Surgeons' assessment versus prognostic risk models for predicting complications of hepato-pancreato-biliary surgery (HPB-RISC): a multicenter prospective cohort study

M. Samim[1,2,3], T.H. Mungroop[2], M. AbuHilal[3], C.J. Isfordink[1], I.Q. Molenaar[1], M.J. van der Poel[2], T.A. Armstrong[3], A.S. Takhar[3], N.W. Pearce[3], J.N. Primrose[3], S. Harris[4], H.M. Verkooijen[5], T.M. Gulik[2], J. Hagendoorn[1], O.R.C. Busch[2], C.D. Johnson[3] *, M.G. Besselink[2,3] * for the HPB-RISC study group

* *Shared senior author*

1 Department of Surgery, University Medical Center Utrecht, the Netherlands

2 Department of Surgery, Academic Medical Center Amsterdam, the Netherlands

3 Department of Surgery, University Hospital Southampton NHS Trust Foundation, United Kingdom

4 Department of Epidemiology, University Hospital Southampton NHS Trust Foundation, United Kingdom

5 Imaging division, University Medical Center Utrecht, the Netherlands

Collaborators: R. van Hillegersberg (critically reviewed the study proposal). M.F. Gerhards, T.M. Karsten and H.A. Marsman (collected data).

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Correspondence: Marc G. Besselink, MD PhD, Academic Medical Center Amsterdam, Department of Surgery, G4.196, PO Box 22660, 1100 DD Amsterdam, the Netherlands, Tel: +31-20-5662558, Fax: +31-20-5669243, E-mail: m.g.besselink@amc.nl

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Although formal risk prediction models are often advised when counseling patients for HPB surgery, the added value of these models over surgeons' assessment is unclear since comparative studies are lacking. This prospective study and systematic review, found no added value of existing models over surgeons' assessment. A new prediction model outperformed surgeon's assessment, but only for pancreas surgery.

ABSTRACT

Objective

To assess whether risk prediction models outperform surgeons' assessment regarding the risk of complications after hepato-pancreato-biliary (HPB) surgery.

Background

Formal risk prediction models are often advised when counseling patients for HPB surgery but studies comparing these models to surgeons' assessment are lacking.

Methods

This prospective study included adult patients scheduled for HPB surgery in 3 centers in the UK and the Netherlands. Primary outcome was the rate of postoperative major complications. Preoperative surgeons' assessment was scored prospectively. Risk prediction models were retrieved via a systematic review and risk scores were calculated. A new HPB-RISC risk model (www.hpb-risc.com) was developed for HPB surgery and internal and external validation was performed. For each model, discrimination and calibration were evaluated.

Results

Overall, 349 patients were included (159 liver, 172 pancreas surgery). The rate of major complications was 27% and mortality 3%. Surgeons' assessment resulted in an AUC of 0.64; 0.71 for liver and 0.56 for pancreas surgery (P=0.02). The AUCs for 9 existing risk prediction models ranged between 0.51-0.73; 0.57-0.73 for liver and 0.51-0.57 for pancreas surgery. The new HPB-RISC model resulted in an AUC of 0.70 (95% CI 0.62-0.78); 0.62 for liver and 0.70 for pancreas surgery and outperformed surgeons' assessment for pancreas surgery (P = 0.01).

Conclusion

Existing risk prediction models have no clear added value to surgeons' assessment in HPB surgery. Both surgeons' assessment and existing risk prediction models predict complications of pancreas surgery poorly. The newly developed HPB-RISC model outperforms surgeons' assessment, but only for pancreas surgery.

Keywords: surgery, risk, prediction, complications, liver, pancreas

INTRODUCTION

HPB surgery carries a high risk of complications of up to 74%.[3,4] This emphasizes the need for adequate preoperative patient counseling regarding the risk of postoperative complications, especially in an era wherein the volume of hepato-pancreato-biliary (HPB) surgery is increasing.[1,2]

Patients increasingly demand reliable counseling and exact data about their surgical risks to perform adequate shared decision making.[5,6] This could be achieved by using one of the existing formal risk prediction models. However, in clinical practice, few surgeons use these models and rather rely on their own assessment of the risk of postoperative complications. It is unclear whether preoperative risk prediction models should be implemented in clinical practices since studies comparing the performance of these models with surgeons' assessment in HPB surgery are lacking.

