의학박사 학위논문

Effect of spleen preservation on the occurrence of sepsis in patients who underwent distal pancreatectomy: a population-based, propensity score matching study

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이 논문을 의학박사 학위 논문으로 제출함

2021년 8월

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국문 요약

췌장미부절제술을 시행받은 환자에 있어서 비장의 보존이 패혈증의 발생에 미치는 영향: 인구기반, 성향점수 분석

황지웅

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연구목적: 비장절제술은 패혈증 및 심각한 감염의 발생을 야기할 수 있다. 이러한 이유로 양성 또는 경계성 췌장 질환이 있는 환자에서 췌장미부절제술을 시행할 때 비장의 보존이 권장되어 왔다. 그러나 지금까지 이에 대한 인구 기반의 연구는 시행된 적이 없다. 따라서, 본 연구에서는 췌장미부절제술을 받은 환자에 있어서 동반된 비장절제술이 수술 이후 패혈증의 발생에 미치는 장기적인 효과를 인구를 기반으로 연구를 진행하고자 한다.

연구재료 및 방법: 건강보험심사평가원 (HIRA) 자료를 이용하여 2010 년부터 2014 년까지 국내에서 췌장미부절제술을 받은 환자를 모집하였다. propensity score matching 을 시행한 뒤, 비장을 절제한 그룹(CDP group)과 비장을 보존한 그룹(SPDP group)을 비교하여 패혈증의 발생에 영향을 줄 수 있는 변수를 비교 분석하였다.

결과: HIRA 데이터베이스를 이용하여 췌장미부절제술을 받은 환자 5613 명 (CDP group: 2560 명, SPDP group: 3053 명)이 모집되었다. propensity score matching 을 시행하여 각각의 그룹에 2262 명의 환자를 매칭하였다. CDP group 과 SPDP group 을 비교하였을 때 패혈증의 발생율은 통계적으로 유의한 차이를 보이지 않았다.

결론: 췌장미부절제술시에 비장의 동반 절제는 비장을 보존한 경우와 비교하여 장기간에 걸친 패혈증의 발생율을 증가시키지 않았다. 따라서 양성 췌장질환이 있는 환자에서 췌장미부절제술 시행시 비장의 보전이 필수적인 것은 아니라고 할수 있다. 그러나 비장절제로 발생할 수 있는 다른 질환들에 대해서도 인구기반의 연구가 필요하다고 하겠다.

주요 단어: distal pancreatectomy, spleen preservation, splenectomy, sepsis, population-based study

Abstract

Purpose: To investigate the long-term effects of splenectomy on sepsis occurrence in patients undergoing distal pancreatectomy. Splenectomy is associated with sepsis and other severe infections. Splenic preservation has been advocated during distal pancreatectomy for benign or borderline pancreatic diseases. To date, no population-based study has investigated the risk of sepsis occurrence with regard to splenectomy in patients undergoing distal pancreatectomy.

Materials and Methods: In this population-based study, the Health Insurance Review & Assessment Service (HIRA) database was used to identify patients who underwent distal pancreatectomy between 2010 and 2014. After propensity score matching, the variables that affect sepsis occurrence were analysed between the spleen-preserving distal pancreatectomy (SPDP) and the conventional distal pancreatectomy (CDP) groups.

Results: A total of 5,613 patients undergoing distal pancreatectomy were included in the HIRA database (2,560 splenectomised patients and 3,053 spleen-preserved patients). We matched 2,262 splenectomised patients to 2,262 spleen-preserved patients. No significant difference was observed in the rate of sepsis occurrence between the SPDP and CDP groups.

Conclusion: Compared to spleen-preservation, splenectomy during distal pancreatectomy is not related to an increased likelihood of long-term sepsis. Thus, preservation of the spleen during distal pancreatectomy may not be mandatory in patients with benign pancreatic disease. However, further population-based studies are warranted to analyse the role of spleen-preserving distal pancreatectomy in other outcomes.

Keywords: distal pancreatectomy, spleen preservation, splenectomy, sepsis, population-based study

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Introduction

Conventional distal pancreatectomy (CDP) usually involves removal of the spleen, which has anatomical proximity to, and shares principal vessels with the left pancreas.[1)] However, patients who undergo splenectomy are likely to develop sepsis and other severe infections because of the loss of the immunologic defence mechanism of the spleen against virulent pathogens, particularly encapsulated bacteria.[2-5)] For this reason, many surgeons have advocated splenic preservation during distal pancreatectomy for non-malignant diseases in the left pancreas.[6,7)]

Since the introduction of spleen-preserving distal pancreatectomy (SPDP), many studies have compared the surgical outcomes of SPDP with CDP, reporting comparable or favourable surgical outcomes of SPDP.[8-10)] However, most of the studies focused primarily on short-term surgical outcomes and not on long-term outcomes related to serious infections following splenectomy. Further, most of these studies were conducted in a single institution, and their sample size seemed insufficient to investigate the benefit of spleen preservation.

A few authors have reported the risk of pneumonia in patients who underwent splenectomy using population-based studies.[11-13)] Only one nationwide study has investigated sepsis occurrence among patients with splenectomy.[14)] To the best of our knowledge, no available nationwide population-based study has investigated the risk of sepsis occurrence with

regard to splenectomy during distal pancreatectomy. Thus, in this population-based study, we aimed to investigate the long-term effects of splenectomy on the occurrence of sepsis in patients undergoing distal pancreatectomy.

Materials and Methods

This was an observational population-based, propensity score-matching study covering the national health insurance program in Korea. It complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15] This study was approved by institutional review board of Kangnam Sacred Heart Hospital (HKS 2018-11-013), and the need for informed consent from each patient was waived because the authors did not have access to identifiable information.

