学位論文

「Influence of cholangitis after preoperative endoscopic biliary drainage on postoperative pancreatic fistula in patients with middle and lower malignant biliary strictures.」

(中下部悪性胆道狭窄例における術前内視鏡的胆道ドレナージ後胆管炎が術後膵液漏に与える影響)

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

要旨

Intoroduction:

胆膵癌は一般的に予後不良であり，外科的手術が根治を望める唯一の治療法である．高度黄疸例では肝機能の低下や易感染性，出血傾向がみられ，耐術能の問題があり，本邦では Endoscopic biliary drainage(EBD)を中心とした術前胆道ドレナージを行うことが一般的であり,有益であると報告されている．術前ドレナージ後の Preoperative Cholangitis(PC)が、術後の合併症、とくに膵液漏を増加させることが報告されている．そこで我々は中下部悪性胆道狭窄例での術前 EBD 後胆管炎が術後膵液漏に与える影響を後ろ向きに検討を行うこととした．

Method:

2004 年 1 月から 2013 年 12 月までの 10 年間に北里大学東病院で施行された,肝切除術を行わない中下部悪性狭窄を伴う悪性腫瘍の手術例の内,EBD を施行した 102 例を対象とした.術後膵液漏に与える影響として患者背景，悪性腫瘍の種類，狭窄長，Total bilirubin 値,手術待機期間，胆管炎の有無を後ろ向きに検討した．

Result:

今回検討とした 102 例の内、術後膵液漏を 33 例（32%）に認めた.また術前ドレナージ後胆管炎(PC)を 56 例に認めた．PC の危険因子について検討を行ったところ,Total bilirubin 値 2.9 以上の群(HR:2.95,95％CI:1.223-7.130，P=0.016),手術待機期間が 29 日以上の群(HR:4.23,95％CI:1.681-10.637, P=0.02)が独立した危険因子であった.PC 群では PC を起こしていない群に比べ有意に膵液漏が多い結果であった(78.8%vs 21.2% P=0.001)．また胆道癌では膵癌に比べ有意に膵液漏が多い結果であった(72.7%vs27.2% P=0.005)。多変量解析では PC 群(HR:4.8,95％CI:1.785-12.992，P=0.001)及び胆道癌(HR:3.5,95％CI:1.335-8.942，P=0.006)で有意に術後膵液漏の独立した危険因子であった．

Conclusion:

術前ドレナージ後胆管炎は術後膵液漏の独立した危険因子であった.術前ドレナージ後胆管炎を防ぐことで術後膵液漏を減らす可能性がある．

目次

1. Introduction

Biliary and pancreatic cancers generally carry a poor prognosis and can be radically treated only by surgery. Cancer of the head of the pancreas and biliary tract cancer are often associated with obstructive jaundice at the time of diagnosis. Patients with severe jaundice have decreased liver function, increased susceptibility to infection, a bleeding diathesis, and decreased ability to endure surgery. In Japan, preoperative biliary drainage is generally carried out by endoscopic biliary drainage (EBD) and has been reported to be beneficial.[1, 2] However, van der Gaag et al. reported that routinely carried out preoperative drainage increases perioperative complications and is thus unnecessary in patients with pancreatic head cancer.[3] Preoperative biliary drainage was discouraged because it can induce retrograde cholangitis or other types of biliary tract infection and because the drainage procedure can directly cause complications.

Sewnath et al. reported that the incidence of postoperative complications was slightly, but not significantly, higher in patients who did not undergo drainage than in those who underwent drainage.[4] However, preoperative drainage can facilitate a preoperative pathological diagnosis and evaluation of the development of the superficial layer of lesions located in the bile duct. Therefore, preoperative biliary drainage, usually involving EBD, is often carried out in Japan.

