Developing nomogram to predict delayed hepaticojejunostomy stricture following pancreaticoduodenectomy

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I will do my best to make the help of many people shine more.

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ABSTRACT

Developing nomogram to predict delayed hepaticojejunostomy stricture following pancreaticoduodenectomy

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Incidence of anastomotic stricture after hepaticojejunostomy(HJS) in pancreaticoduodenectomy(PD) is about 4-10 % in benign disease, less common in malignancy. It is one of long-term complication following PD, however risk factors to predict HJS are not fully investigated. From Jan 2012 to May 2018, the medical records of the patients were retrospectively reviewed, who underwent PD by single surgeon in Severance hospital. HJS was confirmed by abdominal computed tomography and serum bilirubin during follow-up period. Total 283 patients were included, and HJS was found in 27patients (9.5%) during follow up period (median 14.3 months, range 3-60.2 months). Body mass index in HJS group was slightly lower than No-HJS group (22.37 vs 23.41, p=0.071) and proportion of malignancy in diagnosis was higher in HJS group (88.89% vs 73.83%, p=0.084). However, proportion of postoperative bile leak is significantly higher in HJS group than No-HJS group (n=4,14.81%, vs. n=9,3.52%, p=0.026). In multivariate COX regression model, female (HR 0.39, 95% CI 0.16-0.96, p=0.039), bile duct size (HR 1.35, 95% CI 1.08-1.68, p=0.007), postoperative bile leak (HR 3.82, 95% CI 1.25-11.7, p=0.019) were identified to be independent risk factors for HJS following PD. Based on this parameters, 3 year HJS free probability was able to presumed with Harrell's concordance index of 0.7131 (95% CI 0.58-0.82). Delayed occurrence of HJS following PD is able to be predicted with powerful risk factors such as female, bile duct size, postoperative bile leak event. Prospective and large cohort study and validation is mandatory in near future

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Key words: hepaticojejunostomy, stricture, nomogram

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I. Introduction

Pancreaticoduodenectomy(PD) is the treatment choice of periampullary pathological lesions. There are three fundamental sites of reconstruction (pancreaticojejunostomy, duodenojejunostomy, and hepaticojejunostomy) during PD. Although it has become world widely used procedure, it is still reported that mortality is 2-10%(1, 2) and morbidity is 40-50%(3). Postoperative complications related to pancreaticojejunostomy and duodenojejunostomy, such as postoperative pancreatic fistula or delayed gastric emptying are well-investigated. However, hepaticojejunostomy site stricture (HJS) is still considered relatively less important co-morbidity.

Although the incidence rate is lower than other complication, however HJS can accompany the long-term functional derangement to the patient. Incidence of HJS is reported to be about 4-10% in benign disease(3). In addition, it is known that less common in malignancy, like pancreatic ductal adenocarcinoma and cholangiocarcinoma.(4, 5) It is one of the long-term complication, which is able to cause obstructive jaundice. It is also known to be associated with malnutrition, glucose intolerance, exocrine insufficiency.(6-8)

Therefore, it would be clinically useful to analyze the risk factor of HJS and calculate the probability of occurrence following PD for proper postoperative management and follow-up strategy. In this study, we tried to investigate the potential risk factors and develop nomogram to predict HJS following PD.

II. Method and materials

1. Study cohort

From January 2012 to May 2018, total 283 patients underwent PD by single surgeon in the Division of Hepatobiliary and Pancreas at Severance hospital, Yonsei University, Seoul, Korea. Most PD was pylorus-preserving pancreaticoduodenectomy (PPPD). However, total pancreatectomy and conventional Whipple's operation were also performed in small proportion.