Data source

We used the Health Insurance Review & Assessment Service (HIRA) database. Korea has one national health insurance program, which covers 97% of the total Korean population.[16] The database contains information on patient demographics, comorbidities described by diagnostic codes, and medical services including prescriptions, procedures, and surgeries. Diagnoses were codified according to the fifth and sixth Korean Classification of Diseases (KCD-5 in 2010; KCD-6 from 2011 to 2014). KCD-5 and KCD-6 are modified classification systems based on the International Classification of Disease-10.

Study participants

All patients who underwent distal pancreatectomy (Procedure code Q7565) between 2010

and 2014 were identified from the inpatient care of the HIRA database (n = 5,976). Patients of age <19 years (n = 160) and 90-day mortality (n = 203) were excluded, for which we considered immediate postoperative complications (such as pancreatic fistula) rather than splenectomy-related immunocompromised status.

Propensity score matching was performed to minimise the impact of treatment selection bias. Propensity scores were based on age, sex, and comorbidities that might be related to the development of sepsis, such as diabetes mellitus (DM), chronic pulmonary disease, and malignant disease. After matching, 2,262 patients were allocated to the SPDP and CDP groups.

Variables

The demographic factors used in this study included sex, age, and comorbidities. Age was calculated by subtracting the index date from the date of birth. The underlying comorbidities were defined as one or more hospital visits (inpatient and outpatient clinics) with the corresponding disease (including primary and secondary disease codes) within one year before the index date. Among these, comorbidities that affect the patient's immunity or are potentially related to the occurrence of sepsis were selected and investigated: DM (KCD codes E10, E11, E12, E13, and E14), chronic pulmonary disease (KCD codes J40, J41, J42, J43, J44, J45, J46, and J47), and malignant disease (KCD codes C00 to C97). The operative indication was defined as a disease code set at discharge and

was divided into benign or malignant pancreatic diseases.

The index date was defined as the admission date for distal pancreatectomy (whether splenectomy or not) because the exact operative date could not be identified in the HIRA database. The duration from surgery to the onset of sepsis was defined as the period from the index date to the date of hospitalisation for sepsis. We evaluated the patients from the index date until hospital admission due to sepsis, death, emigration, or until April 31, 2018, whichever came first. The occurrence of sepsis was defined as subsequent discharge with a diagosis of sepsis (KCD codes A021, A207, A227, A267, A327, A40, A40X, A41X, A427, B377, and R572).[14] The primary outcome was the rate of sepsis occurrence, which required hospitalisation during the total follow-up between the SPDP and CDP groups. The secondary outcome was hospital stay due to sepsis in each group, which might indirectly reflect the severity of sepsis. In addition, to evaluate the effect of malignant pancreatic disease on the incidence of sepsis after surgery, subgroup analysis was performed according to the diagnosis at the time of surgery (malignant and benign pancreatic disease subgroup).

Statistical analysis

Differences in sex, age, and underlying comorbidities between the SPDP and CDP groups were compared using the chi-square test for categorical variables and Student's *t*-test for continuous variables. A multivariate Cox proportional hazards regression model was used

to measure the hazard ratio (HR) and 95% confidence interval (CI) for sepsis associated with splenic preservation and other variables. The Kaplan-Meier (K-M) estimation method was performed to depict cumulative incidence curves of sepsis in the SPDP and CDP groups, and the log-rank test was used to examine whether these K-M curves differed statistically. All analyses were conducted using SAS version 9·3 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a two-tailed *P*-value < 0·05.

Results

A total of 5,976 patients who underwent distal pancreatectomy were identified in the HIRA database (Figure 1). After applying the exclusion criteria, 5,613 patients were enrolled in this study. There were 2,560 patients in the SPDP group and 3,053 patients in the CDP group during the study period. Table 1 summarises the baseline demographic characteristics of all the patients enrolled in this study. The variables of sex, age, and malignant disease showed statistically significant differences between the groups. The proportion of female patients in the SPDP group was significantly higher than that in the CDP group (54·8% vs. 44·3%). The patients in the SPDP group were significantly younger than those in the CDP group (55·4 ± 14·1 vs. 58·6 ± 12·9). The ratio of spleen preservation in patients with benign pancreatic disease was approximately half. In contrast, in patients with malignant pancreatic disease, concomitant splenectomy was performed more frequently (62·3%). Interestingly, the comorbidities of the patients did not affect the surgical method.

