What is the most adapted indication of prophylactic pancreatic duct stent within the high-risk group of post-ERCP pancreatitis? ～Using the propensity score analysis

Takenaka, Mamoru

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What is the most adapted indication of prophylactic pancreatic duct stent within the high-risk group of post-ERCP pancreatitis?

～Using the propensity score analysis

ERCP 後膵炎の高リスク群において予防的膵管ステントが最も適応となる群の検討
～傾向スコア解析を用いて

竹中 完, 藤田 剛, 杉山 大典
増田 充弘, 塩見 英之, 杉本 真樹, 佐貫 毅, 早雲 孝信, 東 健, 久津見 弘

神戸大学大学院医学研究科医科学専攻
消化器内科学
（指導教員：東 健教授）

竹中 完

Key words: Post-ERCP pancreatitis; pancreatic duct stent; propensity score analysis

What is the most adapted indication of prophylactic pancreatic duct stent within the high-risk group of post-ERCP pancreatitis? ～Using the propensity score analysis

Short title: Propensity analysis for usefulness of PPDS

Mamoru Takenaka[1], Tsuyoshi Fujita[1], Daisuke Sugiyama[2], Atsuhiro Masuda[1], Hideyuki Shiomi[1], Maki Sugimoto[1], Tsuyoshi Sanuki[1], Takanobu Hayakumo[1], Takeshi Azuma[1] and Hiromu Kutsumi[1]

INSTITUTIONS OF AUTHORS

[1] Division of Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

[2] Section of Evidence-based Laboratory Medicine, Division of Clinical Pathology and Immunology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

CORRESPONDING AUTHOR'S ADDRESS

Hiromu Kutsumi M.D.

Department of Endoscopy, Kobe University Hospital 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

Tel.: +81-78-382-6305

Fax: +81-78-382-6309

E-mail: hkutsumi@med.kobe-u.ac.jp

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ABSTRACT

BACKGROUND/PURPOSE: Conducting randomized controlled trial (RCT) for each of the risk factors associated with prophylactic pancreatic duct stent (PPDS) for post-ERCP pancreatitis (PEP) is difficult owing to the volume of cases and ethical considerations.

In this study, we tried to reveal the degree of preventive effects of PPDS for each individual risk factor within the high-risk group of PEP using the propensity score analysis.

METHODS: The clinical data of 1131 ERCP practices performed at Kobe University Hospital from April 2006 to February 2009 were collected prospectively. We investigated their clinical characteristics including the risk factors of PEP, the use of PPDS and complications of ERCP. We conducted the stratification analysis using the propensity score matching analysis.

RESULTS: In 210 propensity score-matched ERCPs, PPDS proved to be effective in preventing PEP in patients with a history of pancreatitis (odds ratio 0.11, 95% CI 0.01-0.76, *p*=0.01) and cases of difficult cannulation (requiring more than 30 minutes) (odds ratio 0.13, 95% CI 0.01-1.14, *p*=0.08).

CONCLUSIONS: Patients with a history of pancreatitis and cases of difficult cannulation

are strongly recommended for PPDS placement. The propensity score analysis can be adapted to the ERCP-related analysis with many procedure-related factors with using retrospective data, and may be adapted to investigate the matters that are unsuitable for RCT by volume and ethical issue.

INTRODUCTION

It is considered that a prophylactic pancreatic duct stent (PPDS) prevents Post-ERCP pancreatitis (PEP) by preserving pancreatic juice flow [1-6], and as the results of randomized controlled trials and meta-analyses show, evidence of the efficacy of pancreatic stents for reducing PEP continues to accumulate. [4, 7-8] The latest meta-analysis estimated the relative risk of pancreatic stent placement in PEP as being 0.32 (95% confidence interval 0.19-0.52; $p<0.001$). [8] In the guidelines for prophylaxis of PEP from the European Society of Gastrointestinal Endoscopy (ESGE), PPDS is in recommendation grade A in patients who are at high risk for the development of PEP. [9] However, never PPDS is placed in all high-risk patients of PEP in real clinical practice. The use of PPDS was reported to be less widespread in the European investigation. [10] There was a blatant discrepancy between the scientific evidence and the routine use of PPDS.

One of the reasons is thought that it is not apparent which group receives the most preventive effects from PPDS within the high-risk group of PEP. In order to clarify the appropriate application of PPDS, it is important to reveal the degree of preventive effects for each individual risk factor within the high-risk group of PEP.

However, conducting RCT for each of the risk factors associated with PEP may be difficult owing to the volume of cases and ethical considerations, especially in ERCP-related procedure which is affected by intraoperative decision.

Therefore, in the present study, we used propensity score analysis which is one of statistical analysis methods for being adapted for retrospective data. The propensity score analysis can balance the effects of many latent confounding risk factors with the element of intraoperative techniques within it.