Whether preoperative biliary drainage should be done in patients with middle and lower malignant biliary strictures remains controversial.[5-8] The development of preoperative cholangitis after preoperative drainage has been reported to increase the incidence of postoperative complications, particularly pancreatic fistula.[9] Pancreatic fistula is a risk factor for surgical site infection.[10, 11] Pancreatic fistula has also been reported to cause postoperative intraperitoneal infection and delayed gastric emptying.[12]

In the present study, we retrospectively evaluated the effects of cholangitis developing after preoperative EBD on postoperative pancreatic fistula in patients with middle and lower malignant biliary strictures.

2. Methods

2-1.Study patients

Among patients who underwent surgery for middle and lower malignant biliary strictures without undergoing hepatectomy in Kitasato University East Hospital during the 10 - year period from January 2004 through December 2013, we studied 102 patients who preoperatively underwent EBD. Effects of patient characteristics, malignant tumor type, stricture length, total bilirubin levels, surgical waiting time, and the presence or absence of cholangitis on the postoperative development

of pancreatic fistula were studied retrospectively.

2-2.Exclusion criteria

Patients were excluded from the study if they underwent percutaneous transhepatic biliary drainage (PTBD) or if they received preoperative chemotherapy.

2-3.Standard management protocol until surgery

Figure 1 shows the standard management protocol until operation in the present study. Patients suspected to have biliary cancer or pancreatic cancer presented at our hospital. Patients with jaundice or liver dysfunction underwent EBD to reduce jaundice. Six patients who had previously undergone EBD in another hospital underwent another session of EBD in our hospital to confirm the pathological diagnosis or to evaluate lesions by techniques such as intraductal ultrasonography (IDUS). Surgical waiting time was defined as the period from completion of EBD or EBD plus pathological diagnosis/IDUS until surgery.

2-4.Diagnosis of preoperative cholangitis

Preoperative cholangitis was diagnosed according to thediagnostic criteria of the revised Tokyo Guidelines 2013.[13]When preoperative cholangitis developed, antimicrobialagents were given, and plastic stents were exchanged inaccordance with the Tokyo Guidelines.

2-5.Procedure for EBD

The following models of duodenoscope were used: JF240, TJF240, JF260V, and TJF260V (Olympus Medical Systems, Tokyo, Japan). To carry out EBD, a catheter was selectively placed into the bile duct, and cholangiopancreatography was carried out. Stricture length was evaluated, and a guidewire was passed through the stricture and fixed in place. The stricture length was measured on cholangiography. Endoscopic sphincterotomy (EST) was carried out depending on each patient's condition. A stent and a pusher catheter were inserted along with the guidewire, and an endoscopic biliary stent (EBS) was placed. Pancreatography and intraductal ultrasonography (IDUS) were carried out as required to evaluate biliary and pancreatic cancers. Pancreatic juice cytology, bile cytology, and biopsy were carried out for pathological examination. A plastic stent was placed in all patients. At the time of EBD, a second - or third - generation cephem antibiotic was prophylactically given i.v. before the procedure, after the procedure, and on the morning of the following day. In patients who concurrently had cholangitis, duration of antibiotic treatment was appropriately extended depending on the status of infection.

2-6.Surgery

The following surgical procedures were carried out: pancreaticoduodenectomy (PD), pylorus - preserving pancreaticoduodenectomy (PPPD), and subtotal stomach - preserving pancreaticoduodenectomy (SSPPD). For reconstruction,

pancreaticojejunostomy was done in all patients. For antibiotic treatment, 1 g flomoxef was given before surgery, every 3 h during surgery, and twice daily on the first two postoperative days.

A 5Fr polyethylene pancreatic stent was placed in the pancreaticojejunostomy. In patients who underwent pancreaticoduodenectomy, drains were placed in the pancreaticojejunostomy and in Winslow's foramen. On the first and third postoperative days, amylase levels in the drainage fluid were measured, and pancreatic fistula was diagnosed according to the guidelines of the International Study Group on Pancreatic Fistula.[14] The drainage tubes were removed on the fourth and fifth postoperative days, respectively.

2-7.Statistical analysis

Variables are expressed as medians and ranges. Countable data were compared using Mann–Whitney U - tests, and categorical data were compared between groups using chi - squared tests.

