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Prediction of complications after pancreaticoduodenectomy: validation of a postoperative complication score

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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

Département de Chirurgie et d'Anesthésiologie
Service de Chirurgie Viscérale

Prédiction des complications après duodénopancréatectomie céphalique: validation d'un score de complications postopératoires

Prediction of complications after pancreaticoduodenectomy: validation of a postoperative complication score

THESE

préparée sous la direction du Professeur associé Markus Schäfer
(avec la co-direction du Professeur Nicolas Demartines)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Prédiction des complications après duodénopancréatectomie céphalique: validation d'un score de complications postopératoires

Prediction of complications after pancreaticoduodenectomy: validation of a postoperative complication score

Lausanne, le 28 avril 2015

pour Le Doyen
de la Faculté de Biologie et de Médecine

Madame la Professeure Stephanie Clarke
Directrice de l'Ecole doctorale

Résumé

Objectifs

La chirurgie pancréatique reste associée à une morbidité postopératoire importante. Les efforts sont concentrés la plupart du temps sur la diminution de cette morbidité, mais la détection précoce de patients à risque de complications pourrait être une autre stratégie valable. Un score simple de prédiction des complications après duodénopancréatectomie céphalique a récemment été publié par Braga *et al*. La présente étude a pour but de valider ce score et de discuter de ses possibles implications cliniques.

Méthodes

De 2000 à 2015, 245 patients ont bénéficié d'une duodénopancréatectomie céphalique dans notre service. Les complications postopératoires ont été recensées selon la classification de Dindo et Clavien. Le score de Braga se base sur quatre paramètres : le score ASA (American Society of Anesthesiologists), la texture du pancréas, le diamètre du canal de Wirsung (canal pancréatique principal) et les pertes sanguines intra-opératoires. Un score de risque global de 0 à 15 peut être calculé pour chaque patient. La puissance de discrimination du score a été calculée en utilisant une courbe ROC (receiver operating characteristic).

Résultats

Des complications majeures sont apparues chez 31% des patients, alors que 17% des patients ont eu des complications majeures dans l'article de Braga. La texture du pancréas et les pertes sanguines étaient statistiquement significativement corrélées à une morbidité accrue. Les aires sous la courbe étaient respectivement de 0.95 et 0.99 pour les scores classés en quatre catégories de risques (de 0 à 3, 4 à 7, 8 à 11 et 12 à 15) et pour les scores individuels (de 0 à 15).

Conclusions

Le score de Braga permet donc une bonne discrimination entre les complications mineures et majeures. Notre étude de validation suggère que ce score peut être utilisé comme un outil pronostique de complications majeures après duodénopancréatectomie céphalique. Les implications cliniques, c'est-à-dire si les stratégies de prise en charge postopératoire doivent être adaptées en fonction du risque individuel du patient, restent cependant à élucider.

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Prediction of complications after pancreaticoduodenectomy: validation of a postoperative complication score

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This paper has been presented in parts at the 101st Annual Congress of the Swiss Surgical Society, May 21-23, 2014, Bern, Switzerland.

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Abstract

Objectives

Pancreatic surgery remains associated with important morbidity. Efforts are most commonly concentrated on decreasing postoperative morbidity, but early detection of patients at risk could be another valuable strategy. A simple prognostic score has recently been published. This study aimed to validate this score and discuss possible clinical implications.

Methods

From 2000 to 2012, 245 patients underwent pancreaticoduodenectomy. Complications were graded according to the Dindo-Clavien classification. The Braga score is based on American Society of Anesthesiologists score, pancreatic texture, Wirsung duct diameter, and blood loss. An overall risk score (from 0 to 15) can be calculated for each patient. Score discriminant power was calculated using a receiver operating characteristic curve.

Results

Major complications occurred in 31% of patients compared to 17% in Braga's data. Pancreatic texture and blood loss were independently statistically significant for increased morbidity. The areas under curve were 0.95 and 0.99 for 4-risk categories and for individual scores, respectively.

