95%CI, 3.15-35.40) were independent risk factors for severe postoperative morbidity. These results are summarized in the **Supplemental table**.

DISCUSSION

The present study confirms the value of the E-PASS models for predicting postoperative in-hospital mortality after resection for PHC. The risk scores showed adequate predictive performance in this external Western validation cohort. These models provide a valuable tool for preoperative risk assessment and shared decision making as early as at the initial outpatient consultation. The mE-PASS model can be used in the preoperative setting, which has obvious benefits to both the clinician and patient.

Liver surgery has improved during the last decades, and preoperative optimization techniques, such as portal vein embolization and biliary drainage, have reduced the risks in subgroups of patients. However, morbidity and mortality following resection of PHC remain high even in specialized, high-volume centers. Mortality rates in the literature range from 5 to 17% in these centers, and operative risk has been reported to be even higher in selected patients who require right hemihepatectomies or extended liver resections.[1, 3-6] Furthermore, preoperative cholangitis remains a major concern because it increases the mortality risk more than three-fold.[3, 24] Such high-risk procedures warrant adequate patient counselling because these high rates might not be acceptable for some patients. Morbidity after PHC resection is also substantial and is reported in up to 68%.[2] However, reporting severe morbidity as the presence of a Clavien-Dindo Grade III or higher complication inadequately addresses the overall postoperative events in patients. Most patients develop several minor and major complications; therefore, the CCI might provide more accurate insight into the burden of postoperative adverse events.

To date, there is no operative risk model specifically addressing PHC. The E-PASS models were originally developed in a large set of gastrointestinal surgical procedures and showed

better predictive performance than well-known scores like the Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (POSSUM).[9-11] Two studies from China and Japan recently found that the models were valuable to predict mortality after surgery for PHC.[12, 13] However, these studies were flawed by a heterogeneous population and relatively small sample sizes. In the study by Wang et al, only 62 patients with PHC underwent resection (23 of whom had hepatectomies), and their analyses also included 38 patients who had unresectable tumors.[12] The study by Haga et al also included patients with gallbladder carcinoma and included only 56 major liver resections. Therefore, the present study comprising 156 patients from a well-defined cohort adds substantial weight to the value of the E-PASS models in PHC.

However, there are some limitations to the E-PASS models. First, because E-PASS contains several operative variables, such as blood loss and operative time, this model might be suboptimal for preoperative risk assessment, with preoperative estimation of these variables possibly resulting in substantial underestimation or overestimation of operative outcomes. The modified model (mE-PASS) uses a fixed surgical stress score, making it suitable for preoperative use and shared decision making. However, calibration analysis showed a poorer fit for the mE-PASS model, which could be explained by underestimation of the surgical stress of formal hemihepatectomy in our cohort, although reweighting of operative risk did not lead to significant improvement in model calibration. Despite imbalance between the predicted mortality risk and the observed mortalities, the mE-PASS model could accurately identify patients at higher risk of dying after surgery. Overall, both models somewhat underpredicted in-hospital mortality. Furthermore, predictors of outcomes in PHC, such as biliary drainage status of the FLR, preoperative cholangitis, and portal vein reconstruction, are not included, rendering the model most likely not the ideal predictive model. Preoperative cholangitis remained an independent risk factor for severe morbidity in our analysis after adjustment for CRS, which includes WHO performance score. Last, severe heart and pulmonary disease were almost non-existent in our cohort, which could be owing to patient selection because patients with New York Heart Association class III or IV, severe arrhythmia, or decreased vital capacity are usually not considered adequate candidates for major liver surgery.

Despite the lack of PHC-specific factors in the E-PASS models, these scores showed acceptable discrimination for mortality in our cohort. Based on their individual CRS and CRSf scores, patients could be categorized into low-risk, intermediate-risk, and high-risk groups. Severe morbidity and mortality varied substantially, with a low (0-3.6%) mortality rate in the low-risk group, an intermediate (8.3-9.0%) mortality rate in the intermediate-risk group and a high (25.0-28.3%) mortality rate in the high-risk group. Severe morbidity and high

CCI were more frequently observed among high-risk patients. We chose to also calculate the CCI for individual patients because it provides more accurate information about the overall postoperative events compared with the Clavien-Dindo classification.[17] Because the CRS and CRSf equations are more difficult to compute compared with a simple point-adding risk score, a CRS-derived total risk points score may be more convenient to use in clinical practice. The total risk points score has previously been described by the E-PASS investigators.[10] To aid the clinician in predicting the operative risks in patients with PHC, a spreadsheet has been included (available online) to allow automatic calculation of the E-PASS scores and in-hospital mortality based on the equations by Haga et al.[11]

There are several limitations to our study. Although this study includes one of the largest single-center series of patients with PHC, to our knowledge, the small sample size resulted in few events. The consequent statistical uncertainty in the analyses is reflected by the relatively wide confidence intervals. A second limitation is the considerable amount (up to 17%) of missing data (mainly intraoperative blood loss) for calculating the CRS values, which was overcome by multiple imputation with 10 imputed datasets. Although this limitation may have introduced some bias, imputation of missing variables has been shown to decrease the risk of bias by not excluding those patients with missing variables.[22]

To conclude, the present study shows that the E-PASS models accurately identify patients at higher risk of postoperative in-hospital mortality after resection for PHC. In the absence of models based on specific risk factors in PHC, the E-PASS models allow risk assessment and patient counseling as early as at the initial outpatient visit and can thus support shared decision making.

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SUPPORTIVE INFORMATION

Supplemental table. Univariable and Multivariable Analysis for Risk Factors of Severe Morbidity (CCI Above Third Quartile)

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Male gender	1.46 (0.67-3.16)	0.340	1.57 (0.52-4.74)	0.425
Preoperative biliary drainage	2.72 (0.59-12.47)	0.198	0.40 (0.06-2.64)	0.343
Preoperative cholangitis	5.98 (2.71-13.20)	<0.001	10.57 (3.15-35.40)	<0.001
Preoperative bilirubin	1.01 (0.99-1.04)	0.375	0.99 (0.95-1.03)	0.498
FLR volume (%)	7.41 (1.18-46.80)	0.033	5.98 (0.57-62.49)	0.135
Vascular reconstruction	2.04 (0.91-4.58)	0.083	1.42 (0.45-4.51)	0.557
CRS	11.00 (3.70-32.73)	<0.001	13.57 (3.34-55.22)	<0.001

CCI, comprehensive complication index; OR, odds ratio; CI, confidence interval; FLR, future liver remnant; CRS, comprehensive risk score.