Univariate analysis was carried out to evaluate clinicopathological risk factors for preoperative cholangitis. P - values <0.05 were considered to indicate statistical significance. Variables associated with significant differences in Mann–Whitney U - tests were included in receiver - operating - characteristic (ROC) curve analysis, and cut - off values were determined by the Youden index. Multivariate analysis was carried out using the cut - off values. Statistical analysis was done with SPSS, version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA).

3. Results

Demographic characteristics of the 102 patients (63 men and 39 women) studied are shown in Table 1. Median age was 67 years (range, 36–83). As for tumor type, 48 patients (47.1%) had pancreatic cancer, and 54 patients (52.9%) had biliary cancer. Although four patients had ampullary carcinoma, this diagnosis is included in biliary cancer according to the General Rules for Clinical and Pathological Studies on Cancer of the Biliary Tract.[15] In the present study, we therefore classified ampullary carcinoma as biliary cancer. Median stricture length in the bile duct was 22 mm (range, 4–64). Median total bilirubin level before EBD was 5.1 mg/dL (range, 0.1–32.4). Median surgical waiting time

was 33.5 days (range, 6–84). Surgical procedure was PD in 12 patients, PPPD in 83 patients, and SSPPD in seven patients. Median postoperative hospital stay was 20.5 days (range, 8–375). As for postoperative complications, pancreatic fistula occurred in 33 patients (32.4%).

Table 1 shows the status of preoperative drainage. A 7 - Fr plastic stent was placed in 100 patients, a 10 - Fr plastic stent was placed in two patients, and no endoscopic nasobiliary drainage tube was placed in any patient. Biliary brushing cytology, biliary biopsy, or both was carried out in 51 patients. EST was carried out in 92 patients and not carried out in 10 patients.

Among the 102 patients who underwent EBD, 56 (54.9%) had preoperative cholangitis. Table 2 shows the results of risk - factor analysis in these 56 patients. Age, sex, tumor type, stricture length, whether or not biliary brushing cytology, biliary biopsy, or both was carried out, and the presence or absence of EST were not significantly related to the development of preoperative cholangitis. A higher total bilirubin level before drainage (P = 0.002) and longer surgical waiting time (P = 0.004) were associated with a significantly higher incidence of preoperative cholangitis.

ROC curves showing the relation of preoperative cholangitis to total bilirubin levels and surgical waiting time are presented in Figures 2 and 3, respectively. Cut - off value for total bilirubin level was 2.85 mg/dL (area under the curve [AUC], 0.675; sensitivity, 75.0%; specificity, 47.8%). The cut - off value for surgical waiting time was 28.5 days (AUC, 0.667; sensitivity, 82.1%; specificity, 50.0%). A total bilirubin level of 2.9 mg/dL or higher and a surgical waiting time of 29 days or longer were defined as cut - off values, and multivariate analysis was carried out.

Clinical characteristics of the 33 patients with pancreatic fistula are shown in Table 4. Sex, age, tumor diameter, stricture length, total bilirubin level, and surgical waiting time did not differ significantly between the patients with pancreatic fistula and those without pancreatic fistula. Patients with preoperative cholangitis had a significantly higher incidence of pancreatic fistula than patients without preoperative cholangitis (78.8% vs 21.2%; P = 0.001). The incidence of pancreatic fistula was also significantly higher in patients with biliary cancer than in patients with pancreatic cancer (72.7% vs 27.2%; P = 0.005).

Results of multivariate analysis are shown in Table 5. Presence of preoperative cholangitis (hazard ratio, 4.8; 95% CI, 1.785–12.992; P = 0.001) and the presence of biliary cancer (hazard ratio, 3.5; 95% CI, 1.335–8.942; P = 0.006) were significant independent risk factors for the development of pancreatic fistula.

4. Discussion

Our study of 102 patients with middle and lower malignant biliary strictures who underwent preoperative endoscopic drainage showed that biliary cancer and preoperative cholangitis were independent risk factors for the development of pancreatic fistula.