The primary objective of this study was to assess whether risk prediction models have additional value compared to surgeons' assessment regarding the risk of major complications after HPB surgery. The secondary objective was to construct a risk prediction model for major complications following HPB surgery.

METHODS

This prospective multicenter study was conducted at three tertiary referral centers for HPB surgery (University Hospital Southampton NHS Trust Foundation, UK (from February 2013 to March 2014); and the Academic Medical Center (AMC) Amsterdam and University Medical Center Utrecht (UMCU) in the Netherlands (from June 2014 to November 2015)). The HPB-RISC (Research Into Surgical Complications in HPB surgery) study protocol was approved by the local Ethics Committees in Portsmouth, United Kingdom, AMC Amsterdam, and UMC Utrecht, the Netherlands. The requirement for informed consent was waived.

The guidelines of the TRIPOD statement for multivariable prediction models were followed for the validation of risk prediction models and surgeons' assessment and development of a new model.[17] We included adult patients in whom the decision for HPB surgery had been made during a multidisciplinary team meeting. Very low risk procedures such as cholecystectomy or diagnostic laparoscopy were excluded. Supplemental table 1 lists the included surgical procedures.

Data were collected prospectively using patient's medical charts and included preoperative, perioperative and postoperative parameters, including patient characteristics, laboratory parameters, disease and treatment specifications, and information on the surgical procedure, postoperative complications and mortality. The selection of preoperative variables to be collected was based on the literature (identified prognostic factors) and the existing risk prediction models, retrieved by systematic review.

Postoperative complications were graded according to the Clavien-Dindo classification.[7] Major complications were defined as in-hospital complications grade III or higher, following the surgical procedure. Data on postoperative complications were collected during and after discharge, using patient's medical chart.

Surgeons' assessment

Surgeons' assessment for postoperative major complications was scored at the outpatient clinic, at least 48 hours pre-operatively on a case record form. A total of 12 HPB surgeons, in the 3 centers, scored the risk of postoperative major complications. The perceived risk of postoperative major complications was scored on a 10-point scale (0-10%, 11-20%, 21-30% etc.). Surgeons were blinded for the outcome of the risk prediction models. These models were not being used in clinical practice.

Existing risk prediction models

A systematic literature search was performed to identify existing risk prediction models (Supplemental material, file 2). Included were preoperative risk prediction models in HPB, gastrointestinal or general surgery with postoperative morbidity or mortality as outcome. Excluded were risk prediction models that predicted a specific postoperative complication (e.g. postoperative pancreatic fistula). Risk prediction models using a classification system of the complications other than Clavien-Dindo were included. Nine pre-operative risk prediction models for liver, pancreas or general surgery were found (supplemental table 3).[8-16] The Donati model[10] was developed for any form of surgery (cardiac surgery and caesarean delivery excluded), 3 models[8,9,14] were developed for liver surgery and 5 models[11-13,15,16] for pancreas surgery. No risk prediction model was specifically designed for HPB surgery. In the subsequent clinical study, all variables that were required for the retrieved risk prediction models were prospectively collected.

New HPB-RISC model

Given that no prediction model for HPB surgery was found, we developed a new model (HPB-RISC) for prediction of postoperative major complications after HPB surgery, using preoperative parameters only. Data of patients undergoing HPB surgery at the AMC Amsterdam and UMC Utrecht were used for development of the HPB-RISC model. Data of patients included in the University Southampton hospital were used for validation of the new HPB-RISC model.

Statistical analysis

Statistical analyses were performed using RStudio version 3.1.2 open-source software and a p-value <0.05 was considered as statistically significant. Continuous parametric data were reported as means and standard deviations (SD) and continuous non-parametric data as medians (with the first and third quartile, p25-p75). Dichotomous data were reported as both the number of observations and percentages.