Laparoscopic PPPD started from January 2008 in our center. In early 6 cases, anastomosis reconstructions were performed through small laparotomy. Pancreaticogastrostomy underwent during that period. Since 2012, purely laparoscopic PPPD is performing. Medical records of patients were reviewed retrospectively. Clinical features of patients were described in terms of age, sex, body mass index, ASA score, preoperative laboratory finding such as CEA (carcinoembryonic antigen), CA 19-9 (carbohydrate antigen 19-9), total bilirubin. Perioperative findings were blood loss during operation, operation time, transfusion, conversion, bile duct size, postoperative bile leakage, neoadjuvant chemotherapy, combined resection, minimally invasive surgery. Also, variables related POPF (postoperative pancreatic fistula) such as pancreas texture, pancreatic duct size, pancreaticojejunostomy(PJ) method, final pathologic diagnosis, tumor size, positive lymph node number, R status, lymphovascular/perineural invasion were included in pathologic features. Internal Review Board of Severance hospital approved this study.

2. Hepaticojejunostomy method

There was no significant differences in both open and laparoscopic approach of HJ in principle. Bile duct size was measured during just before HJ. Basically, all HJ was performed with single lumen, and in the case of bile duct resection margin was made just below bile duct bifurcation, it was assumed as single lumen, same method was applied. After PJ, confirm the tension-free proper site (usually about 5-10 cm distant from PJ), make jejunal lumen with appropriate size using electrocauterization. Considering the elasticity of the jejunum, make a jejunal lumen about 3/4 size of the bile duct.

Continous suture with absorbable multifilament polyglactin (eg. Vicryl ®4-0 (Somerville, NJ, USA)) was performed in posterior wall of bile duct. At the edge of bile duct both side, interrupted suture was done for tagging. Anterior bile duct was closed by interrupted suture using same material.

3. Follow up and definition of hepaticojejunostomy stricture

After patient discharged from general ward, during 90 postoperative days, hepaticojejunostomy site stricture was confirmed in outpatient department. “Stricture” was defined a case in which the patient showed manifestation of jaundice of obstructive pattern, or stricture was confirmed in regular follow-up imaging study, so that intervention such as percutaneous trans bile duct drainage was needed. We excluded local tumor recurrence at the HJ site, such as common bile duct cancer. “Postoperative bile leak” was defined when the bile stain was visually obvious from operation site drain, or intraperitoneal fluid bilirubin level was high during hospital stay.

4. Statistical analysis and nomogram

Continuous variables were expressed as mean ± s.d when normal distribution was satisfied and tested with independent t-test. If the continuous variable does not satisfy the normal distribution, it is expressed as median (Q1, Q3) and tested with Mann-Whitney U-test. For the categorical variables, the frequencies were expressed as percentages and tested using the chi-square test and the Fisher's exact test.

Regarding of Cox regression on hepaticojejunostomy stricture, statistically significant variables of univariate/multivariate analysis were used for establishing most powerful predictiction multiple logstic model. A nomogram was developed by using the package rms in R version 3.1.3 Validation was performed using 10,000 bootstrapped sampling and generated the calibration plot. That model was verified using ROC (Receiver operating characteristic) curve to quantify the discriminative ability of the final model. Using Hosmer-Lemeshow goodnesss-of-fit test, probability was assessed with p-value >0.05 indicating well calibration. P-values <0.05 were considered to be statistically significant.

5. Internal validation for nomogram

From 2012 to 2014, retrospective data of total 268 patient were enrolled. It was collected from four different surgeon working in the same division and department. They did HJ by own method which includes all interrupted suture of anterior/posterior wall of bile duct with absorbable multifilament. Definition of HJS was applied same way described above. For the validation, 10,000 bootstrap and calibration plot was conducted.

