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Does the abdominal ultrasonography reliable in the diagnosis of postoperative pancreatic fistula after pancreaticoduodenectomy in the first postoperative week?

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Purpose: We evaluated the efficacy of ultrasonography (US) in the early postoperative period after pancreaticoduodenectomy (PD) to diagnose postoperative-pancreatic-fistula (POPF). Early diagnosis is important to prevent POPF-dependent mortality after PD. The value of radiological modalities for early diagnosing POPF is not clear.
Methods: Forty-five patients who underwent transabdominal-US in the first postoperative week after PD were retrospectively evaluated. Two types of grouping methods were performed. Firstly, peripancreatic or perianastomotic fluid collections at least 2 cm in diameter were considered to be a primary positive result on US. Patients then divided into 2 groups: group 1, US-positive and group 2, US-negative. Secondly, to increase the power of US, in addition to primary positive results, the presence of fever, leukocytosis or hyperamylasemia was considered to be a secondary positive result (group 1S). The remaining patients were considered to have secondary negative results (group 2S). The sensitivity and specificity for both grouping methods were calculated for the diagnosis of PF and clinically important PF (ciPF), according to the International Study Group on Pancreatic Fistula criteria.
Results: For the first grouping method, the sensitivity was 36% and 28% and the specificity was 80% and 85% for PF and ciPF, respectively. For the second grouping method, the sensitivity was 36% and 29% and the spesificity was 74% and 81% for PF and ciPF, respectively. The unloculated fluid collections were not related to a significant increase in the risk of POPF (P = 0.694).
Conclusion: Abdominal-US has low sensitivity and high specificity for the early diagnosis of POPF after PD.
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Key Words: Intra-abdominal fluid, Pancreatic fistula, Pancreaticoduodenectomy, Ultrasonography

INTRODUCTION

Early diagnosis of postoperative pancreatic fistula (POPF) after pancreaticoduodenectomy (PD) is crucial in order for surgeons to initiate the critical management of this potentially fatal complication. To decide whether a patient has POPF after pancreatic surgery is a challenge for surgeons. Although discharge of a small amount of amylase-rich fluid from abdominal drains is not always a harbinger of POPF, the upper limit for the amount of fluid and its amylase content are controversial. Furthermore, many cases of POPF are not associated with early abdominal discharge of amylase-rich fluid, because leaked fluid can easily collect inside the abdomen for a long time without external discharge [1-3]. International Study Group on

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Pancreatic Fistula (ISGPF) [1] collected widely used definitions of POPF from the literature, and created a new definition and grading system for POPF. Although disagreements on this issue still exist [4,5], this definition and grading system have been widely accepted and cited many times in the literature. This definition includes the following criteria: Any measurable volume of drainage on or after postoperative day (POD) 3, with an amylase content greater than 3 times the upper limit of the normal serum value [1].

The radiological findings are not included in the definition of POPF as a criterion. However, observing abdominal fluid collection on ultrasonography (US) or CT examination is a component of the grading system in patients with a definitive diagnosis of POPF according to ISGPF [1]. However, in this system, the timing of and the warning signs seen on ultrasonographic examination are not clearly defined.

Classically, US is the first-line radiological examination prefered by all medical practitioners, despite some disadvantages in the evaluation of deep abdominal organs. Although routine imaging is generally not used for the early identification of POPF [6,7], with the advances in the technology of US, it is not surprising that surgeons tend to perform an transabdominal US to evaluate the potential abdominal fluid collections. There have been very limited data published on transaabdominal US examination during the early postoperative period after pancreatic surgery. In this study, we aimed to evaluate the efficacy of transabdominal US in the first week after PD to diagnose POPF as early as possible.

METHODS

The medical records of all patients who underwent standard or pylorus-preserving PD at the authors' institution between June 2006 and January 2015 were retrospectively reviewed. The data collected included demographics; intraoperative and postoperative clinical and laboratory findings; histopathological results; and postoperative radiological examinations. The drainage of any measurable volume of amylase rich fluid (×3 of normal serum amylase level; normal upper limit is 120 U/L for our laboratory) from abdominal drains on or after POD 3 was considered to indicate POPF and it was graded according to the grading system of ISGPF [1]. Patients who underwent US examination between POD 3 and POD 7 were selected for inclusion in the study. Any patient who underwent reoperation for any reason in the first week after the index operation or who had a definitive diagnosis of POPF before the first US examination was excluded.