In this study, we tried to reveal the degree of preventive effects of PPDS for each individual risk factor within the high-risk group of PEP.

METHODS

Patients

The clinical data of 1131 ERCP practices performed at Kobe University Hospital from April 2006 to February 2009 were collected prospectively. We investigated their clinical characteristics, including the risk factors of PEP, the use of PPDS and complications of ERCP.

In this study, the risk factors of PEP are defined as follows considering the European Society of Gastrointestinal Endoscopy (ESGE) Guidelines: female gender, difficulty with

cannulation (requiring 15~30 minutes, more than 30 minutes), total procedure time (requiring 30~60 minutes, more than 60 minutes), pancreatic duct injection, pancreatic IDUS, pancreatic juice cytodiagnosis, pancreatic duct brush cytodiagnosis, pre-cut sphincterotomy, previous pancreatitis, and suspected SOD. [7, 11]

The definition of PEP was standardized by a consensus conference held in 1991, and those criteria have become widely accepted. [5] PEP was defined as pancreatic pain and hyperamylasemia within 24 hours of the procedure. Pancreatic pain was defined as persistent pain in the epigastric or periumbilical region. Hyperamylasemia was defined as an increase in serum amylase to more than 3 times the upper normal limit defined by our institution (37-102 U/l). [5, 12]

Patients whose papillae were unphysiological (as follows) were excluded from this study: (1) previous endoscopic sphincterotomy or papillary balloon dilation, (2) pancreas divisum, (3) tumor of papilla of Vater, (4) endoscopic nasopancreatic drainage (ENPD)/pancreatic stent (no spontaneous dislodgement), or (5) post-pancreaticoduodenectomy.

This study was conducted in accordance with the Declaration of Helsinki and its amendments (UMIN-CTR ID: 000007332). This study protocol was approved by the Kobe University School of Medicine Ethics Committee (No.1283).

All authors had access to the study data and had reviewed and approved the final manuscript.

ERCP

ERCPs were performed by the four operators with experience of more than 500 ERCP cases. In our ERCP practice, the proportion of therapeutic procedures was approximately 65%. After the procedure, patients continued fasting until the next morning with a drip infusion. All patients received an infusion of protease inhibitor (nafamostat mesilate, 20 mg/day) and antibiotics for 2 days. Serum amylase levels were measured at baseline, 4 hours later, and 18-24 hours later.

PPDS

Use of a PPDS was attempted when the operator judged that it was necessary, having considered that the case had become a high-risk case of PEP.

The PPDS procedure was carried out using a 5F polyethylene stent (Cook Endoscopy, Inc., Winston-Salem, NC). In all cases, stent dislodgments were confirmed by abdominal radiographs taken within 7 days after the ERCP. If the stent had not been dislodged, it was removed using the duodenoscope.

Statistical analysis

The difference in the incidence of PEP between the stent group and the non-stent group

was analyzed by chi-squared test or Fisher's exact test. The differences of other clinical characteristics between the two groups were analyzed by chi-squared test or Fisher's exact test for categorical variables, and were analyzed by a t-test for continuous variables.

To elucidate the usefulness of PPDS for the prevention of PEP, propensity score matching analysis was performed because PPDS was used in selected patients in this study. The propensity scores of PPDS were generated by a multivariate logistic regression model [13-15] using the possible confounders (i.e. age, sex, difficulty of cannulation, total procedure time, pancreatic duct injection, pancreatic IDUS, biliary IDUS, pancreatic juice cytodiagnosis, biliary juice cytodiagnosis, pre-cut sphicterotomy, endoscopic sphincterotomy, suspected SOD, and previous pancreatitis).

Although difficult cannulation was defined as that requiring greater than 30 minutes for cannulation according to a previous report [1], 95.4%(1079/1131) cases in our cases were intubated within 30 minutes. (Table 2) So, difficulties of cannulation were divided into three categories: requiring 0-15 minutes (as reference) /15-30 minutes/more than 30 minutes.

The differences between 0-15 minutes and 15-30 minutes, 0-15 minutes and 30-minutes were analyzed.

Total procedure times were also categorized into three groups: requiring 0-30 minutes/30-60 minutes/more than 60 minutes.

The propensity score was calculated for each patient based on a logistic regression analysis of the probability of PPDS using clinical characteristics. With these propensity scores, we used matching technique to create a 1-to-1 match of cases with controls. Specifically, using the propensity scores, one-to-one matching [13] with nearest neighbor approach, a “greedy” approach where the closest control match for each treated unit is chosen one at a time,[16] was performed for the stent group and the non-stent group (Figure 1).