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III. Results

1. Clinical characteristic between HJS group and no-HJS group

During the follow-up period (median 14.3 months, range 3-60.2 months) HJS occurred in 27 patients (9.5 %) (**Figure 1**). In HJS group, median age was 62 years old, 19 patients were male. Mean BMI was lower in HJS group, however there was no statistically significant difference. Half of patients in HJS group were underwent minimally invasive surgery. Only one patient had previous neoadjuvant chemotherapy in HJS group. Preoperative serum CA 19-9 level was higher in HJS group with not statistically significance. (**Table 1**)

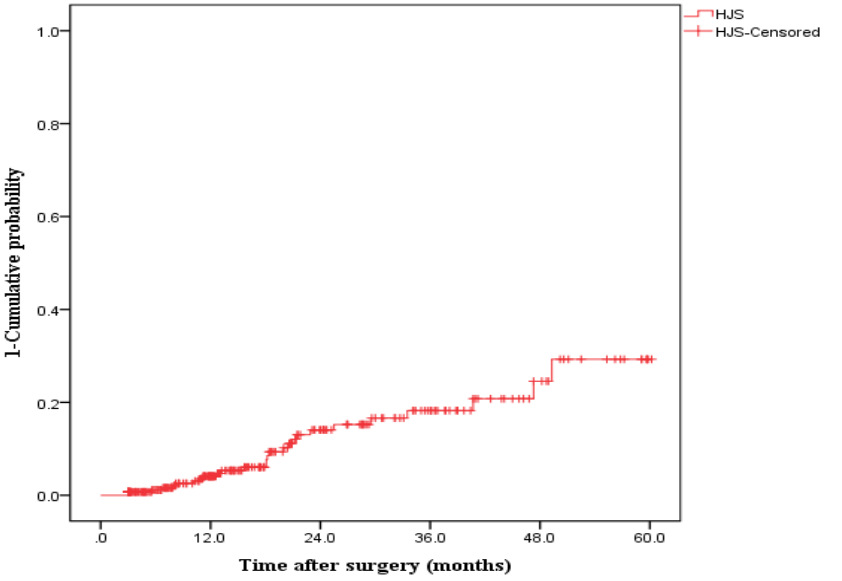

Figure 1. Cumulative probability of HJS

Table 1. Clinical features of two groups.

Variables (% , Q1-Q3, Mean±SD)	No-HJS N=256	HJS N=27	p-value
Sex			0.147
Female	113 (44.14%)	8 (29.63%)	
Male	143 (55.86%)	19 (70.37%)	
Age (years)	65 (56-72)	62 (55-68)	0.681
BMI (kg/m^2)	23.41±2.87	22.37±2.3	0.071
Preoperative symptom			0.961
No	77 (30.08%)	8 (29.63%)	
Yes	179 (69.92%)	19 (70.37%)	
Minimally invasive surgery			0.450

No	104 (40.63%)	13 (48.15%)	
Yes	152 (59.38%)	14 (51.85%)	
Total bilirubin (mg/dL)	0.75 (0.5-1.6)	0.9 (0.5-1.8)	0.334
Preoperative serum CEA	2.24 (1.34-3.95)	1.92 (1.29-2.9)	0.317
Preoperative serum CA 19-9	493.1 ± 1690.7	772.9 ± 1704.2	0.375
Neoadjuvant Chemotherapy			0.489
No	230 (89.84%)	26 (96.3%)	
Yes	26 (10.16%)	1 (3.7%)	

BMI, body mass index ; CEA, carcinoembryonic antigen ; carbohydrate antigen 19-9 ,

2. Comparison of perioperative findings between two groups

More than 90% of patients were underwent PPPD or conventional Whipple's operation, except 12 patients of total pancreatectomy. There was no statistically significant difference regarding of anastomosis method whether manual or minimally invasive approach. Although proportion of malignancy in HJS was higher than non-HJS group, there is no statistically significance. In HJS group, mean operation time was 478 minutes and estimated blood loss was 465.9 ml.(**Table 2**)