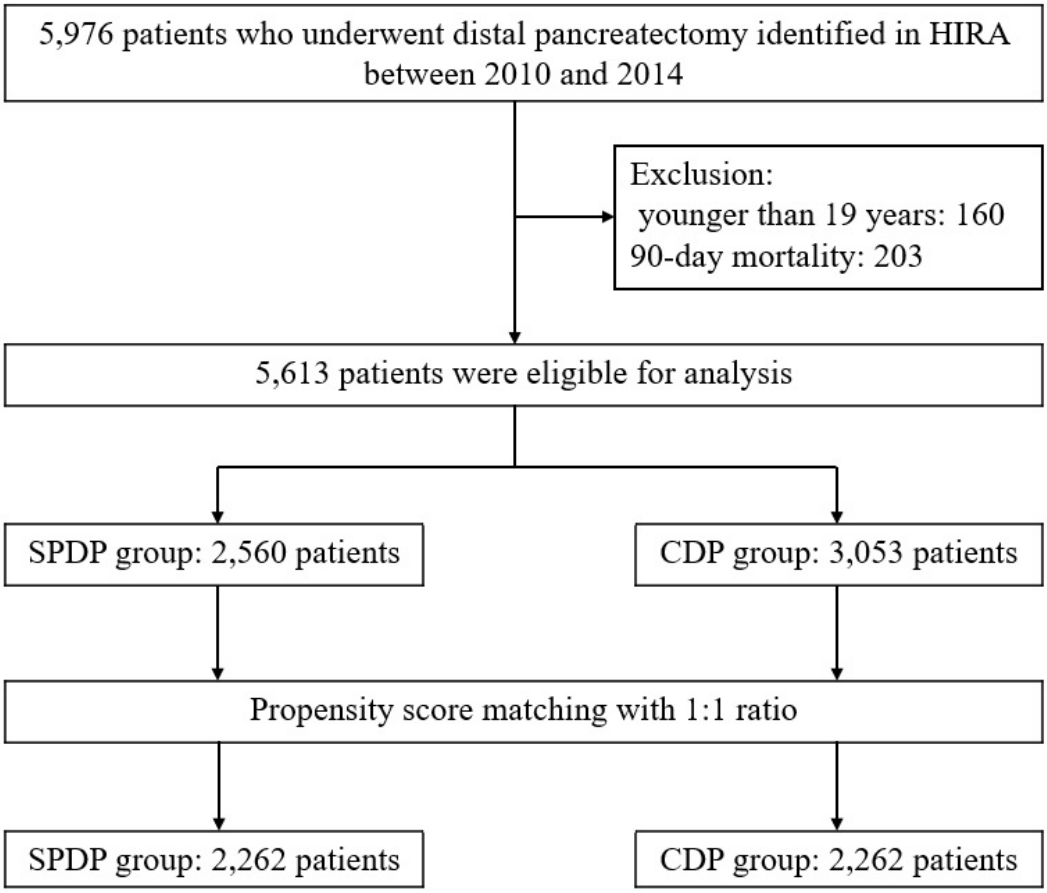


Figure 1. Flowchart of patient selection and matching. SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy; HIRA, Health Insurance Review & Assessment Service.

Table 1. Baseline characteristics of the SPDP and CDP groups in patients who underwent distal pancreatectomy before matching

Variable	SPDP (n = 2,560)	CDP (n = 3,053)	*P* value
Sex			< 0.0001
Male	1,158 (45.2)	1,702 (55.7)	
Female	1,402 (54.8)	1,351 (44.3)	
Age (years)	55.4 ± 14.1	58.6 ± 12.9	< 0.0001
Underlying comorbidity			
Chronic pulmonary disease	248 (9.7)	318 (10.4)	0.3666
DM	483 (18.9)	584 (19.1)	0.8036
Malignant disease	995 (38.9)	1,678 (55.0)	< 0.0001
Indication			< 0.0001
MPD	654 (25.5)	1,080 (35.4)	
BPD	1,906 (74.5)	1,973 (64.6)	

SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy; DM, diabetes mellitus; MPD, malignant pancreatic disease; BPD, benign pancreatic disease.

To minimise the impact of treatment selection bias, patients undergoing SPDP were matched to patients undergoing CDP using propensity scores. After propensity score matching, 4,524 patients were finally included in this study, and no statistical differences were found in age, sex, chronic pulmonary disease, DM, or malignant disease between the two groups (Table 2). The mean follow-up periods were 5·2 ± 2·1 years in the SPDP and 4·6 ± 2·3 years in CDP group ($P < 0·001$).

Table 2. Baseline characteristics of the SPDP and CDP groups in patients who underwent distal pancreatectomy after matching

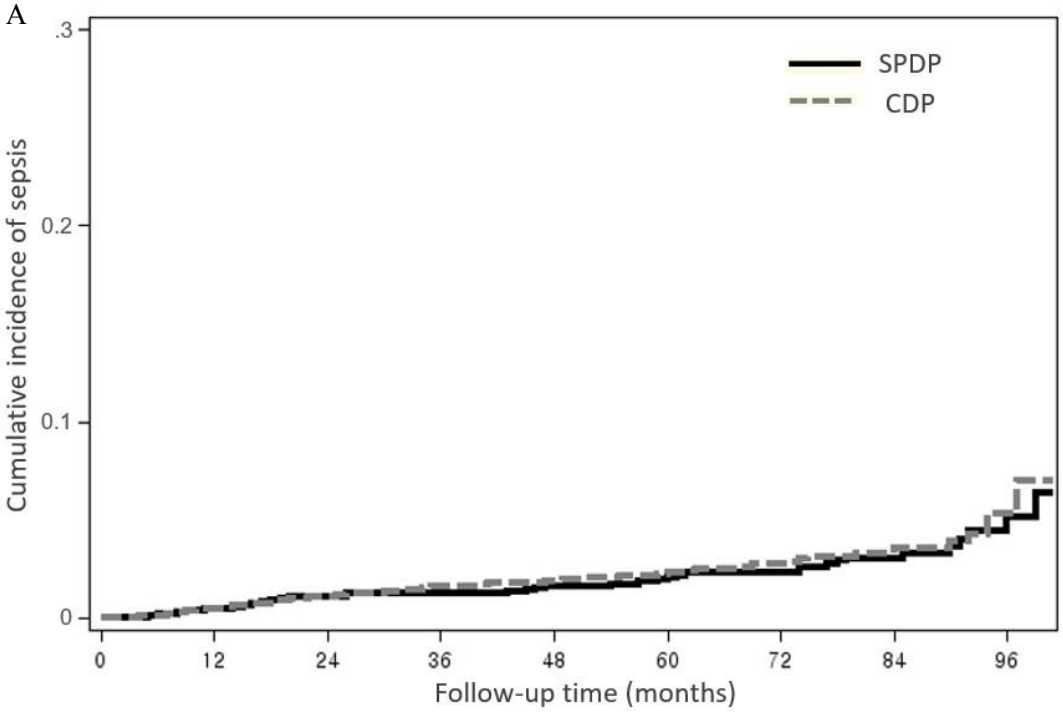
Variable	SPDP (n = 2,262)	CDP (n = 2,262)	*P* value
Sex			0.7212
Male	1,146 (50.7)	1,158 (51.2)	
Female	11,16 (49.3)	1,104 (48.8)	
Age (years)	57.4 ± 13.2	57.4 ± 13.3	0.9973
Underlying comorbidity			
Chronic pulmonary disease	227 (10.0)	240 (10.6)	0.5253
DM	457 (20.2)	419 (18,5)	0.1528
Malignant disease	995 (44.0)	994 (43.9)	0.9761
Indication			0.0012
MPD	634 (28.0)	734 (32.5)	
BPD	1,628 (72.0)	1,528 (67.5)	

SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy; DM, diabetes mellitus; MPD, malignant pancreatic disease; BPD, benign pancreatic disease.