Conclusions

The Braga score discriminates well between minor and major complications. Our validation suggests that it can be used as prognostic tool for major complications after pancreaticoduodenectomy. The clinical implications, i.e., whether postoperative treatment strategies should be adapted according to the patient's individual risk, remain to be elucidated.

Keywords: pancreatic surgery - prognosis after pancreaticoduodenectomy - complication of pancreatic surgery - risk score - external validation.

Introduction

A better perioperative management significantly decreased mortality rates after pancreas surgery during recent two decades, mainly in high-volume centers (1, 2). However, morbidity remains stuck at a high level, and reported complication rates are ranging up to 35-50% (3, 4). Until recently, the surgical community underestimated that, in particular, severe complications negatively impact on postoperative outcomes, i.e., long-term survival, quality of life, and costs (5). Regarding also the facts that pancreatic cancer incidence is increasing in many Western countries, patient populations are getting older, and not to forget, potent oncological treatments become increasingly available, makes it of the utmost importance to effectively decrease postoperative morbidity (6).

As a first step, internationally accepted classification systems taking into account the occurrence as well as the severity of complications have been developed to assess complications after pancreas resection in a comparable and standardized manner (4, 7–9). Then, most efforts have been concentrated on decreasing complications once they have occurred postoperatively. While such an approach may work well for minor complications, anticipation of potentially severe complications and early detection of patients at risk represent another valuable strategy, which is worthwhile to further explore. It is a common clinical observation that complications in an individual patient do occur if too many risk factors are present at the same time (8, 10, 11). Some risk factors are already preoperatively present, such as malnutrition, cardiovascular disease, or smoking, while others become overt intraoperatively, such as soft pancreatic texture, small pancreatic duct diameter, or adverse events as bleeding.

Ideally, a simple prognostic score taking into account some preoperative and intraoperative features would allow identifying patients at risk for postoperative complications. Such

patients could be treated differently and followed more closely during the postoperative course. Moreover, modifiable risk factors, e.g., malnutrition, could be treated already preoperatively.

Recently, such a prognostic score has been published by Braga et al. (12). Briefly, American Society of Anesthesiologists (ASA) classification, pancreatic texture, main pancreatic duct diameter, and intraoperative blood loss are used to calculate a score indicating the risk of developing postoperative complications. The aim of this current study was to validate this prognostic score and to discuss its possible clinical implications.

Materials and Methods

Patients and Data Collection

A large set of more than 150 single items covering preoperative, operative, and postoperative data of every patient undergoing pancreatic surgery at the Department of Visceral Surgery, University Hospital of Lausanne (CHUV) is recorded in an electronic database (5, 13). Since 2009, patient data are collected prospectively, whereas patients operated from 2000 to 2008 have been entered retrospectively.

This current study included only patients who underwent elective pancreatic head resection (pancreaticoduodenectomy (PD), Whipple's procedure) for various benign and malignant diseases from 2000 to 2012. There were 256 patients identified as study patients, but 11 patients were excluded due to incomplete data or other concomitant surgeries in addition to PD. Of note, 52.7% of all pancreas resections have been performed since 2009.

The study was approved by the local Ethics Committee.

Surgical techniques

Most PDs (n=210) have been performed as so-called "classic" pancreatic head resection. Briefly, the pancreatic head was resected en-bloc together with the duodenum, the distal common bile duct, as well as the distal stomach. In addition, the resection included the first jejunal loop, the gallbladder, and loco-regional lymph nodes (14). A pylorus-preserving PD was preferentially used for benign disease (15, 16). The standard reconstruction of the alimentary tract included a pancreatico-enteric drainage, a bilio-enteric drainage, and finally a gastro-enteric anastomosis. In some few cases, a pancreaticogastrostomy was performed by a single surgeon who preferred this technique in case of soft pancreas. Two drains were routinely inserted near the pancreatico-enteric and bilio-enteric reconstructions. Drains were

removed on postoperative day 3 and 5, if there was no suspicion of leakage. Single-shot antibiotics were routinely used.