The predictive performance of the existing risk prediction models was assessed in our cohort using data of all centers. The validation cohort consisted of liver and pancreas surgery patients depending on whether the model was developed for liver or pancreas surgery respectively and therefore contained liver or pancreas specific variables. The surgeons' assessment was validated in the entire cohort and in the liver and pancreas group separately. The predictive performance was assessed by measuring the discriminative ability of the model using receiver operating characteristics analysis and reported as area

under the curve (AUC). Calibration of the models was assessed to compare the predicted versus the observed probability of postoperative major complications. The intercept (estimate of systematically too high/low predicted probability) and the slope (estimate of extremeness of predicted probability) of the calibration curve were reported. Discrimination and calibration of the existing risk prediction models were compared with the surgeons' assessment. The DeLong test was used to compare the difference between 2 AUCs. In order to minimize risk of multiple testing, we performed formal statistics for comparison between AUC of surgeons' assessment for liver and pancreas surgery, the surgeons' assessment and the best risk prediction model and surgeons' assessment and the new HPB-RISC model.

For development of the new HPB-RISC model, a multivariable logistic regression model was fitted and a predictor selection method[18] was used meaning that predictors that did not contribute usefully in the multivariable model were removed. The candidate predictors in the model were chosen based on clinical relevance and the Akaike information criterion was used to determine the best model.[18] The event-per-variable rule was used to decide on the appropriate number of variables in the model. Missing data were imputed by multiple imputation (10 times). Shrinkage of the regression coefficients was performed. The predictive performance was assessed by means of ROC analysis and calibration curves, including the goodness of fit test (Hosmer-Lemeshow). Internal validation of the best model was performed using bootstrap samples and an adjusted AUC was acquired in order to estimate overfitting of the model. An online calculator was developed for for utility or external validation of the new model. The online calculator is available through *www.hpb-risc.com.*

RESULTS

Patient characteristics

The cohort consisted of 349 patients, including 156 (45%) patients undergoing liver surgery and 193 (55%) patients undergoing pancreas surgery (Table 1). There were 5.1% missing values without a specific pattern among variables. The overall rate of postoperative major complications (Clavien-Dindo ≥3) was 27% and mortality 3% (Table 2).

Surgeons' assessment

Validation of surgeons' assessment resulted in an AUC of 0.64 (95% CI 0.58-0.71) in the entire cohort. The discriminative ability of the surgeons' assessment differed between an AUC of 0.71 (95% CI 0.61-0.81) for liver surgery and 0.56 (95% CI 0.47-0.64) for pancreas surgery (P=0.02). Calibration of the surgeons' assessment showed fair agreement between the observed and predicted probabilities for liver surgery, however agreement was poor for pancreas surgery (Supplemental material, table 6).

Risk prediction models

The results of the validation of the existing risk prediction models are shown in Table 3. The AUC for all existing risk prediction models ranged from 0.57 to 0.73 for liver surgery and 0.43 to 0.55 for pancreas surgery. The risk prediction model by Breitenstein *et al.*[9] for liver surgery had the best predictive performance with an AUC of 0.73 (95% CI 0.62-0.85), Calibration of the Breitenstein model showed a fair agreement between the observed and predicted probabilities (intercept -0.03, slope 1.13, Table 3). Calibration of the remaining risk prediction models showed poor agreement between the observed and predicted probabilities showing either somewhat underfitted (Andres, Greenblatt) or overfitted models (Donati, Simons, Ragulyn-Coyne), or combination of the latter with systematically too high or too low predicted probabilities (Uzunoglu, Venkat, Hill).

HPB-RISC model

Since no existing model predicted the risk for HPB surgery, the HPB-RISC model was developed. The development cohort consisted of 172 patients and the validation cohort of 177 patients. Baseline characteristics of the patients stratified per development and validation set are included in supplemental material, tables 4 and 5. Although most variables were comparable, the development set included more reported comorbidities. For pancreas surgery, the proportion of pancreatoduodenectomy (PD) was higher in the

development set. Surgery was performed laparoscopically in 12% of cases in the development set, vs. 40% in the validation set.

Detailed steps for development of the HPB-RISC model are given in supplemental material, table 7. The new HPB-RISC model included the following variables: sex, white blood cell count (10^9/L), age-adjusted Charlson comorbidity index, type (i.e. extent) of surgery and laparoscopic vs. open surgery (Table 4). The predictive performance of HPB-RISC was 0.70 (95% CI 0.62-0.78) in the development cohort (Table 5). The calibration curve showed a good agreement between the observed and predicted probabilities with an intercept of -0.04 and slope of 1.09. The Homser-Lemeshow test resulted in Chi^2 of 3.90 and a non-significant p-value of 0.87 (Figure 1). Internal validation by bootstrapping resulted in an adjusted AUC of 0.67.