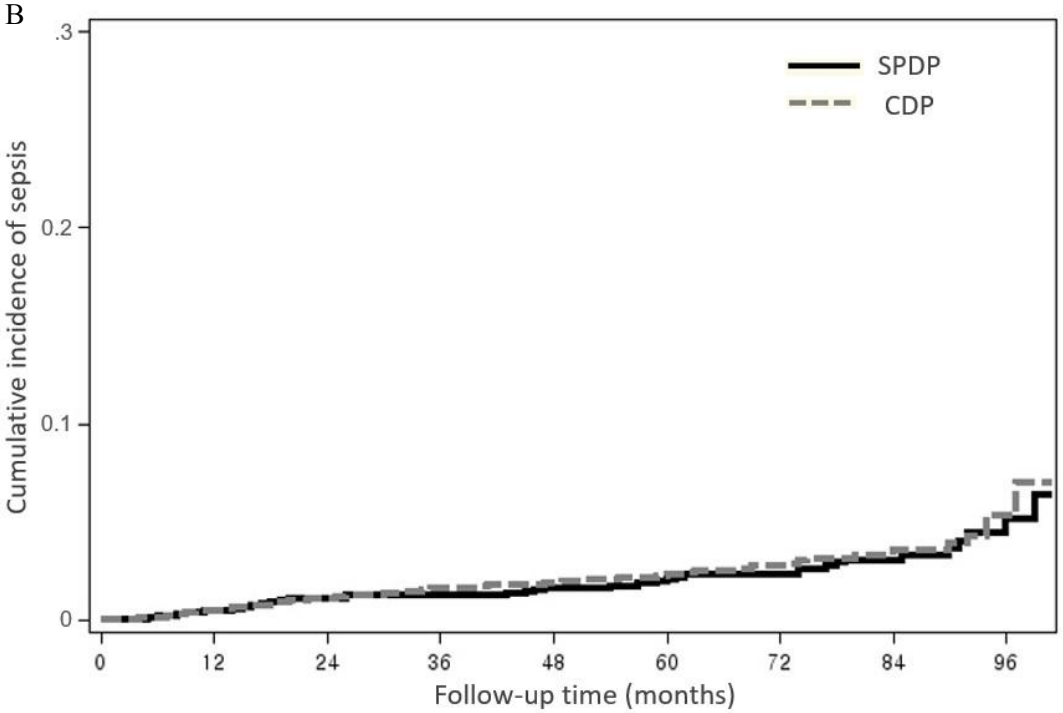
Sepsis occurred in 109 (2·4%) patients in this study (51 [2·3%] patients in the SPDP group, 58 [2·6%] in the CDP group, $P = 0·500$). In the malignant pancreatic disease subgroup, no significant difference was found in the sepsis occurrence rate between the patients in the SPDP and CDP groups (2·4% [n = 15] vs. 2·3% [n = 17], respectively; $P = 1·000$). The occurrence rate of sepsis was not significantly different even in patients with benign pancreatic diseases (2·2% [n = 36] vs. 2·7% [n = 41], SPDP and CDP groups, respectively; $P = 0·420$).

In the long-term follow-up, sepsis after distal pancreatectomy tended to occur steadily with a very low frequency in both groups. Figure 2A shows the cumulative incidence curves of sepsis in the SPDP and CDP groups among all patients. The cumulative incidence rate of sepsis was not significantly different between the SPDP and CDP groups ($P = 0·482$). The cumulative incidence rate of sepsis between the SPDP and CDP groups showed similar patterns, even when they were separated into patients with malignant and benign pancreatic diseases and compared respectively (Figure 2B and 2C, $P = 0·932$ and $P = 0·357$, respectively).

A


SPDP
CDP
Cumulative incidence of sepsis
0
0.1
0.2
.3
0
12
24
36
48
60
72
84
96
Follow-up time (months)

B


SPDP
CDP
Cumulative incidence of sepsis
0
0.1
0.2
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Follow-up time (months)