We also showed that a total bilirubin level of 2.9 mg/dL or higher and a surgical waiting time of 29 days or longer were independent risk factors for preoperative cholangitis. To our knowledge, our study is the first to elucidate risk factors for preoperative cholangitis. Lin et al. reported that in patients who underwent pancreaticoduodenectomy for biliary tract cancer, texture of the residual pancreas was rarely firm, in contrast to patients with cancer of the pancreatic head, and the texture was soft in most patients, similar to the normal pancreas, resulting in a high incidence of pancreatic fistula.[16] Our results support these findings.

Previous studies have reported that the presence of preoperative cholangitis can increase the incidence of postoperative complications such as pancreatic fistula and delayed gastric emptying,[16, 17] which was also consistent with our findings. In patients with preoperative cholangitis, bile infection may occur during surgery, leading to infected ascites and increasing the risk of grade B or C postoperative pancreatic fistula.[18, 19] These findings suggest that decreasing the incidence of preoperative cholangitis may decrease the risk of postoperative pancreatic fistula. However, these previous studies[18-21] did not report risk factors for preoperative cholangitis, whereas our analysis clearly defined the risk factors for preoperative cholangitis. We consider this a strong point of our study.

Whether preoperative biliary drainage should be carried out in patients who have malignant tumors associated with jaundice caused by middle and lower malignant biliary strictures remains controversial.[5-8] However, in Japan, preoperative biliary drainage is generally carried out. This is attributed to the fact that appropriately conducted preoperative biliary drainage can decrease the risk of postoperative complications[22] and that surgical waiting time, including detailed preoperative examinations, is usually several weeks.[9] In patients who undergo preoperative biliary drainage, external biliary drainage techniques such as endoscopic nasobiliary drainage (ENBD) and PTBD have been reported to decrease the risk of postoperative complications as compared with internal biliary drainage techniques such as EBD.[9] However, external biliary drainage can cause positional abnormalities and deviations and preclude the flow of bile into the intestine, increasing the risk of decreased intestinal immunity and bacterial translocation.[23] Therefore, in Japan, internal drainage by EBD is preferred, despite the increased risk of cholangitis.[9]

In our study, preoperative cholangitis developed in 56 patients, more than half of the

study group. A surgical waiting time of 29 days or longer and a total bilirubin level of 2.9 mg/dL or higher were independent risk factors for preoperative cholangitis. Because the surgical waiting time includes the time required to carry out preoperative biliary drainage, examinations required for surgery, and systemic management, it is most likely difficult to shorten the waiting time in Japan.

In the present study, preoperative drainage was carried out with the use of plastic stents in all patients. Plastic stents generally have a short patency period.[24] Obstruction of plastic stents is mainly attributed to adherence of a bacterial biofilm caused by biliary sludge and duodenobiliary reflux and adherence of dietary fiber to the inner surface of the stent.[25, 26] In other words, because many patients with severe jaundice have biliary stasis, biliary sludge is often formed, leading to the high risks of stent obstruction and cholangitis. Our results thus showed that prevention of preoperative cholangitis has an important role in decreasing the incidence of postoperative pancreatic fistula.

Preoperative chemotherapy has been reported to be effective in patients with pancreatic cancer.[27, 28] Increasing numbers of patients will probably receive preoperative chemotherapy in the future. Therefore, methods that effectively prevent obstruction in the long term are needed.

Self - expanding metallic stents (SEMS) have been used to prevent stent obstruction. At present, the effects of preoperatively using SEMS on surgery, histopathological specimens, and postoperative complications remain unclear.[29, 30] However, SEMS remain patent for a significantly longer period of time than plastic stents24 and, therefore, most likely, can decrease the incidence of preoperative cholangitis. However, because some studies comparing SEMS with plastic stents in patients who underwent preoperative biliary drainage reported no difference in postoperative complications[31, 32] and the cost of SEMS is higher than that of plastic stents, SEMS should probably not be used in all patients who undergo preoperative biliary drainage. In our study, a total bilirubin level of 2.9 mg/dL or higher and a surgical waiting time of 29 days or longer were independent risk factors for preoperative cholangitis. In such patients who are at high risk for preoperative cholangitis, including those who have received preoperative chemotherapy, the use of SEMS is most likely warranted as well as economical.