C-statistic calculated by the receiver operating characteristic curve of our model was 0.78, showing that our model had good ability to distinguish stent-use patients from non-stent-use patients. After the matching, the incidences of PEP were compared between the matched stent group and the matched non-stent group. Subgroup analyses limited to high-risk patients were also performed. Influences of risk factors were estimated by odds ratio with a 95% confidence interval. All analyses were performed using R version 2.12 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, p values <0.05 were considered statistically significant.

RESULTS

PPDS

Of 1131 ERCPs, PPDS placements were attempted in 105 (9.0%) ERCPs. Table 1 shows a summary of stent placements. With regard to the frequency of PPDS attempts, the risk factor for which PPDS was attempted at the highest frequency was pre-cut sphincterotomy (37.5%, 6/16), followed by pancreatic IDUS (26%, 17/65), pancreatic brush cytodiagnosis (21.7%, 20/92), and suspected SOD (20%, 4/20).

The proportion of ERCPs in which PPDS was attempted according to the number of risk factors of PEP is shown in Figure 2. With increased number of risk factors, the frequency of PPDS placement became higher. As a result, the cases that the operator judged to insert PPDS having considered that the case had become a high-risk case of PEP had included many risks.

Patient characteristics

The characteristics of the stent group and the non-stent group are shown in Table 2. There were significant differences in cannulation difficulty, total procedure time, the proportion of patients with pancreatic duct injection, pancreatic IDUS, pancreatic duct brush cytodiagnosis, and pre-cut sphincterotomy between the two groups.

With regard to the final diagnoses of both groups, significant differences between the

two groups were observed in the proportions of patients with cholangiocellular carcinoma, intraductal papillary mucinous neoplasm (IPMN), and pancreatic cancer.

Post–ERCP pancreatitis

The overall frequency of PEP was 8.4% (95 of 1131). PEP occurred in 5.9% of the stent group and 9% of the non-stent group (p=0.63) (Table 3). To minimize the effect of selection bias between the two groups, propensity score matching analysis was performed, and 105 matched cases in the non-stent group corresponding to 105 cases in the stent group were chosen in a one-to-one manner. After the matching, there were no significant differences in the clinical characteristics of the patients, including for the risk factors of PEP, between the two groups (Table 2), and the incidence of PEP in the matched stent group was significantly lower than that in the matched non-stent group (6% vs. 18%, p=0.02, odds ratio 0.32, 95% CI 0.12-0.77) (Table 3).

Stratification analysis on preventive efficacy of PPDS in each factors within the high-risk group of PEP

Considering the odds ratio of the patients with each factor, the stratification analysis on preventive efficacy of PPDS in each factor within the high-risk group of PEP revealed that PPDS proved to be effective in preventing PEP in patients with a history of pancreatitis (odds ratio 0.11, 95% CI 0.01-0.76, p=0.01) and in cases of difficult

cannulation (requiring more than 30 minutes) (odds ratio 0.13, 95% CI 0.01-1.14, *p*=0.08) (Figure 3).

DISCUSSION

In order to clarify the refined application of PPDS, it is important to determine which factors are more highly associated with preventive effects of PPDS within the high-risk group of PEP. However, an adequate number of stratification analyses for each factor by RCT have not been carried out. A reason for this is that it is virtually impossible to conduct RCT for each of the many risk factors associated with PEP owing to the limited number of subjects that can be enrolled for each risk factor; this is especially true for the rarer risk factors. Moreover, there is ethical issue that RCT study is performed on high-risk patients of PEP. Furthermore, in cases of investigations on ERCP related events such as PEP in which intraoperative techniques are major influencing factor, even with RCT, it may not be possible to adjust completely for these biases.

This is a significant difference from similar investigations conducted on medications, and these biases—related to intraoperative technique—may influence the outcome and mask the true efficacy of PPDS.

Therefore, in this study, we used a propensity score matching analysis to minimize the

effects of any inherent biases. Propensity score methods are used for reducing the effects of confounding in observational studies, and can be powerful tools in assessing average treatment effects in observational studies.[13, 17,18] Recent study has reported that treatment effects from randomized trials and propensity score analyses were similar in similar populations.[19]

In the present study, we effectively adjusted for biases in the clinical data that we had accumulated prospectively. After the matching, no differences in the clinical characteristics of the patients, including the risk factors of PEP, were observed. The risk reduction rate of PPDS for the development of PEP was found to be 68% (odds ratio 0.32). Here the results obtained from the propensity score analysis—adjusting for biases—were comparable to those presented in previous RCT studies.

In stratification analysis on preventive efficacy of PPDS in each factors within the high-risk group of PEP, we found that the rate of PEP in the patients with a history of pancreatitis was significantly reduced by PPDS (p = 0.01). The odds ratio (OR = 0.11) was lower than that of the whole data (a vertical line in Figure 2: OR = 0.32). Additionally, the confidence intervals in this group (95%CI = 0.01-0.76) were less than 1. From these results, it was thought that the patients with a history of pancreatitis are the most recommended group for PPDS among the high-risk group of PEP.

