Int Surg 2021;**105:**760–765
DOI: 10.9738/INTSURG-D-20-00020.1

Assessment of Preoperative Clinicophysiologic Findings as Risk Factors for Postoperative Pancreatic Fistula After Pancreaticoduodenectomy

Shuji Suzuki[1], Mitsugi Shimoda[1], Jiro Shimazaki[1], Yukio Oshiro[1], Kiyotaka Nishida[1], N. Orimoto[1], Masahiro Shiihara[2], Wataru Izumo[2], Masakazu Yamamoto[2]

[1]*Department of Gastroenterological Surgery, Ibaraki Medical Center, Tokyo Medical University, Ibaraki, Japan*

[2]*Department of Gastroenterological Surgery, Tokyo Women's Medical University, Ibaraki, Japan*

Objective: Postoperative pancreatic fistula (POPF) is one of the severe complications that develop after pancreaticoduodenectomy (PD). This study aimed to assess the utility of preoperative clinicophysiologic findings as risk factors for POPF after PD.

Summary of Background Data: We enrolled 350 patients who underwent PD between 2007 and 2012 at Tokyo Women's Medical University.

Methods: In total, 350 patients who underwent PD between 2007 and 2012 were examined retrospectively. All patients were classified into 2 groups as follows: group A (no fistula/biochemical leak group, 289 patients) and group B (grade B/C of POPF group 61 patients). Variables, including operative characteristics, length of stay in hospital, morbidity, mortality, and data regarding preoperative clinicophysiologic parameters, were collected and analyzed as predictors of POPF for univariate and multivariate analyses.

Results: There were 213 male and 137 female patients. The mean age was 65.4 years (range, 21–87 years). Univariate analysis showed that sex ($P = 0.047$), amylase level ($P = 0.032$), prognostic nutritional index (PNI; $P = 0.001$), and C-reactive protein/albumin ratio ($P = 0.005$) were independent risk factors for POPF. In contrast, multivariate analysis showed that sex ($P = 0.045$) and PNI ($P = 0.012$) were independent risk factors for POPF.

Corresponding author: Shuji Suzuki, MD, PhD, Department of Gastroenterological Surgery, Ibaraki Medical Center, Tokyo Medical University, 3-20-1 Chuo, Amimachi, Inashikigun, Ibaraki 300-0395, Japan.
Tel.: +81 29 887 1161; Fax: +81 29 888 8171; E-mail: ssuzuki@tokyo-med.ac.jp

Conclusions: Our results show that PNI (≤48.64 U/mL) and male sex were risk factors for POPF after PD, and especially, PNI can be suggested as an effective biomarker for POPF.

Key words: Pancreatic fistula – Pancreaticoduodenectomy – Prognostic nutritional index

A gradual decrease in the incidence of short-term complications after pancreaticoduodenectomy (PD) has been observed, and recent improvements in operative technique and perioperative management have resulted in an increase in the number of long-term survivors.[1] PD is an important method for the surgical treatment of tumors of the head and the periampullary parts of the pancreas. In recent years, the mortality rate after PD decreased to less than 5% in high-volume centers; however, the morbidity rate remains high between 30% and 50%.[2–5] One of the main reasons for the high morbidity rate after PD is postoperative pancreatic fistula (POPF).[6,7] POPF occurs in 5% to 30% of patients after PD,[8] and its incidence has been observed to be fairly constant over the past 30 years even in high-volume centers.[9,10] The definition of POPF provided by the International Study Group on Pancreatic Fistula (ISGPF) has been helpful for the accurate comparison of different surgical experiences.[11] After this proposal of POPF, a standardized POPF definition was established: fluid output of any measurable volume via an operatively placed drain with amylase activity greater than 3 times the upper normal serum value. To update the definition of POPF by the ISGPF,[12] the grading of POPF had been changed to include the following 3 grades of severity: biochemical leak, grade B, and grade C. In a previous study, the risk factors of POPF were body mass index,[13–15] sex,[13–15] a narrow pancreatic duct width.[13,14,16] and pancreatic texture.[13,17] To date, only a few studies assessing preoperative clinicophysiologic findings as risk factors for POPF after PD have been performed; thus, we aimed to evaluate preoperative clinicophysiologic findings as risk factors for POPF after PD.