When it comes to variables related to complication of pancreatic anastomosis, there was no statistical significance in pancreatic texture and pancreatic duct size. Meanwhile, Clinical relavant Postoperative pancreatic fistula (POPF) such as Grade B or C occupied 14.6% in non-HJS, however there was no Grade B or C in HJS group. In terms of bile duct size, HJS group showed larger size (1.6cm vs. 1.2cm). Postoperative bile leak was more significantly frequent in HJS group than non –HJS group (3.52% vs. 14.81% , p=0.026) (**Table 3**)

Table 2. Perioperative characteristics

Variables (% , Mean±SD)	**No-HJS (N=256)**	**HJS (N=27)**	**p-value**
Operation			0.320
PPPD or Conventional PD	246 (96.09%)	25 (92.59%)	
Total pancreatectomy	10 (3.91%)	2 (7.41%)	

Pancreatic reconstruction			0.310
Pancreaticojejunostomy	233 (91.0%)	23 (85.2%)	
Duct to mucosa			
Pancreaticojejunostomy	10 (3.9%)	2 (7.4 %)	
Dunking method			
Pancreaticogastrostomy	13 (5.1%)	2 (7.4%)	
Anastomosis			0.591
Manual	132 (52.17%)	15 (55.56%)	
Laparoscopic or robot	123 (48.23%)	12 (44.44%)	
Diagnosis 1			0.439
Non-PDAC	181 (70.7%)	21 (77.78%)	
PDAC	75 (29.3%)	6 (22.22%)	
Diagnosis 2			0.084
Benign	67 (26.17%)	3 (11.11%)	
Malignancy	189 (73.83%)	24 (88.89%)	
Combined vessel resection			0.286
No	184 (71.88%)	22 (81.48%)	
Yes	72 (28.13%)	5 (18.52%)	
Operation time(min)	468.15±95.1	478.67±74.01	0.578
ASA score			0.605
1/2	148 (57.81%)	17 (62.96%)	
3/4	108 (42.19%)	10 (37.04%)	
Estimated blood loss (ml)	428.9±422.0	465.9±323.8	0.164
Transfusion			0.451
No	237 (92.58%)	24 (88.89%)	

Yes	19 (7.42%)	3 (11.11%)	
Open Conversion			>0.999
No	226 (88.28%)	24 (88.89%)	
Yes	30 (11.72%)	3 (11.11%)	

PDAC, pancreatic ductal adenocarcinoma

Table 3. Variables associated with pancreas anastomosis and biliary anastomosis factors.

Variables (Mean±SD)	**No HJS (N=256)**	**HJS (N=27)**	**p-value**
Pancreatic duct size (mm)	4.0 ± 2.6	3.6 ± 2.6	0.433
Pancreatic texture			0.380
Soft	149 (63.14%)	18(72%)	
Hard	87 (36.86%)	7 (28%)	
Postoperative pancreatic fistula (POPF)			0.096
No	151 (59.68%)	18 (66.67%)	
POPF A	65 (25.69%)	9 (33.33%)	
POPF B+C	37 (14.62%)	0 (0%)	
Bile duct size, (mm)	1.2 ± 0.8	1.6 ± 2.1	0.621
Postoperative bile leak			0.026
No	247 (96.48%)	23 (85.19%)	
Yes	9 (3.52%)	4 (14.81%)	

3. Comparison of pathological findings

Mean tumor size was 3.1 cm and mean positive metastatic lymph nodes was 1.8. Regarding of lymphovascular and perineural invasion, there were no statistically significan differences between non-HJS group and HJS group. R0 resection was achieved more than 96% of two groups, and there was no differences between two groups. (**Table 4**)

Table 4. Pathological characteristics

Variables (Mean±SD)	No HJS (N=256)	HJS (N=27)	p-value
Tumor size (cm)	2.7 ± 1.5	3.1± 2.1	0.531
Metastatic Positive lymph nodes	1.1±2.3	1.8±2.9	0.330
Metastasis			0.567
No	241 (97.18%)	26 (96.3%)	
Yes	7 (2.82%)	1 (3.7%)	
Lymphovascular invasion			0.339
No	154 (69.37%)	15 (60%)	
Yes	68 (30.63%)	10 (40%)	
Perineural invasion			0.104
No	99 (45%)	7 (28%)	
Yes	121 (55%)	18 (72%)	
R status			>0.999
R0	242(96.03%)	26 (96.3%)	
R1	10 (3.97%)	1 (3.7%)	