Pancreatic texture was intraoperatively determined by the responsible surgeon and classified as soft or hard. Pancreatic duct diameter was also assessed intraoperatively.

Assessment of postoperative morbidity and mortality

Postoperative morbidity and mortality rates were defined as any adverse events during the first 30 days postoperatively or during hospitalization following pancreatic head resection.

Complications were reported as number of complications, i.e., more than one complication per patient was possible. If appropriate, the highest classified complication was used for final analysis. Complications were graded according to their severity on a validated 5-point scale ranging from grade I to grade V (4, 17). Minor complications were defined as complications grade I and II, whereas major complications included complications grade IIIa to V. Of note, patient's death was considered as lethal complication grade V.

Specific definitions for surgical complications were used as they could be assessed according to internationally accepted guidelines (7–9). Pancreatic fistula: any measurable volume of fluid from a drain on or after postoperative day 3 with an amylase level greater than 3 times the serum amylase activity (7); delayed gastric emptying: inability to return to a standard diet by the end of the first postoperative week or prolonged (≥4 days) nasogastric intubation (8); hemorrhage: blood loss from drain or nasogastric tube, transfusion ≥3 units of packed red blood cells, or need for invasive treatment (9). Other postoperative complications collected were intra-abdominal infection (fluid or abscess), wound infection, bile leak, gastric leak, small bowel obstruction, portal vein thrombosis, cholangitis, and medical complications.

Assessment of complications was primarily performed by the surgical residents. Before entering complications into the database, all charts were reviewed by a single staff surgeon experienced in pancreatic surgery.

Predictive score of major postoperative complications by Braga et al. (12) (Table 1)

This score developed by Braga and colleagues was published in *Annals of Surgery* in 2011. It aims to predict the patient probability of having major postoperative complications after PD without regard to pathologies. Major complications were defined as complications IIIa to V according to Dindo-Clavien classification. After univariate and multivariate analyses four significant predictive factors were found: ASA score (I to III), pancreas texture (soft/hard), pancreatic duct diameter (> or ≤3mm), and blood loss during operation (≥ or <700ml). For each item between 0 and 6 risk points were attributed. Hence, the total score for an individual patient can range from 0 to 15 points. Each score level is related to a certain risk of developing major complications. A higher score should be associated with increased complication risk. For practical reasons, four risk categories have been defined.

For each patient, an individual risk score was calculated to estimate the risk for postoperative complications. All these risk scores were put together to get the four risk categories of the Braga score. The major complication risk of our series was compared to the Braga cohort.

Statistical analysis

Continuous variables were compared and analyzed using a Mann-Whitney *U*-test, as the distribution was not Gaussian. Discrete variables (categorical distribution) were interpreted using a Pearson chi-square test. A p-value <0.05 was considered significant.

The expected and observed numbers of patients of the different outcome categories were compared, and calibration was tested for a possible significance by using Hosmer-Lemeshow

goodness-of-fit statistic. In order to assess the discriminant power of the score, ROC curves were calculated (C-statistic index).

All statistical analyses were performed by using GraphPad Prism 5 for Mac OS X (GraphPad Software Inc.).

Results

Patients' characteristics and intraoperative findings

There were 147 men and 98 women with a median age of 65 years (interquartile range 54 to 75 years) who represent the study cohort. *Table 2* summarizes patients' characteristics and intraoperative findings.

Operative indications were ductal adenocarcinomas (122 patients, 49.8%), ampullary cancers (35 patients, 14.5%), cholangiocarcinomas (12 patients, 4.8%), neuroendocrine tumors (9 patients, 3.6%), intraductal papillary mucinous neoplasms (7 patients, 2.8%), benign lesions (37 patients, 15.1%), and chronic pancreatitis (23 patients, 9.4%). Among the 37 patients with benign lesions, 7 had mucinous cystadenomas, 6 serous cystadenomas, 5 pseudocysts, 4 papillary adenomas, 4 choledochal adenomas, 3 familial polyposis, 3 lymphoepithelial cysts, 2 pancreatic intraepithelial neoplasias, 1 solid pseudopapillary tumor, 1 inflammatory choledochal lesion, and 1 no abnormality (normal tissue).