Materials and Methods

In total, 350 patients who underwent PD between 2007 and 2012 were examined retrospectively at Tokyo Women's Medical University. All patients were classified into 2 groups as follows: group A (no fistula/biochemical leak group, 289 patients) and group B (grade B/C of POPF group, 61 patients). Variables, including operative characteristics, length of stay in hospital, morbidity, mortality, and data regarding clinicophysiologic parameters, including sex, age, body mass index, biliary decompression, total bilirubin, albumin, creatinine, glycated hemoglobin (HbA1c), amylase, C-reactive protein, white blood cell (WBC) count, lymphocyte number, hemoglobin, platelet, carbohydrate antigen (CA)19-9, carcinoembryonic antigen (CEA), neutrophil/lymphocyte ratio (NLR), prognostic nutritional index (PNI), platelet/lymphocyte ratio (PLR), and C-reactive protein/albumin ratio (CAR), were collected and analyzed as predictors of POPF in univariate and multivariate analyses. All clinicophysiologic parameters were measured immediately before pancreatic resection under cholangitis and pancreatitis control.

Operative techniques

All patients underwent PD through duct-to-mucosa pancreaticojejunostomy with or without a stenting tube. An end-to-side two-layer anastomosis was performed between the pancreas and the jejunum. Anastomosis of the outer layer was performed between the pancreatic parenchyma and the jejunal seromuscularis using 4-0 or 5-0 nonabsorbable sutures. In contrast, anastomosis between the pancreatic duct and the jejunal mucosa was performed precisely using 5-0 or 6-0 monofilament absorbable sutures. With a suture placed on the anterior wall and sutures placed on the bilateral walls, the duct lumen was kept open. Continuous sutures were placed on the anterior and posterior walls without a scope, and prophylactic octreotide was not used postoperatively. The Child method was used for reconstruction during PD in all patients.

Statistical analysis

The χ^2 test was used to evaluate differences in categorical data for univariate analyses, and $P < 0.05$ was considered statistically significant. Logistic regression analyses were used to perform the multivariate analyses. The cutoff values for NLR, PNI, PLR, and CAR were calculated by receiver operating characteristics (ROC) curve analysis, and

Table 1 Patient characteristics

Factors	All patients (n = 350)
Average age (range)	65.4 (21–87)
Sex (male/female)	213/137
Diseases (%)	
Pancreatic cancer	131 (37.4%)
Distal bile duct cancer	68 (19.4%)
IPMN	58 (16.6%)
Papilla Vater cancer	42 (12%)
NEN	12 (3.4%)
Duodenal cancer	11 (3.1%)
SCN	4 (1.1%)
SPN	3 (0.9%)
others	21
Operative procedures (%)	
PPPD	280 (80%)
SSPPD	49 (14%)
PD	20 (5.7%)
DPPHR	1 (0.3%)

DPPHR, duodenum-preserving pancreatic head resection; IPMN, intraductal papillary mucinous neoplasm; NEN, neuroendocrine neoplasm; PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm; SSPPD, subtotal stomach-preserving pancreaticoduodenectomy.

the SPSS statistical software package, version 22.0 (IBM Corp., Chicago, IL, USA) was used for the statistical analysis.

Ethical conduct

This study was approved by the Research Ethics Committee of Tokyo Women's Medical University. (approval number 4605). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration. Experiments using animals were not performed by any of the authors in this study. The requirement for obtaining written informed consent from each patient was waived because of the study's retrospective design.