With regard to cases of difficult cannulation, the odds ratio in this group (OR = 0.13) was lower than that of the whole data (OR = 0.32) (Figure 3).

There was not the technical influence of the operators in this result, because the rates of the cases requiring more than 30 minutes in each operators did not have the difference (operator A:4%17/425, B:5.2% 20/384, C:4.7% 8/170, D:4.6% 7/152).

This result was not statistically significant (p = 0.08), but it was thought that cases of difficult cannulation are particularly recommended for PPDS within the high-risk group of PEP.

We strongly recommend insertion of a PPDS in patients with a history of pancreatitis and cases of difficult cannulation.

With regard to the group with pancreatic duct injection, the rate of PEP in the stent group was significantly lower than that in the no-stent group (p = 0.01). The odds ratio of this group was the same as that for all the data because almost all cases were approximately contrasted in terms of pancreatic duct.

The present study has some limitations. First, it was difficult to show the preventive efficacy in pancreatic IDUS cases and cases with suspected SOD because the number of these cases was limited. Second, although we evaluated the effects of the risk factors for PEP from the ESGE Guidelines, the effects of other factors such as younger age and

degree of pancreatic duct filling were not assessed in this study. Third, we cannot adjust for unknown factors by propensity score analysis.

Conclusion

We effectively adjusted for biases in the clinical data that we had accumulated prospectively and conducted stratification analysis on the preventive effects with PPDS in the high-risk group of PEP. This study also strongly suggests that patients with a history of pancreatitis and cases of difficult cannulation are particularly recommended for PPDS placement within the high-risk group of PEP. The propensity score analysis can be adapted to the ERCP-related analysis with many procedure-related factors with using retrospective data, and may be adapted to investigate the matters that are unsuitable for RCT by volume and ethical issue.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author Contribution

Study design: Mamoru Takenaka

Acquisition of data: Mamoru Takenaka

Analysis and interpretation: Mamoru Takenaka, Tsuyoshi Fujita, Atsuhiro Masuda and Daisuke Sugiyama

Manuscript drafted by: Mamoru Takenaka, Tsuyoshi Fujita and Hiromu Kutsumi

Revision: Hideyuki Shiomi, Maki Sugimoto, Tsuyoshi Sanuki, Takanobu Hayakumo, Takeshi Azuma and Hiromu Kutsumi

Study supervision: Takeshi Azuma and Hiromu Kutsumi

REFERENCES

1. Fazel A, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. *Gastrointest Endosc*. 2003; **57**: 291-4.

2. Tarnasky PR, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology*. 1998; **115**: 1518-24.

3. Smithline A, Silverman W, Rogers D, Nisi R, Wiersema M, Jamidar P*, et al.* Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. *Gastrointest Endosc*. 1993; **39**: 652-7.

4. Singh P, Das A, Isenberg G*,* Wong RC, Sivak MV Jr, Agrawal D *et al.* Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc*. 2004; **60**: 544-50.

5. Cotton PB, Lehman G, Vennes J*,* Geenen JE, Russell RC, Meyers WC, *et al.* Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc*. 1991; **37**: 383-93.

6. Brackbill S, Young S, Schoenfeld P, Elta G. A survey of physician practices on prophylactic pancreatic stents. *Gastrointest Endosc*. 2006; **64**: 45-52.

7. Sofuni A, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, *et al.* Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. *Clin Gastroenterol Hepatol*. 2007; **5**: 1339-46.

8. Mazaki T, Masuda H, Takayama T. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: a systematic review and meta-analysis. *Endoscopy*. 2010; **42**: 842-53.

9. Dumonceau JM, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH *et al.* European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy*. 2010; **42**: 503-15.

10. Dumonceau JM, Rigaux J, Kahaleh M, Gomez CM, Vandermeeren A, Deviere J. Prophylaxis of post-ERCP pancreatitis: a practice survey. *Gastrointest Endosc*. 2010; **71**: 934-9, 9 e1-2.

11. Freeman ML. Pancreatic stents for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis. *Clin Gastroenterol Hepatol*. 2007; **5**: 1354-65.

12. Freeman ML. Role of pancreatic stents in prevention of post-ERCP pancreatitis. *JOP*. 2004; **5**: 322-7.

13. Gum PA, Thamilarasan M, Watanabe J, Blackstone EH, Lauer MS. Aspirin use and all-cause mortality among patients being evaluated for known or suspected coronary artery disease: A propensity analysis. *JAMA*. 2001; **286**: 1187-94.