Median blood loss in the overall, minor complication, and major complication groups were 400 ml, 400 ml, and 500 ml, respectively. By classifying the amount of blood loss according to the Braga score (≥700ml vs <700ml), blood loss was significantly correlated with the occurrence of major complications ($p=0.02$). By classifying pancreatic texture according to the Braga score (soft vs hard), patients with major complications had significantly softer pancreas ($p<0.01$).

Postoperative complications and length of hospital stay (Table 3)

The overall complication rate was 68.6%, indicating that 168 out of 245 patients had at least one complication. While minor complications occurred in 93 patients (38%), major complications were observed in 75 patients (30.6%). The highest ranked complication was grade I in 29 patients (11.8%), grade II in 64 patients (26.1%), grade IIIa in 22 patients (9%),

grade IIIb in 18 patients (7.3%), grade IVa in 12 patients (4.9%), grade IVb in 13 patients (5.3%), and grade V in 10 patients (4.1%), respectively.

Specific complications related to pancreatic resection, in particular, pancreatic fistula, delayed gastric emptying, and bleeding occurred in 47 (16.2%), 58 (19.9%), and 27 (9.3%) cases, respectively. Surgery-related infectious complications, such as wound infections and intra-abdominal abscess formation were observed in 52 (17.9%) and 35 (12%) cases. Non-surgical infections, e.g., urinary tract infections, cholangitis, or pancreatitis occurred in <3% each.

Length of hospital stay was correlated to the occurrence of major complications. The overall median length of stay for all patients was 18 days (interquartile range 13 to 27 days), but in case of major complications, the median hospital stay was significantly prolonged to 29 days (interquartile range 20 to 44 days).

Braga risk prediction score (Figures 1, 2, and 3)

For each patient, an individual risk score and its predicted risk were calculated. Thereby, the predicted mean risk for major complications in the overall group was 15.6% (38 patients out of 245 patients). The effectively observed rate was 30.6% (75 patients out of 245 patients). Patients with major complications (75 out of 245 patients) had a mean risk score of 8 points, meaning 18.4% risk for major complications.

The predictive performance of the Braga score in our patient cohort, using the four risk categories is shown in Figure 1. Compared to the Braga paper, our effective major complication risks are 2-3-fold increased in each of the four risk groups.

Predicted and observed mean risks for major complications were similar for all four risk categories and for progressive values, respectively ($p=0.68$ and $p=0.82$, Hosmer-Lemeshow test). ROC curves (four risk groups and progressive values) were calculated to determine the

discriminant power of the score. C-statistic index was 0.95 for four risk groups and 0.99 for progressive values (Figure 2 and 3).

Subgroup analysis

A subgroup analysis of all patients operated since 2009 and collected prospectively (n=130) was performed. Major complications occurred in 36.9% of the patients (48 patients). ROC curve for score categorized in four risk groups showed a C-statistic index of 0.956 ($p<0.0001$). ROC curve for score in progressive values showed a C-statistic index of 0.994 ($p<0.0001$).

Discussion

To decrease morbidity rates has come to the fore in pancreas surgery since there is good evidence that postoperative complications are associated with multiple negative consequences. This current study aimed to validate a recently published risk prediction score for major postoperative complications in a large single-center series of pancreatic head resections. Despite the fact that the major complication rate was 2-fold higher in our series compared to Braga's original series (31% vs 17%), the discriminant power of the score was preserved, and it can be considered as a potentially valuable adjunct tool to early identify patients at risk.

Braga et al. developed their score aiming to identify patients at risk for all types of major complications after pancreaticoduodenectomy, while other groups only focused their attempts on the prediction of pancreas-specific complications, e.g., pancreatic fistula (18–21). This latter aspect considers predominantly the surgeon's perspective on complications specifically related to pancreas surgery, but from a patient's perspective, the general occurrence, the severity of complications, and its consequences are much more relevant.