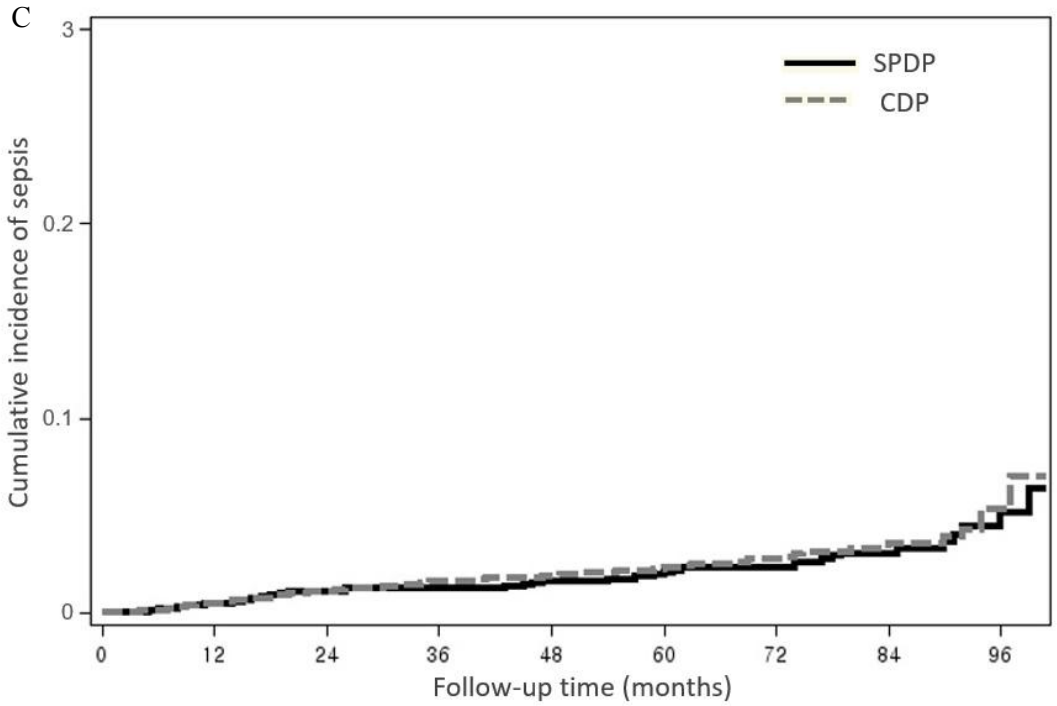


Figure 2. Kaplan-Meier graph for the cumulative incidence of sepsis for the SPDP and CDP groups. **A**: All patients (P = 0·4819). **B**: Malignant pancreatic disease subgroup (P = 0·9323). **C**: Benign pancreatic disease subgroup (P = 0·3572). SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy.

The multivariate Cox proportional hazards regression model demonstrated that splenectomy did not increase the risk of sepsis in patients who underwent distal pancreatectomy (HR = 0·871, 95% CI = 0·598-1·269) (Table 3). Age, female sex, DM, and even malignant disease were not associated with sepsis. Only chronic pulmonary disease increased the risk of sepsis by approximately twofold, although statistical significance was not shown.

Table 3. Hazard ratio and 95% confidence interval for sepsis in patients who underwent distal pancreatectomy

Variable	Crude		Adjusted	
	HR	95% CI	HR	95% CI
Splenectomy	0.874	0.600–1.273	0.871	0.598–1.269
Age	1.006	0.991–1.020	1.008	0.993–1.023
Sex	0.902	0.620–1.313	0.893	0.611–1.304
Chronic pulmonary disease	2.045	0.898–4.657	2.113	0.925–4.825
DM	1.056	0.648–1.711	1.073	0.656–1.757
Malignant disease	0.985	0.675–1.436	0.997	0.678–1.466

HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

Table 4 shows the effect of splenectomy on the occurrence of sepsis in the malignant and benign pancreatic disease subgroups. In the malignant pancreatic disease subgroup, the risk of sepsis occurrence was not significantly different between the SPDP and CDP groups (HR = 1·004, 95% CI = 0·498-2·024). Similar results were also observed in patients with benign pancreatic disease (HR = 0·804, 95% CI = 0·513-1·260).

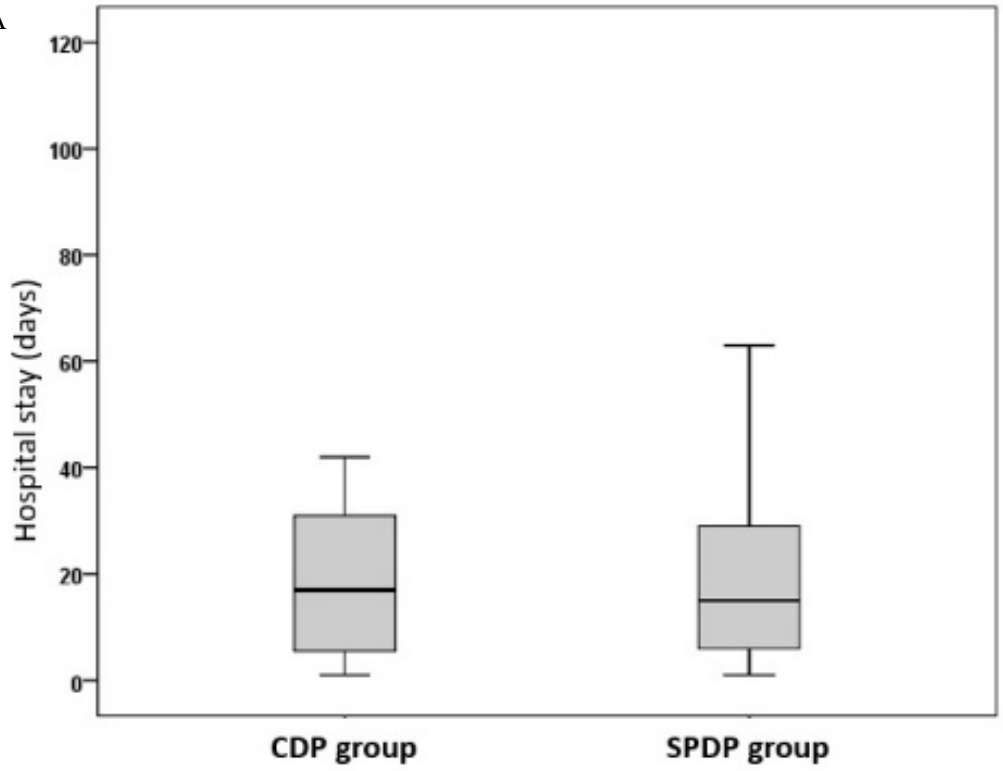
Table 4. Subgroup analyses of the risk of sepsis among patients who underwent distal pancreatectomy with malignant or benign pancreatic disease

Variable	Unadjusted analysis		Adjusted analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Malignant pancreatic disease		0.932		0.991
SPDP group	Reference		Reference	
CDP group	1.031 (0.515–2.064)		1.004 (0.498–2.024)	
Benign pancreatic disease		0.358		0.341
SPDP group	Reference		Reference	
CDP group	0.811 (0.518–1.268)		0.804 (0.513–1.260)	