14. Rubin DB, Thomas N. Matching using estimated propensity scores: relating theory to practice. *Biometrics*. 1996; **52**: 249-64.

15. Abidov A, Rozanski A, Hachamovitch R, Hayes SW, Aboul-Enein F, Cohen I, *et al.* Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med*. 2005; **353**: 1889-98.

16. Bergstralh EJ, Konsanke JL. Computerized Matching of Cases to Controls: Technical Report No. 56 . Rochester, MN: Dept of Health Science Research, Mayo Clinic; 1995.

17. Luo Z, Gardiner JC, Bradley CJ. Applying propensity score methods in medical research: pitfalls and prospects. *Med Care Res Rev*. 2010; **67**: 528-54.

18. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res*. 2011; **46**: 399-424.

19. Kuss O, Legler T, Borgermann J. Treatments effects from randomized trials and propensity score analyses were similar in similar populations in an example from cardiac surgery. *J Clin Epidemiol*. 2011; **64**: 1076-84.

Figure Legends

Figure 1

Schematic representation of the propensity score matching analysis in this study.

In an effort to balance the patient groups, we used propensity score analysis to generate a set of matched cases (patients with PPDS) and controls (patients without stent).

The propensity score was calculated for each 1031 patients based on a logistic regression analysis of the probability of PPDS using clinical characteristics.

Using propensity scores, we selected 105 patients from 1026 patients without stent, and generated 105 sets of matched cases.

Figure 2

The proportion of ERCPs in which use of a PPDS was attempted according to the number of risk factors of PEP. With increasing number of risk factors, the frequency at which use of a PPDS was performed became higher.

Figure 3

The stratification analysis on preventive efficacy of PPDS in each factors within the

high-risk group of PEP (S vs. m-N). A vertical line represents the odds ratio of the whole data. The odds ratio in patients with a history of pancreatitis (OR = 0.11) was lower than that for the whole data (a vertical line in Figure 3: OR = 0.32). Additionally, the confidence interval in this group (95%CI = 0.01-0.76) was less than 1. From these results, it was thought that the patients with a history of pancreatitis are those most recommended to receive PPDS among patients in the high-risk group of PEP. Furthermore, the odds ratio in cases of difficult cannulation (requiring more than 30 minutes) (OR = 0.13) was lower than that for the whole data. This result was not statistically significant, but it was thought that cases of difficult cannulation are particularly recommended for PPDS within the high-risk group of PEP.

Table 1 Summary of PPDS placement

Number of patients in whom a PPDS insertion was attempted	105
Number of patients in whom a PPDS was placed	102 (97.0%)
Dislodgement	
Spontaneous dislodgement	96 (94.1%)
Endoscopic removal	6 (5.9%)
The mean duration of dislodgement (day)	2.0
Complications	
Migration	0 (0%)
Hemorrhage	0 (0%)
Perforation	0 (0%)
PEP	6 (5.9%)

PPDS: prophylactic pancreatic duct stent
PEP: post-endoscopic retrograde cholangiopancreatography pancreatitis

Table 2 Characteristics of patients

	Stent group n=105	Non-stent group n=1026	Non-stent group (after matching) n=105
Mean age (±SD)	66±13	65±12	68±11
Male/female	65/40	658/368	65/40
Time required for cannulation			
0~15min	59 (58%)	767 (74.5%) [a]	51 (48.6%)
15~30min	31 (29%)	222 (21.7%)	38 (36.2%)
30~min	15 (13%)	37 (3.8%)	16 (15.2%)
Total procedure time			
0~30min	23 (22%)	314 (31%) [a]	22 (21%)
30~60min	41 (39%)	506 (49%)	41 (39%)
60~min	41 (39%)	206 (20%)	42 (40%)
Pancreatic duct injection	103 (98%)	705 (69%) [a]	102 (97%)
Pancreatic IDUS	17 (16%)	48 (5%) [a]	11 (10%)
Biliary IDUS	14 (13%)	89 (8%)	12 (11%)
Pancreatic juice cytodiagnosis	15 (14%)	108 (11%)	10 (10%)
Biliary juice cytodiagnosis	4 (4%)	62 (6%)	6 (6%)
Pancreatic duct brush cytodiagnosis	20 (19%)	72 (7%) [a]	20 (19%)
Biliary duct brush cytodiagnosis	14 (13%)	104 (10%)	9 (9%)
Precut sphincterotomy	6 (6%)	10 (1%) [b]	5 (5%)
Endoscopic sphincterotomy	14 (14%)	92 (9%)	14 (14%)
previous pancreatitis [c]	11 (10%)	79 (8%)	15 (14.2%)
Suspected SOD	4 (3.8%)	16 (1.6%)	5 (4.7%)

p-value: t-test for continuous variables, χ-squared test or Fisher's exact test for categorical variables