Results

There were 213 male and 137 female patients, with a mean age was 65.4 years (range, 21–87 years). The enrolled patients had the following diseases: pancreatic cancer, 131 patients (37.4%); distal bile duct cancer 68 (19.4%); intraductal papillary mucinous neoplasm 58 (16.6%); papilla Vater cancer 42(12%); neuroendocrine neoplasm 12 (3.4%); serous cystic neoplasm 4 (1.1%); solid pseudopapillary neoplasm 3 (0.9%); and others 21 (6%) (Table1). Furthermore,

Table 2 Preoperative clinicophysiologic characteristics

Variable	Factors	Average ± SE
Sex	Male/female	213/137
Age		65.42 ± 0.59
BMI (kg/m^2)		21.65 ± 0.16
Biliary decompression	(−)/(+)	220/130
Total bilirubin (mg/dL)		1.18 ± 0.07
Albumin (mg/dL)		3.92 ± 0.02
Creatinine (mg/dL)		0.76 ± 0.02
HbA1C (%)		6.33 ± 0.06
Amylase		101.06 ± 4.46
CRP (mg/dL)		0.59 ± 0.08
WBC (/μL)		5407.96 ± 85.17
Lymphcyte (/μL)		1436.77 ± 25.50
Hemoglobin (g/dL)		12.67 ± 0.08
Platelet ($\times 10^4$/μL)		23.06 ± 0.41
CA19-9 (U/mL)		279.04 ± 73.15
CEA (ng/mL)		4.66 ± 0.63
mGPS	0, 1/2	244/105
NLR		2.73 ± 0.11
PNI		46.40 ±0.28
PLR		176.69± 4.23
CAR		0.1640 ± 0.022

BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CAR, CRP/albumin ratio; CEA, carcinoembryonic antigen; CRP, C-reactive protein; mGPS, modified Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PNI, prognostic nutritional index.

operative procedures were pylorus-preserving PD, 280 (80%); subtotal stomach-preserving PD, 49 (14%); PD, 20 (5.7%); and duodenum-preserving pancreatic head resection 1 (0.3%; Table 1). Table 2 shows the preoperative clinicophysiologic findings of this study. The univariate analysis showed that sex ($P = 0.047$), amylase level ($P = 0.032$), PNI ($P = 0.001$), and CAR ($P = 0.005$) were independent risk factors for POPF, between group A and group B regarding preoperative clinicophysiologic findings (Table 3). In contrast, multivariate analysis showed that sex ($P = 0.045$) and PNI ($P = 0.012$) were independent risk factors for POPF between group A and group B regarding preoperative clinicophysiologic findings (Table 4).

Discussion

PF has been reported to be a potentially lethal complication because it could result in delayed massive hemorrhage and septicemia after PD.[18–21] However, there is still no established procedure to prevent POPF after PD; thus, preoperative identification of patients at high risk for POPF is important for improving the morbidity and clinical outcome. Previous studies on preoperative clinicophysiologic

Table 3 Univariate analyses between group A and group B on preoperative clinicophysiologic findings

Variable	Factors	Number	Group A	Group B	*P*
Sex	Male	213	169	44	0.047
	Female	137	120	17	
Age	≦70	219	185	34	0.225
	>70	131	104	27	
BMI (kg/m^2)	≦25	311	260	51	0.152
	>25	39	29	10	
Biliary decompression	(−)	220	187	33	0.119
	(+)	130	102	28	
T-bil (mg/dL)	≦1.2	256	215	41	0.334
	>1.2	93	74	19	
Albumin (mg/dL)	≦3.6	90	70	20	0.164
	>3.6	260	219	41	
Creatinine (mg/dL)	≦1.1	325	269	56	0.725
	>1.1	25	20	5	
HbA1C (%)	≦6.2	198	158	40	0.056
	>6.2	125	110	15	
AMY	≦125	284	228	56	0.032
	>125	61	56	5	
CRP (mg/dL)	≦0.3	238	202	36	0.09
	>0.3	111	86	25	
WBC (/μL)	≦8500	337	279	58	0.584
	>8500	13	10	3	
Lymphcyte (/μL)	≦2000	315	261	54	0.772
	>2000	54	28	5	
Hb (g/dL)	≦13	203	171	32	0.335
	>13	147	118	29	
Plt (×10^4/μL)	≦15	37	33	4	0.259
	>15	312	255	57	
CA19-9 (U/mL)	≦37	194	155	39	0.173
	>37	152	130	22	
CEA (ng/mL)	≦5	293	237	56	0.098
	>5	52	47	5	
mGPS	0.1	244	206	38	0.153
	2	105	82	23	
NLR	≦3.07	255	217	38	0.091
	>3.07	93	72	21	
PNI	≦48.6	224	175	49	0.001
	>48.6	124	114	10	
PLR	≦218.2	266	226	40	0.086
	>218.2	82	63	19	
CAR	≦0.043	183	161	22	0.005
	>0.043	166	127	39	