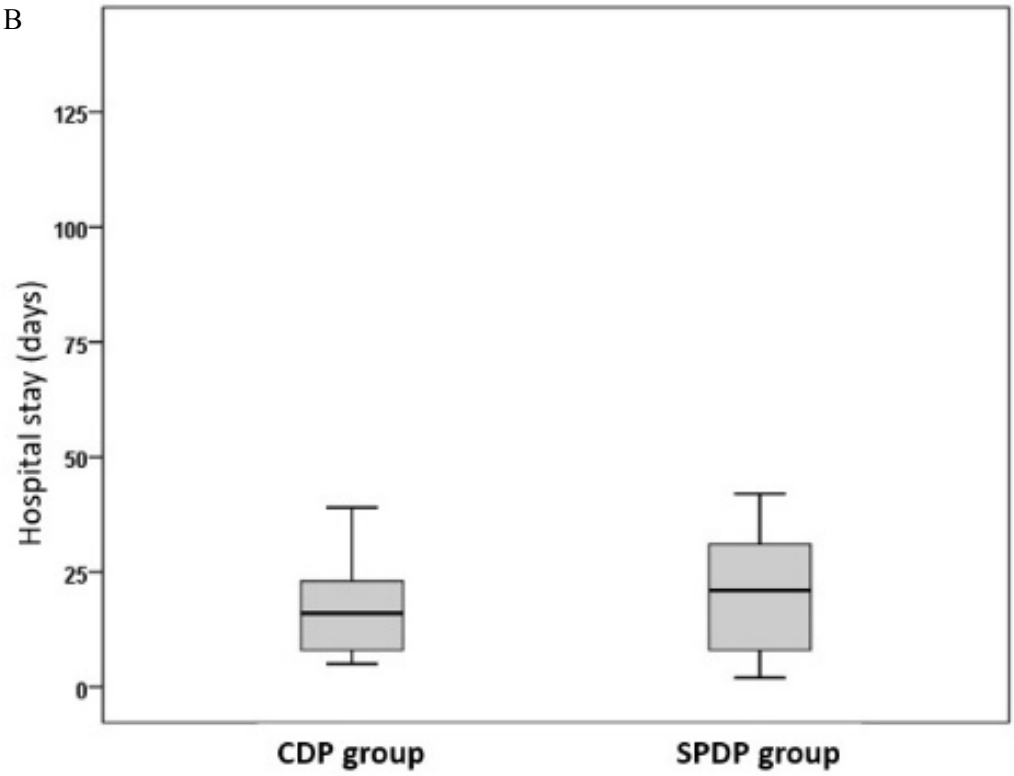
HR, hazard ratio; CI, confidence interval; SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy.

To compare the severity of sepsis that occurred between the SPDP and CDP groups, the hospital stays for sepsis were analysed (Figure 3). Among all enrolled patients, the mean hospital stay was not significantly different between the SPDP and CDP groups (24·9 ± 26·4 vs. 25·3 ± 30·0 days, respectively; $P = 0·941$) (Figure 3A). In patients with malignant pancreatic disease, the mean hospital stay showed no statistical difference (24·5 ± 30·5 days in the SPDP group and 28·1 ± 33·1 days in the CDP group; $P = 0·753$) (Figure 3B). The mean hospital stay in patients with benign pancreatic disease was also not significantly different in both groups (25·1 ± 25·0 days in the SPDP group, 24·2 ± 29·0 days in the CDP group; $P = 0·883$) (Figure 3C).

A


120
100
80
60
40
20
0
Hospital stay (days)
CDP group
SPDP group

B


125
100
75
50
25
0
Hospital stay (days)
CDP group
SPDP group

C

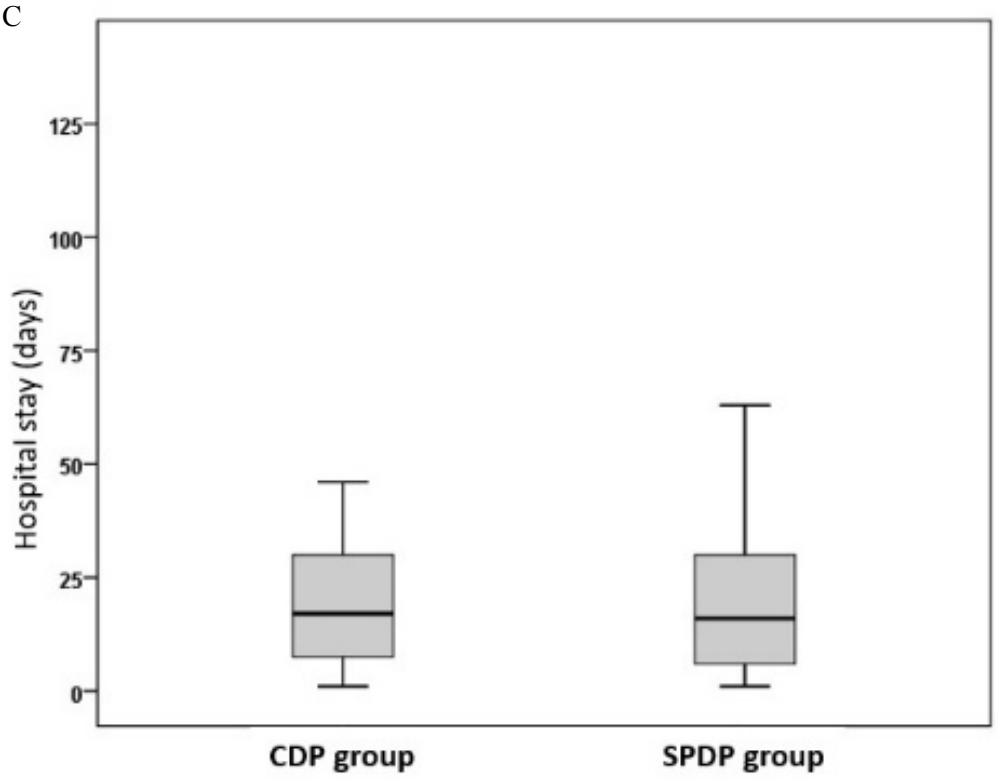


Figure 3. Box plot demonstrating the duration of hospital stays due to sepsis. **A**: All patients (P = 0·969). **B**: Malignant pancreatic disease group (P = 0·753). **C**: Benign pancreatic disease group (P = 0·848). SPDP, spleen-preserving distal pancreatectomy; CDP, conventional distal pancreatectomy.