Whether predictive scores are really used in daily clinical practice is mainly dependent on their applicability, their robustness to reliably predict adverse events, and finally if effective prophylactic and therapeutic interventions are available to improve individual patient's outcome. A basic prerequisite is furthermore an external validation performed in other institutions using independent patient groups. The Braga score fulfills several of the above mentioned criteria. The application is easy as the score is only based on four criteria, all of which are pre- or intraoperatively already available. Hence, there is time to react if considered necessary, e.g., to adapt the type of reconstruction, to insert drains, to use feeding tubes, as well as a closer postoperative surveillance with prolonged ICU stay, to perform early

imaging, or reinterventions. However, the score has never been externally validated until now, and it remains unclear, whether risk prediction is feasible and reliable in other patient groups after pancreas resection and other surgical institutions.

Compared to other predictive scores like the PREPARE score that are based only on preoperative items, the Braga score includes intraoperative parameters which precludes undertaking preventive measures before the operation (22). Nevertheless, the Braga score is easy to calculate and allows a clinical estimation of the postoperative risk for complications. The Braga score offers therefore additional insights and can be complementary to other preoperative risk scores like the PREPARE score.

The overall complication rates of our series and the Braga series were similar with 68.6% and 61.7%, respectively (12). However, the overall severe complication rates were very different with 30.6% in our series compared to only 16.7% in the Braga series. While the mortality rates (grade V complications) were within the same range (4.1% our series vs. 3.9% Braga series), we had an important general tendency to a higher rating of all complications, in particular complications grade III and IV. This finding is in line with the fact that we observed fewer complications grade I (11.8% vs. 16.4%) and had a lower rate of patients without complications (31.4% vs. 38.2%).

Another important issue is the correct assessment of complications. In this context, it is not known who performed the assessment of complications in the Braga series. One single staff surgeon was responsible for the correct assessment in our series (23). Of note, a potential bias in our and the Braga patient group may be that the grading of complications has been performed retrospectively in some early operated patients as the Dindo-Clavien complication classification has only been published in 2004 (17).

Regarding the types of complications, our series had increased rates of infectious complications, as wound infections, intra-abdominal abscess formation, as well as pneumonia.

In contrast, intraperitoneal bleeding, pancreas-specific complications, i.e., pancreatic fistula and delayed gastric emptying occurred less frequently.

The predicted major complication rate in our series was 15.6% using the risk prediction score, but the observed effective rate was 30.8%. This underestimation is in contrast to the findings of the Braga group, where predicted and effectively observed major complication rates were very close. It can be concluded that our patient group (validation group) and the original patient group of Braga et al, revealed similar characteristics as predicted major complication rates were comparable. Observed discrepancies may be related to the tendency to "overrate" complications in our series as complications are recorded prospectively as soon as they occurred clinically. In addition, the management of complications varies between institutions, e.g., a more aggressive approach to treat complications automatically increases the grading. Thus, single institutions may have to adjust the score to their overall and major complication rates. Presumably the score may need further adaptations if novel techniques for complication management develop.

ROC curves confirmed the discriminant power of the score in our patient group. This means that the somewhat subjective grading of complications is not a confounding factor impairing the robustness of Braga score. The Braga score offers reliable and reproducible risk estimation for major postoperative complications in different patient populations (24, 25). Its criteria represent known risk factors in pancreatic surgery. The ASA classification is a surrogate parameter estimating pre-existing comorbidities, such as cardiovascular disease that is known to increase postoperative morbidity (26). As already published and confirmed also in this series, pancreas texture represents an important prognostic factor of major complications (10). The pancreatic duct diameter is a surrogate for the degree of technical difficulty to perform a safe entero-pancreatic anastomosis. Blood loss can be considered as parameter for the magnitude of the operative trauma.

In conclusion, the Braga risk prediction score represents an interesting tool for clinicians to potentially influence postoperative outcome after pancreas head resections. Further exploration by using a predefined risk score and therapeutic interventions is worthwhile.