4. Cox regression analysis of HJS

In Cox regression analysis of HJS occurrence, male (HR 0.39, 95% CI 0.16-0.96, p=0.039) and bile duct size (HR 1.35, 95% CI 1.08-1.68, p=0.0077) , postoperative bile leak (HR 3.82, 95% CI 1.25-11.7, p=0.019) were significant factors that contributing occurrence of HJS. In univariate analysis, positive metastatic lymph node numbers showed statistically significance, however there was no significance in multivariate analysis. (**Table 5**)

Table 5. Cox regression analysis

	Univariate			Multivariate		
Variables	p-value	HR	95% CI	p-value	HR	95% CI
Gender						
Female	0.068	0.46	0.2-1.06	0.0399	0.39	0.16-0.96
Age (years)	0.696	0.99	0.96-1.03			
BMI (kg/m^2)	0.142	0.91	0.79-1.03			
Neoadjuvant CTx	0.45	0.46	0.06-3.42			
Tumor size (cm)	0.15	1.15	0.95-1.39			
Positive lymph nodes	0.036	1.13	0.10-1.27	0.170	1.09	0.96-1.24
R status						
R_1	0.953	0.94	0.13-6.95			
Operation						
Total pancreatectomy	0.186	2.66	0.62-11.3			
Pancreaticojejunostomy						
Dunking	0.860	0.88	0.2-3.77			
Anastomosis						
Laparoscopic or robot	0.477	1.34	0.6-2.97			
Diagnosis 1						
PDAC	0.805	0.89	0.36-2.22			
Diagnosis 2						
Malignancy	0.141	2.46	0.74-8.17			
Transfusion	0.869	1.11	0.33-3.69			
Pancreatic duct size (mm)	0.681	0.97	0.81-1.15			
Soft pancreas	0.639	0.81	0.34-1.95			

POPF						
No vs. POPF A	0.988	0.99	0.44-0.22			
No vs POPF B+C	0.144	0.12	0.01-2.09			
Bile duct size, (mm)	0.005	1.37	1.1-1.71	0.0077	1.35	1.08-1.68
Postoperative bile leak	0.010	4.1	1.4-12.02	0.0190	3.82	1.25-11.7

5. Nomogram for prediction of 3-year HJS free probability

Using meaningful variable that appeared from Cox regression analysis, nomogram for 3-year HJS free probability was investigated. Bile duct size, postoperative bile leak, number of positive metastatic lymph nodes, gender are consist of nomogram. It was found that 3-year HJS free probability of C-index of nomogram was 0.715 (95% CI 0.5889-0.8248) by using 10,000 bootstrap resampling. (**Figure 2**). In calibration plot, actual probability of 3-year HJS was underestimated in 0.5-0.7 interval period. However above that period, accuracy was well-correlated to the actual probability. (**Supplement 1)**

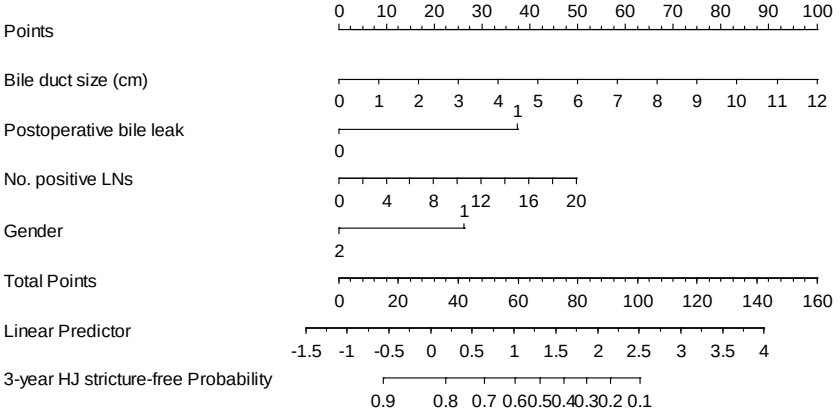

Figure 2. Nomogram for 3-year HJS free probability.