Discussion

We performed a nationwide population-based study of the effect of splenic preservation on the occurrence of sepsis in patients undergoing distal pancreatectomy using the HIRA database. As shown in Figure 1, splenectomy did not significantly affect the incidence of sepsis in patients undergoing distal pancreatectomy. Multivariate analysis showed that splenectomy was independent of sepsis occurrence. In the present study, sepsis had steadily occurred at a low rate during long-term follow-up. Less than 3% of patients undergoing distal pancreatectomy experienced sepsis during the total follow-up, regardless of the splenectomy. In addition, the hospital stays due to sepsis, which may reflect the severity of sepsis, were not related to splenectomy. These results were the same in patients with malignant and benign pancreatic diseases.

Toutouzas et al. reported that the incidence of infection is highest in the first two years after splenectomy (50-75%), however, the risk could persist throughout life.[17] In our nationwide study, less than half of the patients who developed sepsis after distal pancreatectomy had experienced sepsis in the first two years, which is consistent with other previous studies. However, even two years after surgery, the occurrence of sepsis was steadily observed; therefore, constant surveillance for patients undergoing distal pancreatectomy may be required.

Patients who have undergone splenectomy are well-known to have an increased risk of developing severe septic complications such as overwhelming post-splenectomy infection syndrome.[2,18] Many studies have investigated the risk of infection after splenectomy, and most of them demonstrated that splenectomy increases the incidence rate of sepsis.[19-21] Edgren et al.[16] conducted a population-based study of sepsis risk after splenectomy, however, as most patients enrolled in that study underwent splenectomy before 2000, there may be limitations in applying the results to the current patients. In addition, a recent population-based study by Lee et al. reported that splenectomy in trauma patients is related to no increase in the rates of sepsis in a population-based, propensity score matching study.[13]

Splenic preservation has been generally recommended for patients undergoing distal pancreatectomy with benign pancreatic diseases because splenectomy can lead to serious infections.[8,10,22] For this reason, many surgeons have attempted to salvage the spleen during distal pancreatectomy and reported the feasible surgical outcome of spleen preservation in patients with distal pancreatectomy.[8,23] However, some authors have suggested that splenic preservation during distal pancreatectomy could be more time-consuming, with higher intraoperative blood loss, perioperative infection rate, and subsequent increased morbidity, including pancreatic fistulas.[24] Most of the comparative studies focused on short-term surgical outcomes and enrolled a small number of patients as research was conducted mainly in a single institution. Therefore, a long-term and large-

scale study is warranted to determine the effect of spleen preservation during distal pancreatectomy. Although several population-based studies have been conducted on the long-term effects of splenectomy alone, to the best of our knowledge, nationwide population studies on the long-term outcomes in patients undergoing distal pancreatectomy are currently scarce. In our nationwide study, splenectomy had no significant effect on the occurrence and severity of sepsis in patients. This finding indicates that preservation of the spleen may not be necessary during distal pancreatectomy, particularly in patients with benign pancreatic diseases.

In previous studies, trauma patients accounted for the majority of the patients who underwent splenectomy alone. These patients were commonly followed up for only the first several months or were not routinely checked for medical status after surgery. Thus, they may not receive adequate treatment prior to progressing to a serious infection. However, most of the patients enrolled in our study were routinely examined for their health status and received long-term regular follow-up after surgery because they had malignant or benign pancreatic diseases. Thus, their health abnormalities can be assumed to have been properly managed before the occurrence of serious conditions, such as sepsis. For this reason, the occurrence of sepsis in our patients seemed to be independent of splenectomy.

Although detailed immunisation medical records could not be obtained in the HIRA database, vaccination protocols in splenectomised patients seem to have been generally

well followed by most surgeons in South Korea. In addition, owing to its National Immunization Program in South Korea, pneumococcal and influenza vaccination rates are comparatively high and have steadily increased.[25-27] This sufficient vaccination may help to prevent sepsis occurrence in splenectomised patients.

En bloc splenectomy combined with distal pancreatectomy is clearly indicated in most patients with malignant pancreatic disease, as the preservation of the spleen might compromise oncologic resection.[23] However, the spleen was preserved in about half of the patients with malignant pancreatic disease in this study. In most cases, these patients were expected to have benign pancreatic disease based on preoperative workup but were pathologically confirmed as malignant pancreatic disease after surgery. This can be explained by the following reasons. First, malignant pancreatic disease is initially misdiagnosed as chronic pancreatitis or autoimmune pancreatitis.[28] Second, in cases of benign cystic diseases, such as mucinous cystic neoplasm and intraductal papillary mucinous neoplasm, invasive components may be found on biopsy after surgery.[29] Third, early pancreatic cancer could be difficult to detect on preoperative imaging or biopsy.[30] Fourth, the procedure code “splenectomy” may not have been entered in the HIRA database, although concomitant splenectomy was performed in patients with malignant pancreatic disease.

This is the first population-based study of patients undergoing distal pancreatectomy. The strength of our study is the use of nationwide data with long-term follow-up, which

increases the generalisability of the results. In contrast to previous studies on distal pancreatectomy, long-term follow-up was performed in this study to evaluate the incidence rate of sepsis more precisely in splenectomised patients undergoing distal pancreatectomy.

There are some limitations associated with studies that use nationwide data. First, we could not obtain detailed information on the patients and surgical outcomes from the HIRA database. Sepsis was diagnosed based on the KCD codes recorded in hospital discharge registries. The validity of our findings depends on the accuracy of coding for distal pancreatectomy and the diagnosis of hospitalisation due to sepsis. Second, the exact cause of sepsis was not identified in our data. Some patients may develop sepsis from serious infections such as peritonitis and other organisms than encapsulated bacteria associated with splenectomy. Third, we could not identify the type, number, and timing of vaccinations administered after surgery. The immunisation status is a major limitation because vaccination records are not included in the HIRA database.