Ultrasonographic examination

US examinations were performed with a GE Logiq 7 (General Healthcare, Chicago, IL, USA). Early transabdominal US examination was carried out for any patient with a deviation from the expected clinical course in the early postoperative period other than diagnostic criteria of POPF, or if the surgeon had concerns about the intraoperative findings, including a soft texture of the pancreas, intraoperative transfusions, or a very small diameter of pancreatic duct. Transabdominal US was preferred as an imaging method during the early postoperative period, because it is faster and easier than a CT examination and does not require contrast agents. The US examinations were performed by eight different radiologists who were not aware of the amount of fluid from the abdominal drains and the levels of amylase. Included US examinations were performed before the definitive diagnosis of POPF.

Grouping

The presence of fluid collection at least 2 cm in diameter in the pancreatic bed (peripancreatic) or around the pancreaticojejunostomy (PJ) and/or hepaticojejunostomy (HJ), was considered to be a positive result on US. All other results were recorded as negative. The patients were then divided into 2 groups, an US-positive (group 1) and an US-negative (group 2). Two different terms were used to define the clinical state of patients with POPF: the presence of fistula, meaning a patient has any grade of POPF (A, B, or C) and the presence of a clinically important pancreatic fistula (ciPF), meaning a patient has a grade B or C fistula. Using these definitions, the sensitivity and specificity of US were calculated.

To eleminate any concerns about the effects of additional findings on predicting the risk of POPF or an inflammatory response, a second evaluation was performed and a new method of categorizing the patients was used, resulting in groups 1S and 2S. In this evaluation, the presence of significant abdominal fluid collection as described above with the presence of at least one of the following findings was considered as a positive result (group 1S): (1) fever ≥ 38°C before the first US examination; (2) last WBC count ≥11,000/mm^3 before the first US examination; (3) serum amylase level greater than three times the normal serum level (120 U/L for our laboratory) on POD 1. The rest of patients were considered to be negative (group 2S). It should be emphasized that, the patients with significant abdominal fluid collection were included in group 2S, even if the afformentioned laboratory findings were not present. Finally, as before, according to the presence of PF or ciPF, sensitivity and specificity were calculated.

Summary of surgical procedure

Pylorus-preserving PD was carried out as a routine operation. Standart PD was performed in patients where the lesion disturbed the anatomy of the pylorus or when tumors had infiltrated to the distal part of the stomach. According to the surgeons' preference, end-to-side PJ or end-to-end dunking PJ

was carried out by using 3/0 or 4/0 interrupted polypropylene sutures. End-to side HJ was performed 7 to 10 cm distally to the PJ with 4/0 propylene or polydioxanone interrupted sutures. Finally, end-to-side double layer duodenojejunostomy was performed 40 cm distally to the HJ. In standard PD, gastrojejunostomy was performed 50 cm distally to the HJ and a Braun anastomosis was added. Two suction drains (Jackson-Pratt drains) were placed in each patient: one posterior to the PJ and HJ extending along the hepatorenal area, and the other on the anterior surface of the pancreatic remnant and extending along the anterior surface of the PJ. In some patients, another nonsuction drain was placed in the splenorenal area according to the surgeons' preference. Prophylactic octreotid (Sandostatin LAR, Novartis AG, Basel, Switzerland) (0.1 mL X 4; subcutaneous) was started on POD 1 and continued until POD 7. Low-molecular weight heparin (Clexane 4000 IU, Sanofi S.A., Gentilly, France) was started 1 day before the operation and continued until POD 30. First-generation cephalosporins were used for perioperative antibiotic prophylaxis.

Statistical analysis

IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) software was used for statistical analysis. Normally distrubuted continuous variables were expressed as mean (standard seviation) and compared using a t-test. Variables not normally distributed were expressed as median (range) and compared using the Mann-Whitney U-test. Nominal data were expressed as case numbers and percentages and compared using Fischer exact test. All tests were two-sided, and $P < 0.05$ was accepted as statistically significant.

RESULTS

Between June 2006 and January 2015, 107 patients underwent PD at our center. Of these patients, eight patients who underwent total pancreatectomy were excluded, along with 54 patients who did not undergo US examination in the first postoperative week. The main indication for abdominal US was to test for the presence of abdominal fluid collection. Most of the excluded patients underwent abdominal US examination after POD 7. The remaining 45 patients were included in our study. Demographic, surgical and histopathological details are shown in Table 1.

Oral contrast-enhaced CT examination is not a standard evaluation method after PD in our center. Traditionally, we have not started oral intake until fifth day after PD. Therefore, there were only 5 cases (11%) with oral contrast-enhanced CT examination during the first seven PODs in our series. Thus, the CT findings were not included in this study.