Our study was retrospective and had several limitations. First, procedures for preoperative drainage have yet to be standardized and depend on the preferences of surgeons, most likely causing bias. Second, surgical waiting time and surgical procedures were also not standardized. In fact, surgical waiting time might have been prolonged by the development of cholangitis. However, because plastic stents generally have a shorter patency time,24 a longer surgical waiting time is considered a risk factor for cholangitis,

and this may be one of the limitations of the present study. Further studies without such limitations in larger numbers of patients are thus needed to confirm our results.

5. Conclusions

Prevention of preoperative cholangitis, a risk factor for postoperative pancreatic fistula, will probably decrease the incidence of postoperative pancreatic fistula. Because a surgical waiting time of 29 days or longer and a total bilirubin level of 2.9 mg/dL or higher were risk factors for preoperative cholangitis, the use of SEMS should be considered in patients with these conditions.

6. ACKNOWLEDGMENTS

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8. Table and Figure

Table 1. Patient Characteristics

Age (years)	67 (36-87)
Sex (M/F)	63/39
Pancreatic cancer/biliary tract cancer	48/54
Tumor diameter (mm)	25 (10-32)
Stricture length (mm)	22 (4-64)
Total bilirubin level (mg/dL)	5.1 (0.1-32.4)
Surgical procedures (PD/PPPD/SSPPD)	12/83/7
Reconstruction (pancreaticojejunostomy/pancreaticoduodenostomy/pancreaticogastrostomy	102/0/0
Surgical waiting time (days)	33.5 (6-84)
Presence or absence of preoperative cholangitis	56/46
Length of postoperative hospital stay (days)	20.5 (8-375)
Postoperative pancreatic fistula	33
Initial EBS(7-Fr PS/10-Fr PS/ENBD)	100/2/0
Biliary brushing cytology and/or biliary biopsy (yes/no)	51/51
Endoscopic sphincterotomy (yes/no)	92/10

Table 2. Risk Factors for Preoperative Cholangitis (Univariate analysis)

	Patients with cholangitis	Patients without cholangitis	P value
Age median(range)	68 (43-83)	66.5 (36-82)	0.449
Sex (M/F)	35/21	28/18	0.514
Pancreatic cancer/biliary tract cancer	24/32	24/22	0.230
Stricture length (mm)(range)	2.2 (0.7-4.0)	2.5 (0.4-6.4)	0.093
Presence or absence of EST	52/4	40/6	0.340
Biliary brushing cytology and/or bile duct biopsy	26/30	25/21	0.275
Total bilirubin level (mg/dL) median (range)	7.1 (0.3-32.4)	2.8 (0.1-24.7)	0.002
Surgical waiting time (days)	38.0(10-84)	28.5(6-78)	0.004

Table 3. Risk Factors for Preoperative Cholangitis (Multivariate analysis)

	P value	Hazard ratio	95% confidence interval	
			Lower limit	Upper limit
Surgical waiting time >28.5 days	0.020	4.230	1.681	10.637
Total bilirubin level >2.85 mg/dL	0.016	2.950	1.223	7.130

Table 4. Risk Factors for Pancreatic Fistula (Univariate analysis)