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Table 1. Braga risk score (adapted from reference 12)

Predictor	**Categories**	**Risk score**
Pancreatic texture	Hard	0
	Soft	4
Main pancreatic duct diameter	>3mm	0
	≤3mm	1
Operative blood loss	<700ml	0
	≥700ml	4
ASA score	I	0
	II	2
	III/IV	6

Table 2. Patients' characteristics and intraoperative findings[1]

	All patients n=245		**Grade 0-II** n=172		**Grade III-V** n=73		**P-value**
Age (yrs)	65	54-75	64	54-74	67	53-76	0.34
Gender							0.48
Men	147	60.0%	106	61.6%	41	56.2%	
Women	98	40.0%	66	38.4%	32	43.8%	
BMI (kg/m^2)	24.1	21.6-26.5	24.2	21.6-26.6	23.6	21.6-26.2	0.74
ASA							0.27
I	15	6.1%	12	7.0%	3	4.1%	
II	166	67.8%	120	69.8%	46	63.0%	
III	62	25.3%	39	22.7%	23	31.5%	
IV	2	0.8%	1	0.6%	1	1.4%	
Operative indication for malignant disease	169	69.0%	112	65.1%	57	78.1%	0.45
Blood loss (ml)	400	300-800	400	300-700	500	400-800	0.01
Blood loss							0.02
<700ml	183	74.7%	136	79.1%	47	64.4%	
≥700ml	62	25.3%	36	20.9%	26	35.6%	
Pancreatic texture							<0.01
Soft	94	38.4%	49	28.5%	45	61.6%	
Hard	151	61.6%	123	71.5%	28	38.4%	
Main pancreatic duct diameter							0.12
≤3mm	138	56.3%	91	52.9%	47	64.4%	
>3mm	107	43.7%	81	47.1%	26	35.6%	
Pancreatic anastomosis							0.39
PJ	145	59.2%	105	61.0%	40	54.8%	
PG	100	40.8%	67	39.0%	33	45.2%	

[1]*Data are number of patients (with percentage) or median (with interquartile range).*

Table 3. Postoperative complications and length of hospital stay

	All patients (245)		Grade 0-II	Grade III-V	P-value
Absence of complications	77	31.4%	77 (31.4%)		
Dindo-Clavien classification[1]					
I	29	11.8%	29 (11.8%)		
II	64	26.1%	64 (26.1%)		
IIIa	22	9.0%		22 (9.0%)	
IIIb	18	7.3%		18 (7.3%)	
IVa	12	4.9%		12 (4.9%)	
IVb	13	5.3%		13 (5.3%)	
V	10	4.1%		10 (4.1%)	
Number of complications	291				
Pancreatic fistula	47	16.2%			
Delayed gastric emptying	58	19.9%			
Wound infection	52	17.9%			
Abdominal abscess	35	12.0%			
Bile leak	12	4.1%			
Intraperitoneal bleeding	27	9.3%			
Ileus	6	2.1%			
Pneumonia	15	5.2%		¨	
Urinary tract infection	4	1.4%			
Atrial fibrillation	4	1.4%			
Respiratory failure	3	1.0%			
Cholangitis	8	2.7%			
Acute pancreatitis	2	0.7%			
Myocardial infarction	3	1.0%			
Pulmonary embolism	5	1.7%			
Acute renal failure	5	1.7%			
Other medical complications	5	1.7%			
Length of hospital stay (days)[2]	18 (13-27)		15 (11-20)	29 (20-44)	<0.001

[1] *The highest ranked complication per patient was included.*

[2] *Median with interquartile range.*

Figure 1. Risk prediction of major complication rate using four risk classes of the score

Figure 2. ROC curve for score categorized in four risk groups (C-statistic index: 0.9494, P<0.0001, 95% confidence interval: 0.933 to 0.966)

Figure 3. ROC curve for score in progressive values (C-statistic index: 0.992, P<0.0001, 95% confidence interval: 0.983 to 1)

Figure 1.