BMI, Body mass index; CRP, C-reactive protein; CA19-9, Carbohydrate antigen 19-9; CEA, Carcinoembryonic antigen; mGPS, modified Glasgow Prognostic Score; NLR, Neutrophil/lymphocyte ratio; PNI, Prognostic nutritional index; PLR, Platelet/lymphocyte ratio; CAR, CRP/Albumin ratio.

findings for POPF are unavailable. In previous reports, preoperative serum-based inflammatory and nutritional indicators derived from clinicophysiologic findings, such as NLR, PLR, modified Glasgow prognostic score, PNI, and CAR, have been linked to prognosis in many types of cancer.[22–25] In this study, we evaluated preoperative clinicophysiologic findings as risk factors for POPF after PD and suggested PNI (≤48.64 U/mL) to be an effective biomarker for POPF.

Table 4 Multivariate analyses between group A and group B on preoperative clinicophysiologic findings

Variable	Hazard ratio	95% confidence interval	*P*
Sex	0.524	0.278–0.985	0.045
AMY	0.996	0.994–1.001	0.145
PNI	0.928	0.875–0.984	0.012
CAR	0.564	0.211–1.510	0.254

As obtained in previous reports,[13–15] male sex was observed to be an independent POPF-related factor and was repeatedly revealed as a risk factor of POPF.[26] Mathur *et al*[27] reported that patients with POPF have significantly more pancreatic fat and less fibrosis than those without POPF. In addition, the presence of increased fat in the pancreas, along with a small nondilated duct, may be associated with decreased local blood flow and may increase the risk of perioperative pancreatitis. Dixon[28] described that men had significantly more fat within the abdominal cavity than women, even among people with similar total amounts of fat. This may be one of the causes of the significantly high incidence of POPF in men compared with women.

PNI had been considered a predictive factor of the prognosis and postoperative complication of various cancers.[29–31] PNI included a combination of the albumin and total lymphocyte count and was initially used to evaluate immunologic and nutritional status.[32] Aida *et al*[33] revealed that preoperative immunonutrition, which modulates prostaglandin E2 production and T-cell differentiation, may prevent postoperative complications in patients after PD. Low PNI level was considered to have resulted from hypoalbuminemia and/or lymphocytopenia. Hypoalbuminemia is associated with poor tissue healing and impairment of immune responses related with macrophage activation and granuloma formation.[34,35] Lymphocytopenia has been known to decrease the antitumor effect induced by the cellular immunity of T lymphocytes.[36] An immunonutritional disorder causes a decline in albumin concentration and total lymphocyte count, including helper T cells, interleukins 2 and 3, and T cell blastogenic responses.[37] Kanda *et al*[38] reported an association of PNI with overall survival and postoperative complications, particularly pancreatic fistula, in patients with pancreatic cancer. They revealed that PNI less than 45 U/mL was a significant predictor of POPF in patients with pancreatic cancer, a result that is

strongly similar to our finding of PNI $\leq$ 48.64 U/mL as a predictive risk factor for POPF. Therefore, PNI may be used as a biomarker of POPF after PD.

There are several limitations to this study. First, this study was retrospective in design; however, the PD cases were consecutive. Second, some of the parameters whose data could not be measured all round. Hence, additional multicenter investigations involving larger patient populations are needed before definitive conclusions can be drawn.

In conclusion, PNI ($\leq$48.64 U/mL) and male sex are significant risk factors for POPF after PD, and low PNI level was suggested to be an effective biomarker for POPF after PD.