	Patients with pancreatic fistula	Patients without pancreatic fistula	P value
Age median(range)	68.0 (43-83)	67.0 (47-81)	0.611
Sex (M/F)	22/11	41/28	0.315
Pancreatic cancer/biliary tract cancer	9/24	39/30	0.005
Tumor diameter (mm) median (range)	22.0 (10-45)	25.0 (12-56)	0.074
Stricture length (mm) median (range)	22.0 (9-64)	22.0 (4-60)	0.886
Total bilirubin level (mg/dL) median (range)	3.7 (0.1-17.5)	5.5 (0.3-32.4)	0.520
Surgical waiting time (days) median (range)	38.0 (18-84)	32.0 (6-78)	0.777
Presence or absence of preoperative cholangitis	26/7	30/39	0.001
Bilirubin level >2.85 mg/dL	22/11	42/27	0.664
Surgical waiting time >28.5 days	26/7	43/26	0.116
Post-ERCP pancreatitis	5/28	6/63	0.255

Table 5. Risk Factors for Pancreatic Fistula (Univariate analysis)

	P value	Hazard ratio	95% confidence interval	
			Lower limit	Upper limit
Preoperative cholangitis	0.002	4.800	1.785	13.000
Biliary tract cancer	0.011	3.500	1.335	8.942