SD: standard deviation
IDUS: intraductal ultrasonography
SOD: sphincter of oddi dysfunction
[a] $p<0.001$ vs. Stent group
[b] $p<0.01$ vs. Stent group
[c] Acute exacerbation of chronic pancreatitis in 13 patients (2 in the stent group, 11 in the non-stent group, 1 in the non-stent group after matching)

Table 3 The details of PEP

	All cases	Stent group	Non-stent group	Non-stent group (after matching)	*p*-value (Odds ratio : 95% CI)	
	n=1131	n=105	n=1026	n=105	S vs. N	S vs. m-N
PEP (%)	95 (8.4%)	6 (5.9%)	89 (9%)	19 (18%)	0.63	0.02 (0.32 : 0.12-0.77)

p-value: χ-squared test

PEP: post-endoscopic retrograde cholangiopancreatography pancreatitis

CI: confidence interval

S: stent group

N: non-stent group

m-N: non-stent group (after matching)

Figure 1

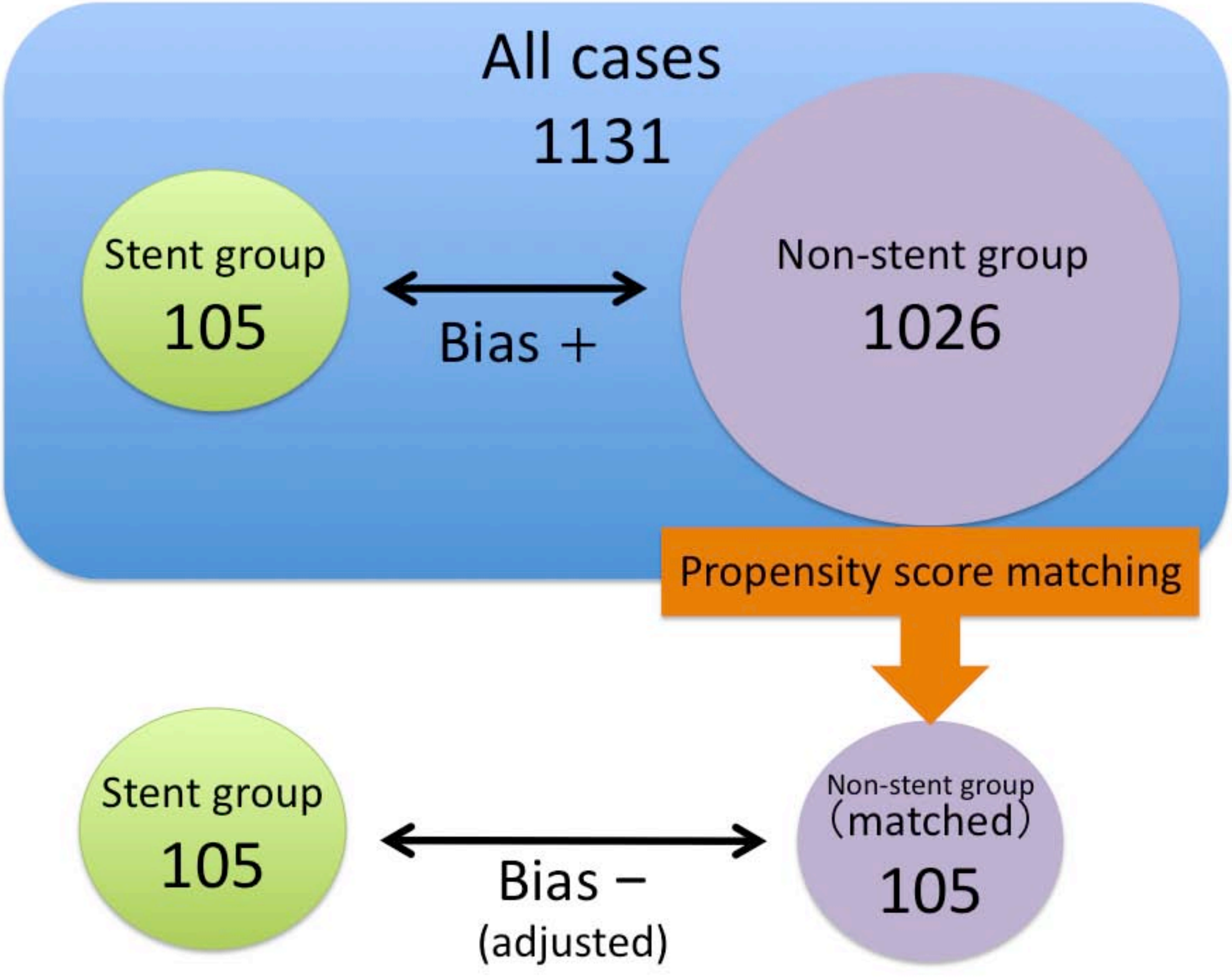

All cases
1131
Stent group
105
Bias +
Non-stent group
1026
Propensity score matching
Stent group
105
Bias −
(adjusted)
Non-stent group
（matched）
105