There was no significantly different parameters between groups 1 and 2, nor between groups 1S and 2S. Only WBC count was different between groups 1S and 2S (Table 2). However, the WBC was already a criterion for differantiating between the patients in groups 1S and 2S; therefore, this difference was not considered to be important. The presence of PF or ciPF were also not significantly different between the groups. US was want to have low sensitivity (28% to 36%) and high specificity (74% to 85%) for all patients (Table 3).

In 12 of 32 patients (37.5%) without significant abdominal fluid collection as described above (in group 2), some minor findings were visible on the abdominal US examination. A small amount of free fluid around the intestines, in the peripancreatic or perianastomotic area without formation of loculation was present in 11 patients. Bilateral pleural effusions, not exceeding to 1 cm in the largest diameter, were detected by US in 2 patients, one of which also had minor abdominal findings. In these 12 patients, five were suffered from ciPF (42%). In the remaining 20 patients without any US findings, ciPF was diagnosed in 5 (25%). There was no significant difference in the rate of ciPF according to the presence or absence of these minor findings (42% and 25% repectively; $P = 0.694$).

Table 1. Demographic, surgical and histopathological details (n = 45)

Variable	Value
Sex	
Male	33 (73)
Female	12 (27)
Age (yr)	59.1 ± 15.2
Hospital stay (day)	19.4 ± 10.0
Type of PJ	
End to end dunking	34 (74)
End to side duct to mucosa	11 (26)
Histopathologic diagnosis	
Malign	41 (91)
Benign	4 (9)
Pancreatic fistula (ISGPF grading system)	
No fistula	20 (45)
A	11 (24)
B	4 (9)
C	10 (22)
Abdominal fluid collection on ultrasonography[a]	
Yes	13 (29)
No	32 (71)

Values are presented as number (%) or mean ± standard deviation.
ASA, American Society of Anesthesiologists; PJ, pancreaticojejunostomy; ISGPF, International Study Group of Pancreatic Fistula.
[a]The presence of fluid collection at least 2 cm in diameter in pancreatic bed or around the anastomoses.

Table 2. Comparison of groups

Variable	Group 1 (n = 13)	Group 2 (n = 32)	P-value	Group 1S (n = 10)	Group 2S (n = 35)	P-value
Age (yr)	58.7 ± 11.2	59.2 ± 15.3	0.916	57.4 ± 11.1	59.5 ± 15.1	0.690
Body mass index (kg/m^2)	24.2 ± 3.0	25.5 ± 5.1	0.396	23.9 ± 2.9	25.5 ± 4.9	0.332
WBC (/mm^3)	13.8 ± 5.9	12.2 ± 4.3	0.316	15.4 ± 6.2	11.9 ± 4.3	0.046*
Median serum amylase in POD1	222	121	0.456	222	140	0.275
Type of PJ			0.703			0.687
Dunking	9	25		7	27	
Duct to mucosa	4	7		3	8	
Histopathologic diagnosis			0.990			0.990
Malign	12	29		9	32	
Benign	1	3		1	3	
Pancreatic fistula (ISGPF grading system)			0.584			0.461
No Fistula	4 (31)	16 (50)		3 (30)	17 (48)	
A	4 (31)	7 (22)		3 (30)	8 (23)	
B	2 (15)	2 (6)		2 (20)	2 (6)	
C	3 (23)	7 (22)		2 (20)	8 (23)	
Presence of fistula (grades ABC)	9 (69)	16 (50)	0.327	7 (70)	18 (52)	0.472
Presence of clinically important fistula (grades BC)	5 (38)	9 (28)	0.990	4 (40)	10 (29)	0.700

Values are presented as mean ± standard deviation or number (%).
Group 1, patients with significant abdominal fluid collection on ultrasonographic examination; group 2, patients without significant abdominal fluid collection on ultrasonographic examination; group 1S, patients with significant abdominal fluid collection and one of the defined clinical findings; group 2S, patients excluded from the group 1S; POD, postoperative day; PJ, pancreticojejunostomy.
*P < 0.05, statistically significant.

Table 3. Sensitivity and specificity of ultrasonography with a concomitant finding

Group	PF (ISGPF grading system)				ciPF			
	Grades A, B, C	No fistula	Sensitivity	Specificity	Grades B, C	No ciPF	Sensitivity	Specificity
1	9	4	36%	80%	5	8	36%	74%
2	16	16			9	23		
1S	7	3	28%	85%	4	6	29%	81%
2S	18	17			10	25		

Group 1, patients with significant abdominal fluid collection on ultrasonographic examination; group 2, patients without significant abdominal fluid collection on ultrasonographic examination; group 1S, patients with significant abdominal fluid collection and one of the defined clinical findings; group 2S, patients excluded from the group 1S; PF, pancreatic fistula; ISGPF, International Study Group of Pancreatic Fistula; ciPF, clinically important pancreatic fistula.