6. Validation for nomogram

Among 268 patients, 27 patients (10.1%) occurred HJS. Compared to training set, 28 patients underwent postoperative bile leak and median bile duct size was 1 cm (0.7-1.5). Harrell's c-index for 3-year HJ free probability in validation set was 0.6312 (95% CI 0.5009-0.7578). (**Supplement 3**)

IV. Discussion

In recent years, standardization of PD procedure itself has led to incredible decreasing of morbidity and mortality. However, still reported more than 40-50% of patients who underwent PD suffering from postoperative complication. Among them HJ site stricture has not been considered as serious complication, because mostly it is not life-threatening compared to severe complication such postpancreatectomy hemorrhage or postoperative pancreatic fistula, and also one of the long-term insidious complication(9, 10). In fact many studies showed median time to diagnosis was 8 months to more than 60 months. (11, 12) Furthermore, it is reported that cumulative probability of biliary stricture at 1 year is 2.9 % and at 5 year is 8.2 %.(5) Meanwhile, report of early stricture occurred in only 90 postoperative days was 2%.(13) However, once it occured, patient may suffered from obstructive jaundice, cholangitis, and another post-intervention complication. Therefore, recent some studies on HJ anastomosis complication are reported in accordance with the world tendency to management the quality of life after PD.

To the best of our knowledge, this study is first report of HJS occurrence and nomogram for predicting HJS free probability. In present study, postoperative bile duct leak, bile duct size, metastatic nodal status, male gender were major risk factor for HJS.

Small Bile duct size was commonly suggested risk factor for HJS in previous studies. Although it was regarding of early bilio-enteric anastomosis stricture (in 90 postoperative days), Malgras et al. found that common bile duct less than 5 mm was potent significant factor for HJS, along with younger age($\leq$60), suture material (6-0 caliber) and blood transfusion.(13) Ducon et al. also reported that less than 5mm bile duct is only predisposing factor for biliary stricture. (14) It seems to be totally opposite result of this study, however, it should be considered with correlation in concept of HJ wall suture method previously presented. HJ suture method (posterior wall-continous, anterior wall-interrupted) is based on the concept that is able to prevent postoperative bile leakage by continuous suture in posterior wall and prevent HJS by interrupted suture in anterior wall. This concept, learned from other previous studies allows surgeon to have a tendency to make the stitches much closer when the bile duct is large. This interpretation is complementary to the other result of present study, namely that postoperative bile leak is a potent risk factor for HJS.

Male gender is significant risk factor for HJS in present study. Dimou et al. reported male gender is risk factor (Hazard ratio 1.12, 95% CI 0.92-1.37) for HJS in study of 3374 patients who underwent HJ(15). It might be correlate with large bile duct size, because in male patients, they showed relatively large bile duct size than female patients. In addition, they reported younger age was

another significant factor associated with stricture formation. Hypothesis was that younger patients have more time at risk, to develop stricture formation. This is because of its characteristic that appears commonly later in the postoperative period. Unlikely, however, result of present study did not show the age as significant risk factor.