Acknowledgments

This article did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

References

1. Suzuki S, Kaji S, Koike N, Harada N, Hayashi T, Suzuki M *et al*. Pancreaticoduodenectomies with a duct-to-mucosa pancreaticojejunostomy anastomosis with and without a stenting tube showed no differences in long-term follow-up. *J Hepatobiliary Pancreat Sci* 2011;**18**(2):258–262
2. Cameron JL, Pitt HA, Yeo CJ, Lillemoe KD, Kaufman HS, Coleman J. One hundred and forty-five consecutive pancreaticoduodenectomies without mortality. *Ann Surg* 1993;**217**(5): 430–435
3. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA *et al*. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997;**226**(3):248–257
4. Gouma DJ, van Geenen RC, van Gulik TM, de Haan RJ, de Wit LT, Busch ORC *et al*. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. *Ann Surg* 2000;**232**(6):786–795
5. Balcom JH 4th, Rattner DW, Warshaw AL, Chang Y, Fernandez-del Castillo C. Ten-year experience with 733 pancreatic resections. Changing indications, older patients, and decreasing length of hospitalization. *Arch Surg* 2001; **136**(4):391–398
6. Büchler MW, Friess H, Wagner M, Kulli C, Wagener V, Z'Graggen K. Pancreatic fistula after pancreatic head resection. *Br J Surg* 2000;**87**(7):883–889
7. Kim JH, Yoo BM, Kim JH, Kim WH. Which method should we select for pancreatic anastomosis after pancreaticoduodenectomy? *World J Surg* 2009;**33**(2):326–332
8. Pratt W, Callery M, Vollmer C. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg* 2008;**32**(3):419–428
9. Poon RTP, Lo SH, Fong D, Fan ST, Wong J. Prevention of pancreatic anastomotic leakage after pancreaticoduodenectomy. *Am J Surg* 2002;**183**(1):42–52
10. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006; **244**(1):10–15
11. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al*. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;**138**(1):8–13
12. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M *et al*. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. *Surgery* 2017;**161**(3):584–591
13. Hu BY, Wan T, Zhang WZ, Dong JH. Risk factors for postoperative pancreatic fistula: analysis of 539 successive cases of pancreaticoduodenectomy. *World J Gastroenterol* 2016; **22**(34):7797–7805
14. Tranchart H, Gaujoux S, Rebours V, Vullierme MP, Dokmak S, Levy P *et al*. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. *Ann Surg* 2012;**256**(1):139–145
15. House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M *et al*. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg* 2008;**12**(2):270–278
16. Yamamoto Y, Sakamoto Y, Nara S, Esaki M, Shimada K, Kosuge T. A preoperative predictive scoring system for postoperative pancreatic fistula after pancreaticoduodenectomy. *World J Surg* 2011;**35**(12):2747–2755
17. Gaujoux S, Cortes A, Couvelard A, Noullet S, Clavel L, Rebours V *et al*. Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. *Surgery* 2010;**148**(1):15–23
18. Akamatsu N, Sugawara Y, Komagome M, Shin N, Cho N, Ishida T *et al*. Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy: the significance of the ratio of the main pancreatic duct to the pancreas body as a predictor of leakage. *J Hepatobiliary Pancreat Sci* 2010;**17**(3):322–328
19. Weber CE, Bock EA, Hurtuk MG, Abood GJ, Pickleman J, Shoup M *et al*. Clinical and pathologic features influencing survival in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma. *J Gastrointest Surg* 2014;**18**(2):340–347
20. Shrikhande SV, Barreto SG, Somashekar BA, Suradkar K, Shetty GS, Talole S *et al*. Evolution of pancreatoduodenectomy in a tertiary cancer center in India: improved results from service reconfiguration. *Pancreatology* 2013;**13**(1):63–71
21. Katsaragakis S, Larentzakis A, Panousopoulos SG, Toutouzas KG, Theodorou D, Stergiopoulos S *et al*. A new pancreatico-