The performance of the model in the validation cohort was evaluated with the regression coefficients (after shrinkage), resulting in an AUC of 0.68 (95% CI 0.58-0.79), which was in line with the predictive performance after internal validation (supplemental material, file 8). Calibration of the model in the validation cohort showed a good agreement between the observed and predicted probabilities (Homser-Lemeshow test, $Chi^2 = 10.60$, $P = 0.23$). The intercept and the slope of the calibration were 0.02 and 0.85 respectively, suggesting a slightly overfitted model (too extreme predicted probabilities). Validation of the HPB-RISC model was stratified separately for the liver and pancreas cohorts (Table 4). The AUC was 0.62 (95% CI 0.50-0.75) for liver surgery and 0.70 (95% CI 0.63-0.78) for pancreas surgery.

Comparing surgeon's assessment with the existing and new risk models

Of the 9 existing models, only the Breitenstein model for liver surgery scored slightly better than surgeons' assessment, although not statistically significant (AUC 0.73 vs 0.71; $P = 0.73$). The new HPB-RISC model outperformed surgeons' assessment, only for pancreas surgery (AUC 0.70 vs 0.56; $P = 0.01$).

DISCUSSION

This first prospective, comparative multicenter study demonstrated that in HPB surgery, existing risk prediction models have no clear added value to surgeons' assessment for prediction of postoperative complications. Both surgeons' assessment and risk prediction models have a poor predictive performance (AUC <0.57) for pancreas surgery, significantly worse than for liver surgery. The newly developed HPB-RISC model, the first risk prediction model specifically designed for HPB surgery, outperformed all existing models except the Breitenstein model.[9] The HPB-RISC model predicted risk of complications better than surgeons' assessment for pancreas surgery (AUC 0.70 *vs.* 0.56), indicating its relevance for clinical practice in these patients.

Only one previous study scored surgeon's assessment prior to a broad range of gastrointestinal, vascular and gynecologic surgery, using a visual analog scale for prediction of perioperative major complications.[19] Surgeons' assessment was found to be a meaningful prediction tool for major complications (AUC 0.67), comparable with other significant predictors. However, surgeons' assessment was not compared with existing risk prediction models, but was incorporated in a previously developed multifactorial model with an improved discrimination as a result (AUC 0.77).[19] A second study scored surgeon's assessment immediately after gastrointestinal (mostly colorectal) surgery and demonstrated that it could indeed predict clinical outcome.[20] Surgeons' assessment (predicted risk of complications 32%) outperformed the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) score (predicted risk of complications 46%) as the actual complication-rate was 30%.[20] However, the strategy of predicting risk after surgery has no clinical relevance when counseling patients preoperatively.

The poor predictive performance of the existing risk prediction models in this study might be attributed to three possible factors. Firstly, risk prediction models usually perform worse when used in settings other than in the patient group in which the model was developed.[21] Most models tend to overperform in the original cohort, even after corrections from internal validation procedures such as bootstrapping.[21] These models are 'overfitted', resulting in underestimation of the probability of an event in low risk patients and overestimated in high-risk patients.[22] Secondly, we assessed the predictive performance of models that were actually developed for the prediction of postoperative mortality instead of major complications.[10,12-14,16] The rationale behind this was that the risk of mortality and the predicted risk are related to the risk of major complications. Finally, although 4 risk prediction models were validated for prediction of postoperative

complications[8,9,11,15] there was heterogeneity in the definition of major (Clavien-Dindo grade ≥3) complications. One study[8] used an older version of this classification and another study[11] listed a series of complications as outcome parameter. Although most of these complications would meet the criteria of a grade 3 or higher complication according to Clavien-Dindo classification, it might have biased the results of the external validation somewhat.