Number of metastatic positive lymph node was also predisposing risk factor for HJ. It seemed to be related to the blood supply around bile duct anastomosis. Although there was no statistically significant difference, HJS was more frequent in patients with malignancy. Based on this environment, blood supply of bile duct would be insufficient as extended dissection of soft tissue and lymph nodes around bile duct was performed. Asano et al also reported that nodal status was important factor for HJS. (16)

Nomogram consist with these significant variable showed potent predictability for HJS occurrence at 3 year after surgery.(C-index 0.715) It is considered fact that HJS occurred mostly late postoperative period after more than 3 years. In present data showed most event occurred after 3 years of postoperative period. Regarding of internal validation of HJS from other surgeons, it showed moderately acceptable predictability for HJS considering internal validation would be lower than training set mostly. When internal validation group divided into two groups by totally different HJ suture method (all interrupted suture with tie knot placed in inside of lumen), it is also showed similar validity (C-index 0.6444 / 0.6207). These results may represents that HJ method itself is not potent HJS factor rather than patient status or surgical environment factors such as, bile duct size, nodal status, gender.

However, because of present study is retrospective single center study, investigated cohort is relatively small so that HJ occurrences were not frequent. Also, there are possibilities that not precise data might be collected such as, bile duct size. To overcome these limitations, large cohort prospective study is mandatory in near future.

V. Conclusion

In conclusion, HJS after PD is relatively rare but long-term complication. Delayed HJS is able to be predicted by predisposing risk factor such as bile duct size, postoperative bile leak, positive lymph node, gender. In addition, with developed nomogram base on these potent parameters, it is calculated risk percentage for delayed HJS after PD.

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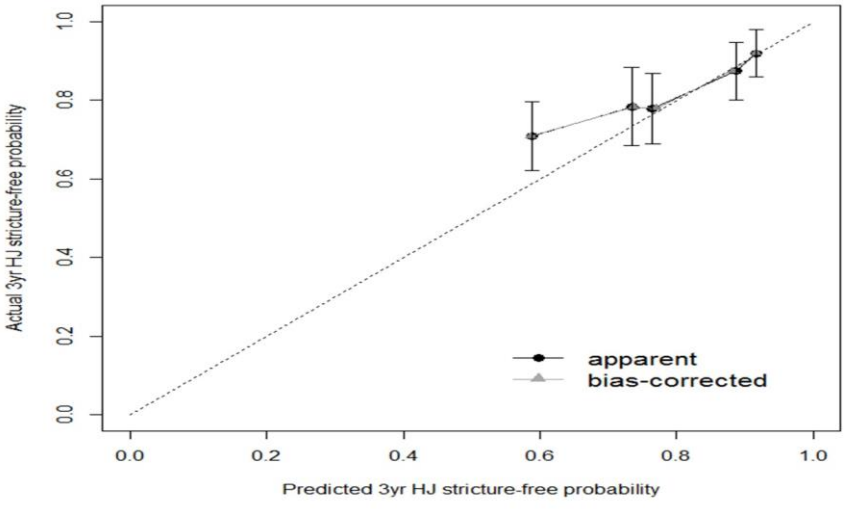
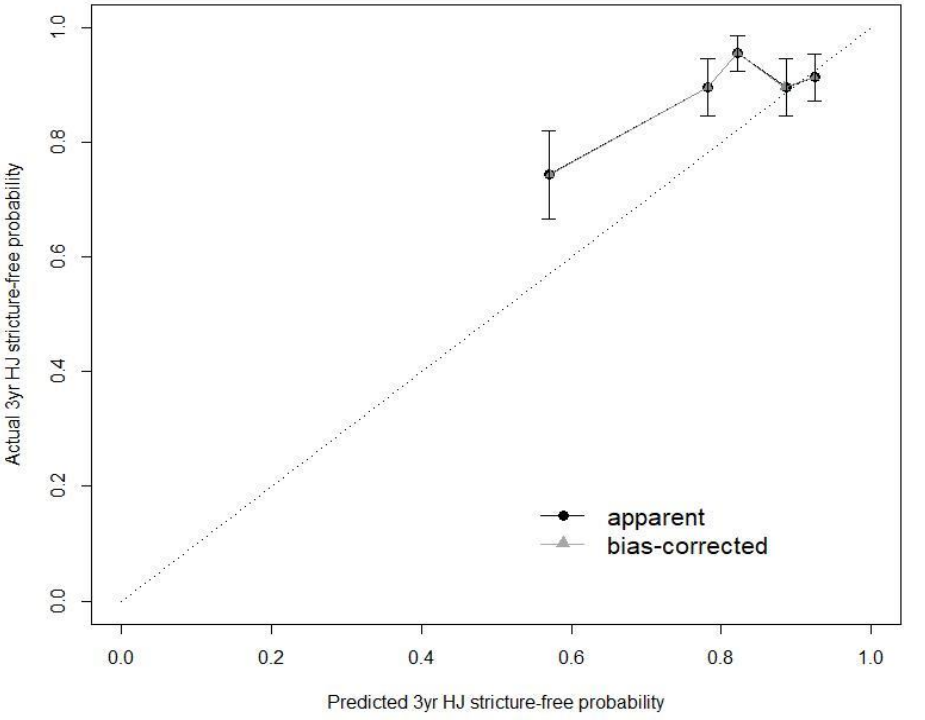
APPENDICES