Figure 2

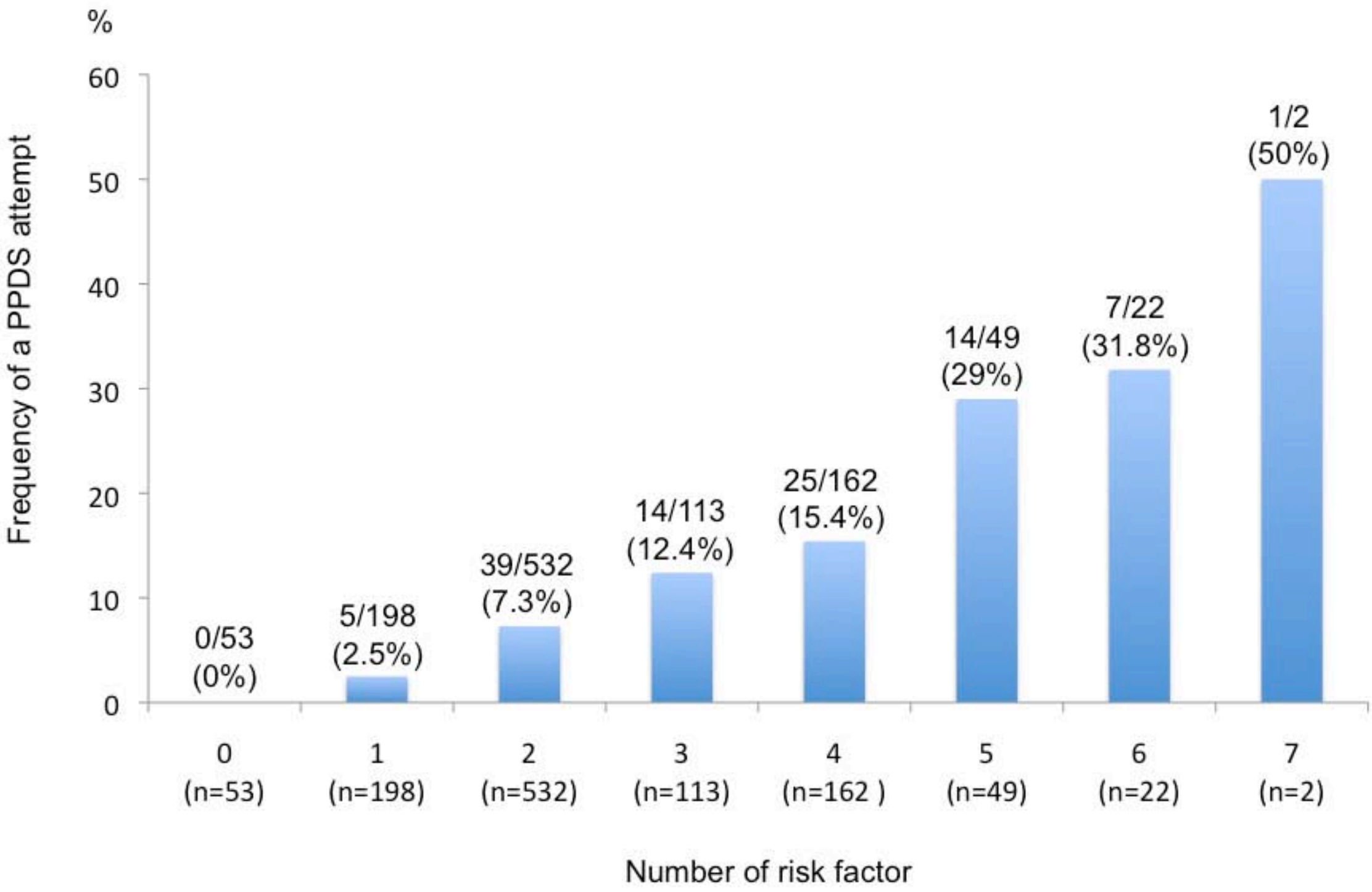
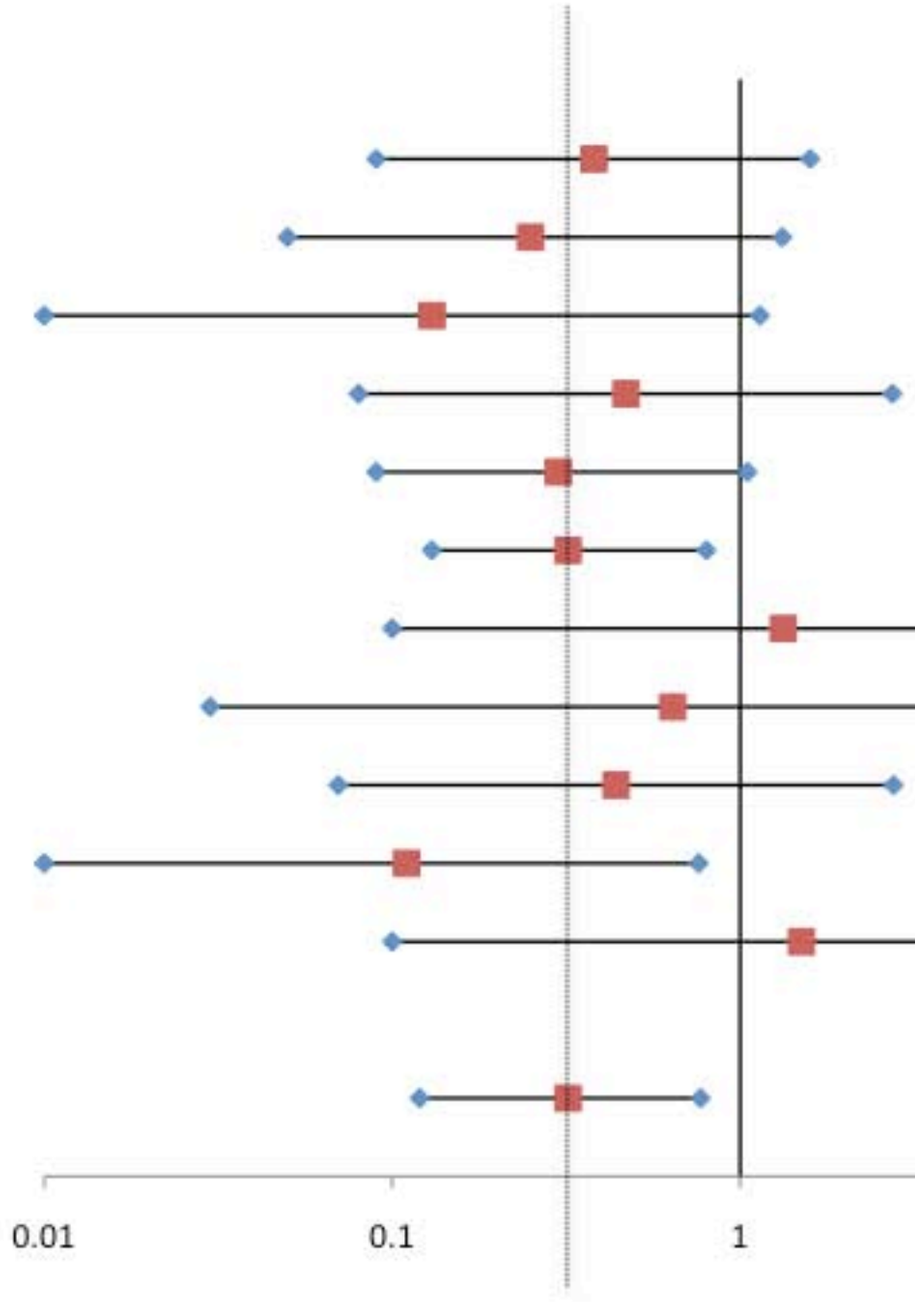