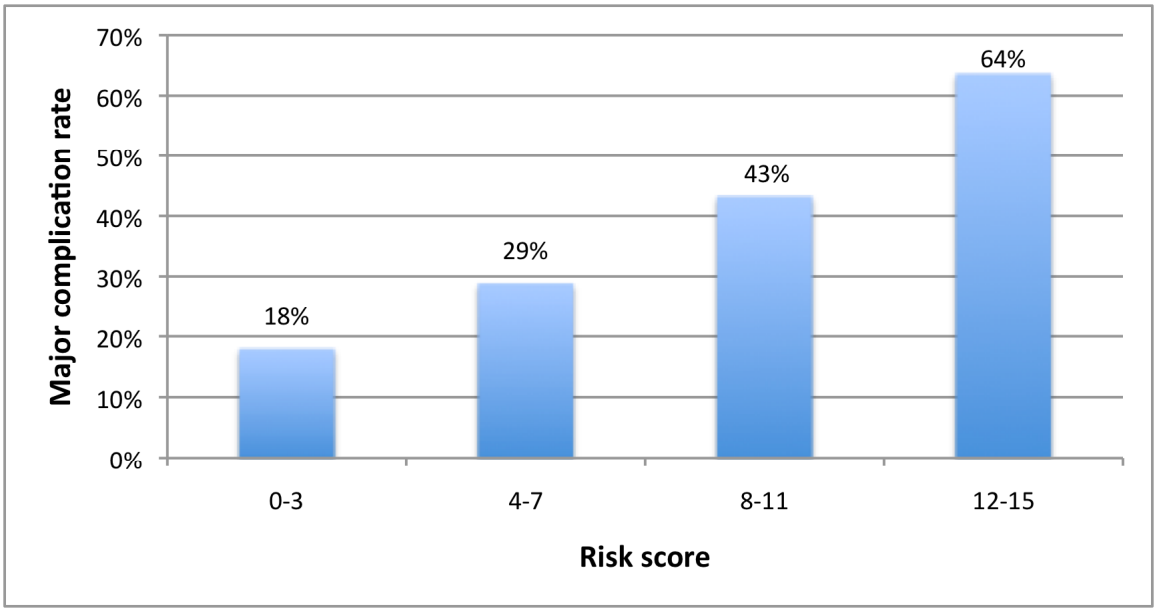

70%
60%
50%
40%
30%
20%
10%
0%
Major complication rate
18%
29%
43%
64%
0-3
4-7
8-11
12-15
Risk score

Figure 2.