Supplement 1. Calibration plot for 3-year HJ stricture free probability.

Total points	3-yr HJ stricture free Probability
101	0.1
91	0.2
83	0.3
75	0.4
67	0.5
59	0.6
49	0.7
36	0.8
15	0.9

Supplement 2. Prediction value by nomogram and its HJ stricture free probability.



Supplement 3. Calibration plot for internal validation set

ABSTRACT(IN KOREAN)

췌십이지장절제술의 지연성 담도공장문합술 부위 협착을 예측하는 노모그램의 개발

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췌십이지장절제술에서 담도공장문합부위의 협착은 양성질환에서 4-10% 이고, 췌장암 등과 같은 악성 종양에서는 그 보다 덜한 것으로 알려져 있다. 본 연구에서는 2012년 1월부터 2018년 5월까지 췌십이지장절제술에서 담도공장문합술을 시행 받은 환자를 후향적으로 분석하였다. 수술후 90일동안 추적관찰하면서 영상의학적 검사상 담도공장문합 부위 협착이 관찰된 환자를 분석하였다. 총 283명을 분석하였고, 그 중 27명 (9.5%)이 담도공장문합부위 협착이 확인되었다. 협착발생군의 평균 체질량지수는 22.37 kg/ m^2 로, 비협착군 평균 체질량지수 23.41 kg/ m^2보다 작았고 (p=0.071), 협착 발생군의 악성 종양의 비율은 88.89 %로, 비협착군에서의 악성 종양 비율 73.83% 보다 높았다. (p=0.084) 협착 발생군의 수술후 담즙유출 발생 비율은 14.81 %(4명)로, 비협착군의 3.52%(9명)보다 통계적으로 유의미하게 더 높았다. (p=0.026). COX 회귀 분석에서 여성 (HR 0.39, 95% CI 0.16-0.96, p=0.039), 담도 크기 (HR 1.35, 95% CI 1.08-1.68, p=0.007), 수술후 담즙 유출 (HR 3.82, 95% CI 1.25-11.7, p=0.019)가 담도공장부위 협착 발생의 유의미한 인자였다. 이러한 인자를 바탕으로 3년 담도공장부위 협착 발생도를 예측하는 노모그램을 개발하였고, C-index 가 0.7131 (95% CI 0.58-0.82) 였다. 이 노모그램으로 췌십이지장 절제술에서 지연성 담도공장문합 부위 협착의 발생을 예측할 수 있으며,

추후 전향적이고 좀더 많은 환자를 대상으로 한 연구가 필요할 것으로 생각된다.

핵심되는 말 : 췌십이지장절제술, 담도공장문합술, 협착, 노모그램