%
60
50
40
30
20
10
0
Frequency of a PPDS attempt
0/53
(0%)
5/198
(2.5%)
39/532
(7.3%)
14/113
(12.4%)
25/162
(15.4%)
14/49
(29%)
7/22
(31.8%)
1/2
(50%)
0
(n=53)
1
(n=198)
2
(n=532)
3
(n=113)
4
(n=162)
5
(n=49)
6
(n=22)
7
(n=2)
Number of risk factor

Figure 3



	OR	95%CI	*p*-value
Female gender	0.38	0.09-1.59	0.17
Time required for cannulation 15～30 min	0.25	0.05-1.32	0.17
30～min	0.13	0.01-1.14	0.08
Total procedure time 30～60 min	0.47	0.08-2.74	0.39
60～min	0.3	0.09-1.05	0.051
Pancreatic duct injection	0.32	0.13-0.8	0.01
Pancreatic IDUS	1.33	0.1-16.7	0.82
Pancreatic juice cytodiagnosis	0.64	0.03-11.63	0.76
Pancreatic duct brush cytodiagnosis	0.44	0.07-2.76	0.38
Previous pancreatitis	0.11	0.01-0.76	0.01
suspected SOD	1.5	0.1-21.3	0.76
Total	0.32	0.12-0.77	0.02