We developed the HPB-RISC model using 5 easily available variables: 3 patient-related (sex, WBC and age-adjusted Charlson comorbidity index) and 2 surgery-related (type of surgery and minimally invasive versus open approach). The HPB-RISC model was developed and validated in a cohort of patients who received a broad spectrum of liver and pancreas surgery, excluding minor procedures such as cholecystectomy and diagnostic laparoscopy. The HPB-RISC model includes preoperative variables that are easy to obtain, even in a retrospective setting and is therefore suitable for validation in different study populations and case-mix correction in benchmark analyses. The internal validation showed good discrimination and calibration of the model in the development cohort. Although the HPB-RISC model was validated in an entirely different cohort in terms of surgical characteristics and outcome, the discriminative ability was similar to the results of the internal validation. Calibration of the HPB-RISC model in the validation cohort showed that the model was slightly overfitted as is often seen in external validation. A possible explanation for this is the differences between the development and validation cohort in the type of surgery and the surgical approach, which could have led to suboptimal calibration of the model. In future external validation of the model, further shrinkage of the regression coefficients will improve the calibration of the model and improve the models' usability.[21]

As seen in other risk prediction models and known from the literature, comorbidity is an important prognostic parameter for postoperative outcomes.[11-14,16] We tested both the age-adjusted Charlson and the Elixhauser comorbidity indexes in our cohort. However, only the age-adjusted Charlson comorbidity index showed to be a significant predictor for postoperative major complications. Although Elixhauser comorbidity index has been identified as a better predictor for postoperative mortality[4], the Charlson comorbidity index has been confirmed as a good predictor for postoperative complications in several surgical settings.[25-27] Practical online tools are available for calculation of the (age-adjusted) Charlson comorbidity index.[28]

The ASA score was not found to be a significant predictor of postoperative major complication in our cohort. This is remarkable since the ASA score is routinely used as a measurement of patients' pre-surgical health and several risk prediction models did find ASA to be a significant predictor for clinical outcome.[8-10] This might in part explain the poor predictive probability of those models in our cohort. On the other hand, the Charlson comorbidity index is an extensively studied and widely used comorbidity index in the medical literature and has been included in risk prediction models frequently.[12-14, 16] As opposed to the ASA score, the age-adjusted Charlson comorbidity index accounts for patients' age and is a more objective assessment of the patients' health status, which might explain why it is a better predictor of clinical outcome.

When comparing surgeons' assessment versus existing risk prediction models, it becomes clear that all models perform poorly in pancreas surgery. Pancreas surgery is known for its unpredictable risk of common complications such as delayed gastric emptying.[29] Therefore, prediction of postoperative outcome in these patients is challenging. Validation of the new HPB-RISC model, separately in liver and pancreas surgery showed a good predictive performance of the model for pancreas surgery. In fact, for pancreas surgery, the performance of the HPB-RISC model was superior to the surgeons' assessment.

The present study has some limitations. For external validation of the existing models, it was not possible to use the entire cohort since some models were developed for liver or pancreas surgery and included liver- or pancreas specific parameters. Therefore, we assessed the predictive performance of the models in the available data for pancreas and liver surgery separately. Second, for the development of the new risk prediction model, we chose for a split sample method because of the different baseline risk for major complications (most notably delayed gastric emptying) in the Amsterdam/Utrecht cohort compared to the Southampton cohort. Although this method allowed external validation of the new developed model, the validation sample size would ideally have been larger. As always with new predictive models, further validation of the model is required.

CONCLUSION

This study demonstrated that, in general, it is valid to use surgeons' assessment when counseling patients about the risks of complications after HPB surgery. The existing risk prediction models have a limited role in clinical practice, which may differ from their role in research projects. The new HPB-RISC model is the

first designed specifically for HPB surgery. This model outperformed surgeons' assessment for pancreas (but not liver) surgery and is therefore advised in this setting.