Conclusion

We demonstrated that splenectomy during distal pancreatectomy did not increase the incidence rate of sepsis in a long-term follow-up. Thus, preservation of the spleen during distal pancreatectomy may not be necessary in patients with benign pancreatic disease. However, further population-based studies are warranted to analyse the role of spleen-preserving distal pancreatectomy in other outcomes such as pneumonia.

Acknowledgment

All authors declare no interests with any company enlisted in this study

References

1. Cooperman AM, Hoerr SO. Surgery of the pancreas: a text and atlas: Mosby; 1978.

2. Di Sabatino A, Carsetti R, Corazza GR. Post-splenectomy and hyposplenic states. *Lancet* 2011; **378**(9785): 86-97.

3. Morris DH, Bullock FD. The Importance of the Spleen in Resistance to Infection. *Ann Surg* 1919; **70**(5): 513-21.

4. Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late postsplenectomy infection. *Br J Surg* 1991; **78**(6): 716-21.

5. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. *The Journal of infection* 2001; **43**(3): 182-6.

6. Warshaw AL. Conservation of the spleen with distal pancreatectomy. *Arch Surg* 1988; **123**(5): 550-3.

7. Kimura W, Inoue T, Futakawa N, Shinkai H, Han I, Muto T. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein. *Surgery* 1996; **120**(5): 885-90.

8. Shi N, Liu SL, Li YT, You L, Dai MH, Zhao YP. Splenic Preservation Versus Splenectomy During Distal Pancreatectomy: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 2016; **23**(2): 365-74.

9. Milito P, Aiolfi A, Asti E, Rausa E, Bonitta G, Bonavina L. Impact of Spleen Preserving Laparoscopic Distal Pancreatectomy on Postoperative Infectious Complications: Systematic

Review and Meta-Analysis. *J Laparoendosc Adv Surg Tech A* 2019; **29**(2): 167-77.

10. Dai MH, Shi N, Xing C, et al. Splenic preservation in laparoscopic distal pancreatectomy. *Br J Surg* 2017; **104**(4): 452-62.

11. Fair KA, Connelly CR, Hart KD, Schreiber MA, Watters JM. Splenectomy is associated with higher infection and pneumonia rates among trauma laparotomy patients. *American journal of surgery* 2017; **213**(5): 856-61.

12. Lai SW, Lin CL, Liao KF. Risk of pneumonia among patients with splenectomy: a retrospective population-based cohort study. *Annals of Saudi medicine* 2017; **37**(5): 351-6.

13. Lee HJ, Cheng CT, Chen CC, et al. Increased long-term pneumonia risk for the trauma-related splenectomized population - a population-based, propensity score matching study. *Surgery* 2020.

14. Edgren G, Almqvist R, Hartman M, Utter GH. Splenectomy and the risk of sepsis: a population-based cohort study. *Ann Surg* 2014; **260**(6): 1081-7.

15. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**(12): 1495-9.

16. Kim DS. Introduction: health of the health care system in Korea. *Soc Work Public Health* 2010; **25**(2): 127-41.

17. Toutouzas KG, Velmahos GC, Kaminski A, Chan L, Demetriades D. Leukocytosis after posttraumatic splenectomy: a physiologic event or sign of sepsis? *Arch Surg* 2002; **137**(8): 924-8;

discussion 8-9.

18. Hansen K, Singer DB. Asplenic-hyposplenic overwhelming sepsis: postsplenectomy sepsis revisited. *Pediatr Dev Pathol* 2001; **4**(2): 105-21.

19. Theilacker C, Ludewig K, Serr A, et al. Overwhelming Postsplenectomy Infection: A Prospective Multicenter Cohort Study. *Clin Infect Dis* 2016; **62**(7): 871-8.

20. Kristinsson SY, Gridley G, Hoover RN, Check D, Landgren O. Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up. *Haematologica* 2014; **99**(2): 392-8.

21. Rieg S, Bechet L, Naujoks K, et al. A Single-Center Prospective Cohort Study on Postsplenectomy Sepsis and its Prevention. *Open Forum Infect Dis* 2020; **7**(3): ofaa050.

22. Moekotte AL, Lof S, White SA, et al. Splenic preservation versus splenectomy in laparoscopic distal pancreatectomy: a propensity score-matched study. *Surg Endosc* 2020; **34**(3): 1301-9.

23. Shoup M, Brennan MF, McWhite K, Leung DH, Klimstra D, Conlon KC. The value of splenic preservation with distal pancreatectomy. *Arch Surg* 2002; **137**(2): 164-8.

24. Benoist S, Dugue L, Sauvanet A, et al. Is there a role of preservation of the spleen in distal pancreatectomy? *Journal of the American College of Surgeons* 1999; **188**(3): 255-60.

25. Seo J, Lim J. Trends in influenza vaccination coverage rates in South Korea from 2005 to 2014: Effect of public health policies on vaccination behavior. *Vaccine* 2018; **36**(25): 3666-73.

26. Yun JW, Noh JY, Song JY, Chun C, Kim Y, Cheong HJ. The Korean Influenza National

Immunization Program: History and Present Status. *Infect Chemother* 2017; **49**(4): 247-54.

27. Yang TU, Kim E, Park YJ, et al. Successful introduction of an underutilized elderly pneumococcal vaccine in a national immunization program by integrating the pre-existing public health infrastructure. *Vaccine* 2016; **34**(13): 1623-1629.

28. Munigala S, Kanwal F, Xian H, Agarwal B. New diagnosis of chronic pancreatitis: risk of missing an underlying pancreatic cancer. *Am J Gastroenterol* 2014; **109**(11): 1824-30.

29. Tanaka M. Intraductal Papillary Mucinous Neoplasm of the Pancreas as the Main Focus for Early Detection of Pancreatic Adenocarcinoma. *Pancreas* 2018; **47**(5): 544-50.

30. Kanno A, Masamune A, Hanada K, et al. Multicenter study of early pancreatic cancer in Japan. *Pancreatology* 2018; **18**(1): 61-7.