Figure 1. Standard Management Protocol

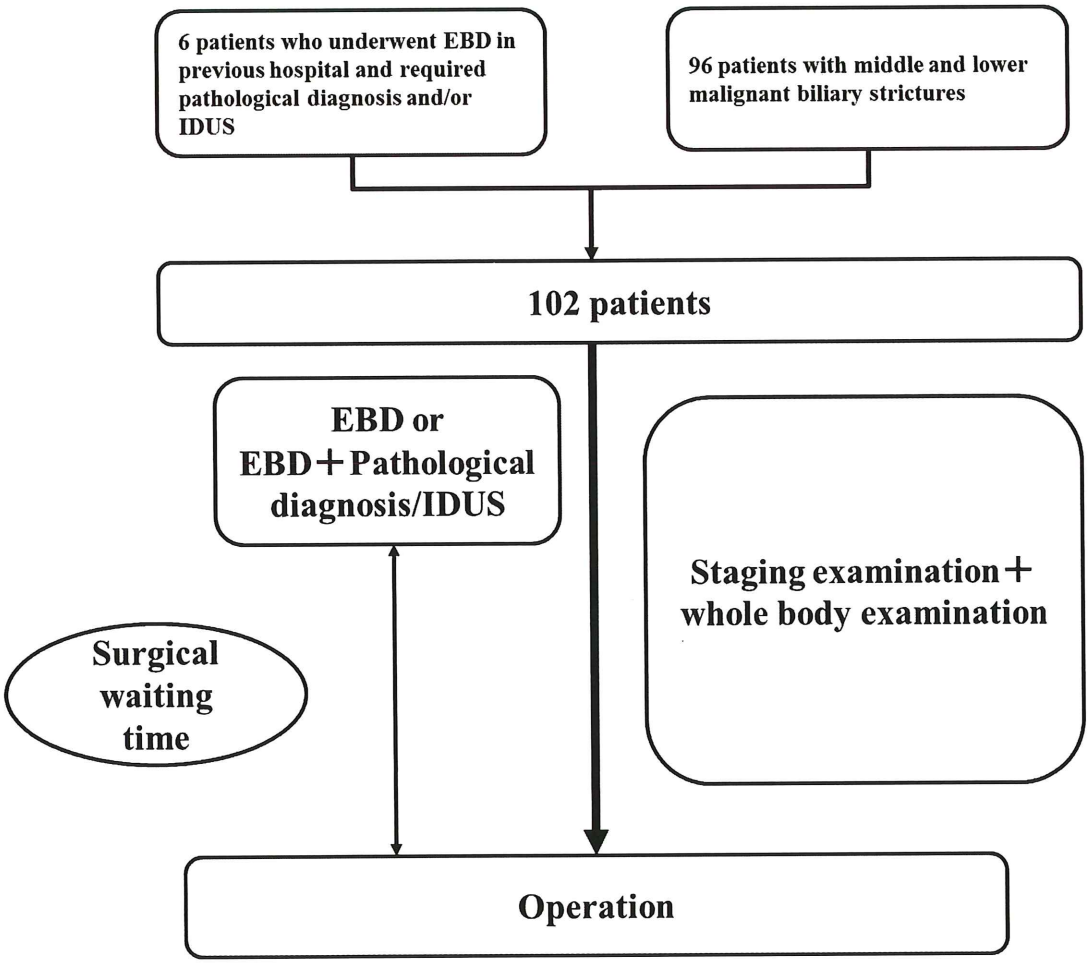


Figure 2. ROC Curve for Total Bilirubin Levels

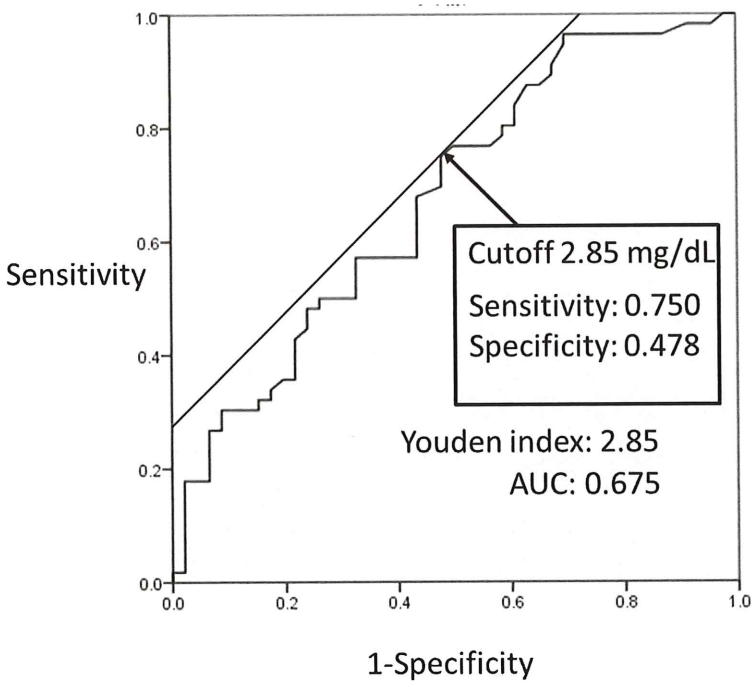
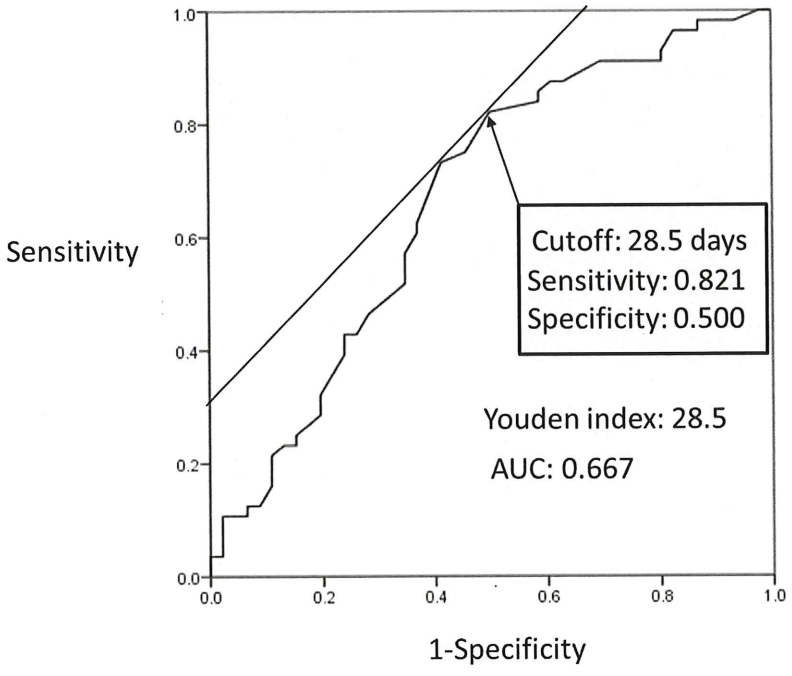


Figure 3. ROC Curve for Surgical Waiting Time



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