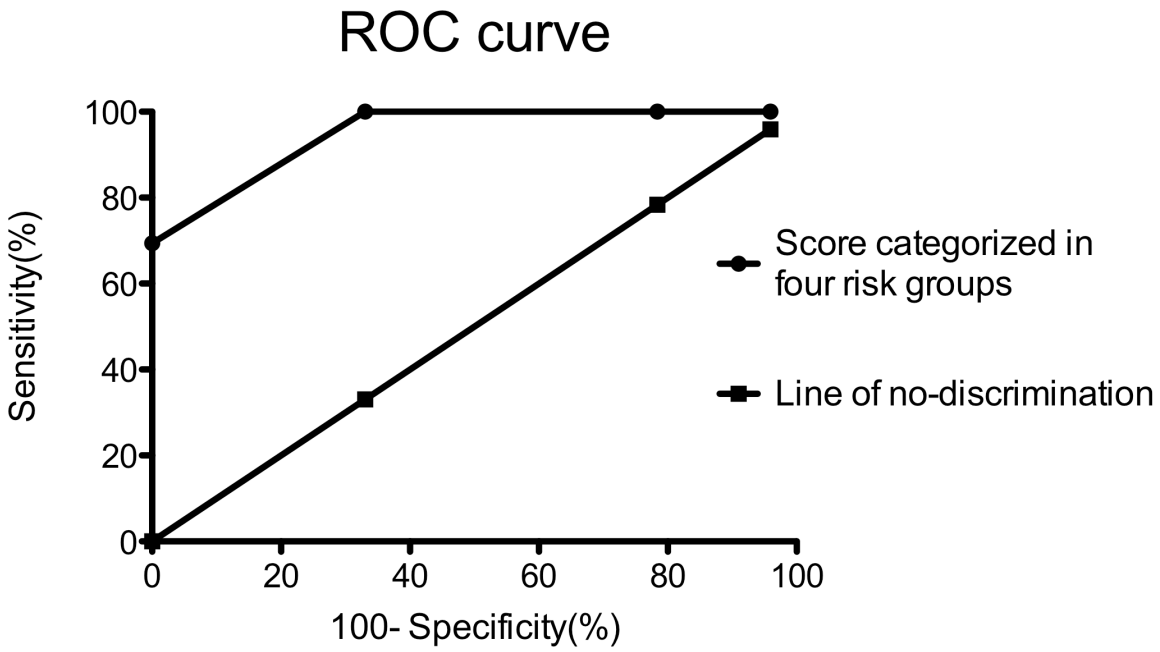
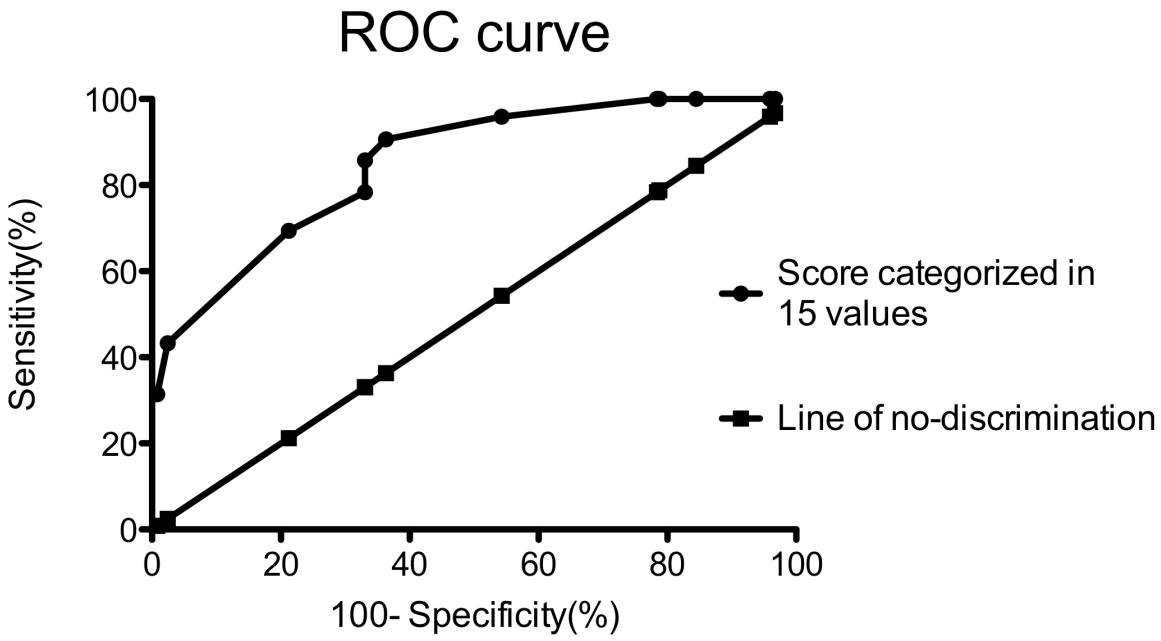

ROC curve
Sensitivity(%)
100
80
60
40
20
0
0
20
40
60
80
100
100- Specificity(%)
Score categorized in four risk groups
Line of no-discrimination

Figure 3.


ROC curve
Sensitivity(%)
100
80
60
40
20
0
0
20
40
60
80
100
100- Specificity(%)
Score categorized in 15 values
Line of no-discrimination