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Table 1. Baseline characteristics in 349 patients undergoing HPB surgery

	N (%)
Age, median (p25-p75)	66 (57-72)
BMI, median (p25-p75)	26 (23-29)
Male sex	177 (50.7)
Smoking (yes)	58 (16.6)
DM	72 (20.6)
COPD	21 (6.0)
History of pancreatitis	19 (5.4)
History of cardiac disease	58 (16.6)
Elixhauser comorbidity index	
0	16 (4.6)
1	74 (21.2)
2	99 (28.3)
3	79 (22.6)
4	45 (12.9)
≥5	36 (10.3)
Age-adjusted Charlson comorbidity index	
0	12 (3.4)
1-3	88 (25.2)
4-6	163 (46.7)
≥7	86 (24.6)
Liver surgery	159
Segment resection	97 (65.1)
Hemihepatectomy	41 (27.5)
Enucleation	11 (7.4)
Pancreas surgery	172
Pancreatoduodenectomy	118 (68.6)
Distal pancreatectomy	38 (22.1)
Total pancreatectomy	13 (7.6)
Necrosectomy	3 (1.7)
Approach	
Open	256 (73.4)
Laparoscopic	93 (26.6)
Pathology	
Malignant	279 (80.6)
Benign	67 (19.4)

BMI: Body mass index; COPD: chronic obstructive pulmonary disease; DM: diabetes Mellitus; p25-p75: first quartile-third quartile.

Table 2. Outcomes in 349 patients undergoing HPB surgery

Outcome parameter	Median or %
Operation time (min), median (p25-p75)	253 (195-359)
Blood loss (ml), median (p25-p75)	431 (200-885)
Hospital stay (days) median (p25-p75)	5 (7-11)
In-hospital postoperative complications (%)	195 (55.9)
Clavien-Dindo≥3 complications (%)	94 (26.9)
Postoperative 30-day mortality (%)	10 (2.9)

Table 3. Performance of the individual Risk Prediction Models in our cohort

Model	All patients		Liver surgery		Pancreas surgery	
	Calibration	Discrimination	Calibration	Discrimination	Calibration	Discrimination
	Intercept Slope	AUC (95% CI)	Intercept Slope	AUC (95% CI)	Intercept Slope	AUC (95% CI)
Donati[10]	-0.12 1.25	**0.62** (0.56-0.68)	0.05 0.69	**0.68** (0.57-0.78)	-0.22 1.47	**0.55** (0.46-0.63)
Breitenstein[9]			-0.03 1.13	**0.73** (0.62-0.85)		
Simons[14]			0.08 0.64	**0.57** (0.46-0.69)		
Andres[8]			-0.04 1.24	**0.57** (0.45-0.69)		
Hill[12]					-0.11 1.32	**0.55** (0.47-0.64)
Venkat[16]					-0.28 1.77	**0.55** (0.46-0.64)
Greenblatt[11]					-0.06 1.15	**0.57** (0.46-0.67)
Ragulin-Coyne[13]					0.01 0.86	**0.53** (0.45-0.62)
Uzunoglu[15]					-0.47 2.33	**0.51** (0.39-0.60)
Surgeons' assessment	-0.01 1.04	**0.64** (0.58-0.71)	0.01 0.92	**0.71** (0.61-0.81)	-0.16 1.50	**0.56** (0.47-0.64)

Table 4. The variables included in the HPB-RISC model

	B	B (after shrinkage)	SE	P	OR (after shrinkage)
Intercept	-2.629	-1.956	0.688	-	-
Male sex	0.610	0.430	0.334	0.068	1.54
WBC (10^9/L)	0.045	0.032	0.027	0.097	1.03
Type of surgery*	0.766	0.540	0.343	0.026	1.72
Age-adjusted Charlson comorbidity index	0.289	0.203	0.121	0.018	1.23
Open approach	0.361	0.254	0.549	0.512	1.29

B= regression coefficient; OR= odds ratio; SE= standard error
*Pancreatoduodenectomy and (extended) hemihepatectomy
See *www.hpb-risc.com*

Table 5. Performance of the HPB-RISC model in the development and validation cohort.

Model	Calibration	Discrimintation
	Intercept Slope	AUC (95% CI)
HPB-RISC Developement cohort	-0.04 1.09	**0.70** (0.62-0.78)
HPB-RISC Validation cohort	0.02 0.84	**0.68** (0.58-0.79)
HPB-RISC Pancreas cohort	0.02 0.93	**0.70** (0.63-0.78)
HPB-RISC Liver cohort	-0.01 1.05	**0.62** (0.50-0.75)

Figure 1. The predictive performance of the novel HPB-RISC model in the development cohort