jejunostomy technique: a battle against postoperative pancreatic fistula. *World J Gastroenterol*. 2013;**19**(27):4351–4355
22. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Fushiya N *et al*. Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma. *Br J Cancer*. 2012;**107**(6):988–993
23. Inoue D, Ozaka M, Matsuyama M, Yamada I, Takano K, Saiura A *et al*. Prognostic value of neutrophil–lymphocyte ratio and level of C-reactive protein in a large cohort of pancreatic cancer patients: a retrospective study in a single institute in Japan. *Jpn J Clin Oncol* 2015;**45**(1):61–66
24. Ishizuka M, Oyama Y, Abe A, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients undergoing surgery for gastric cancer. *J Surg Oncol* 2014;**110**(8):935–941
25. Okamura Y, Ashida R, Ito T, Sugiura T, Mori K, Uesaka K. Preoperative neutrophil to lymphocyte ratio and prognostic nutritional index predict overall survival after hepatectomy for hepatocellular carcinoma. *World J Surg* 2015;**39**(6):1501–1509
26. Kawai M, Kondo S, Yamaue H, Wada K, Sano K, Motoi F *et al*. Predictive risk factors for clinically relevant pancreatic fistula analyzed in 1, 239 patients with pancreaticoduodenectomy: multicenter data collection as a project study of pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 2011;**18**(4):601–608
27. Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ *et al*. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg* 2007;**246**(6):1058–1064
28. Dixon AK. Abdominal fat assessed by computed tomography: sex difference in distribution. *Clin Radiol* 1983;**34**(2):189–191
29. Li P, Wang X, Lai Y, Zhou K, Tang Y, Che G. The prognostic value of pre-treatment prognostic nutritional index in esophageal squamous cell carcinoma: a meta-analysis. *Medicine (Baltimore)* 2019;**98**(22):e15280
30. Luo Z, Zhou L, Balde AI, Li Z, He L, ZhenWei C *et al*. Prognostic impact of preoperative prognostic nutritional index in resected advanced gastric cancer: a multicenter propensity score analysis. *Eur J Surg Oncol* 2019;**45**(3):425–431
31. Wang Z, Wang J, Wang P. The prognostic value of prognostic nutritional index in hepatocellular carcinoma patients: a meta-analysis of observational studies. *PLoS One* 2018;**13**(10): e0202987
32. Nozoe T, Kimura Y, Ishida M, Saeki H, Korenaga D, Sugimachi K. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. *Eur J Surg Oncol* 2002;**28**(4):396–400
33. Aida T, Furukawa K, Suzuki D, Shimizu H, Yoshidome H, Ohtsuka M *et al*. Preoperative immunonutrition decreases postoperative complications by modulating prostaglandin E2 production and T-cell differentiation in patients undergoing pancreatoduodenectomy. *Surgery* 2014;**155**(1):124–133
34. Rivadeneira DE, Grobmyer SR, Naama HA, Mackrell PJ, Mestre JR, Stapleton PP *et al*. Malnutrition-induced macrophage apoptosis. *Surgery* 2001;**129**(5):617–625
35. Reynolds JV, Redmond HP, Ueno N, Steigman C, Ziegler MM, Daly JM *et al*. Impairment of macrophage activation and granuloma formation by protein deprivation in mice. *Cell Immunol* 1992;**139**(2):493–504
36. Wada Y, Nakashima O, Kutami R, Yamamoto O, Kojiro M. Clinicopathological study on hepatocellular carcinoma with lymphocytic infiltration. *Hepatology* 1998;**27**(2):407–414
37. Fujiwara Y, Shiba H, Shirai Y, Iwase R, Haruki K, Furukawa K *et al*. Perioperative serum albumin correlates with postoperative pancreatic fistula after pancreaticoduodenectomy. *Anticancer Res* 2015;**35**(1):499–503
38. Kanda M, Fujii T, Kodera Y, Nagai S, Takeda S, Nakao A. Nutritional predictors of postoperative outcome in pancreatic cancer. *Br J Surg* 2011;**98**(2):268–274