DISCUSSION

According to widespread opinions in the literature, postoperative complications after pancreatic surgery including POPF, can be identified by cross-sectional imaging [7-9]. It is also generally accepted that US is not a reliable imaging modality for deep abdominal organs and pathologies. Additionally, the results of US are also directly linked to the skill and experience of the radiologist [10]. Nonetheless, US examination has some considerable advantages. First of all, it is faster, cheaper and more readily available than cross-sectional imaging modalities. In addition, with the significant recent advances in US technology, more accurate results can be achieved. Finally, US does not expose the patient to X-rays and does not require radiocontrast agents [6,10].

In the present case series, the diagnostic acuracy of abdominal US for POPF during the first postoperative week was quite low (sensitivity 28%–36% and specificity 74%–85%). We also evaluated the combination of abdominal fluid collection on US examination with the presence of at least one of the following findings, which are accepted indicators for POPF or a systemic inflammatory response: fever (>38°C), last WBC

count before the first US examination >11,000/mm^3, and a high amylase level on POD 1 (>360 U/L) [11-13]. However, the addition of these parameters did not increase the accuracy of US examination in our patients. Nonetheless, it can be concluded that the absence of significant abdominal fluid collection on US examination with or without the other three findings was associated with a lower risk of POPF (specificity 74%–85%). Malleo et al. [6] reported very similar results for transabdominal US examination as a diagnostic test method with high specificity (97.5%) and low sensitivity (40.7%) in the early postoperative period. In a study reported by Bruno et al. [9], the sensitivity and specificity of perianastomotic fluid collection detected by CT on POD 7 were reported as 63% and 83% respectively. According to these results, CT and US have very similar specificity, although CT is more sensitive than US.

In the present study, peripancreatic or perianastomotic fluid collection at least 2 cm in diameter as seen on transabdominal US was found in 29% of patients between POD 3 and POD 7. Previously, in a study including many types of pancreatic surgery, this rate was reported as approximately 12% in the first week after surgery by US examination [14]. In 2 other studies, abdominal fluid collection was seen in 15% of patients on POD 3 after PD or distal pancreatectomy (DP) [6,15]. In all three of these studies, other types of pancreatic resections with a lower risk of fistula were included in the study populations, such as DP, total pancreatectomy, and enucleation. This could be the reason for the relatively high rate found in our study.

According to the results of the current study, most of the patients (38%) with significant abdominal fiuid collection on transabdominal US examination during the first week after PD did not develop ciPF, even with accompanying fever, leukocytosis or hyperamylasemia in POD 1 (40%). However, when the presence of fistula of any grade (including grade A) was considered, the rate of POPF rose to 69%. Sierzega et al. [14] reported this rate as 17% in their 83 patients with early abdominal fluid collection detected by transabdominal US. In another study, peripancreatic fluid collection on POD 3 was associated with any grade of POPF in 88% of patients who underwent PD or DP [6]. These differences can be related to diversity in surgical procedures and the timing of the US examination. Pancreatic-digestive anastomosis is the higest-risk part of pancreatic surgery; therefore, we thought that our results may be more suitable for PD due to the restriction of our patients to this specific operation. During CT examination on POD 7, the rate of fluid collection in any part of the abdomen and perianastomotic fluid collection were reported as 60 % and 41%, respectively, by Bruno et al [9]. Hashimoto et al. [7] noted the diagnostic significance of fluid collection around the PJ or in the pancreatic bed. However, in this study, the timing of CT examination varied greatly (POD 4 to POD 30).

In this study, the rate of diagnosis of ciPF in patients with minor findings on transabdominal US examination, including small amounts of unloculated free fluid and/or insignificant pleural effusions was not significantly different from that of patients without any radiological findings (P = 0.694). However, it was very close to the rate of ciPF in patients with significant (>2 cm) perianastomotic and/or peripancreatic loculated fluid collections in transabdominal US examination (38% for significant fluid collections, 42% for minor findings). It is well-known that, loculated abdominal fluid collection adjacent to an anastomosis is generally a sign of leakage from that anastomosis for PJ, HJ, or gastrojejunostomy [2]. However, there is very limited available data about postoperative abdominal fluid collections far from the pancreatic and anastomotic areas, and pleural effusions. The most valuable data about distant collections were reported by Hashimoto et al. [7] in a study concerning CT examinations. According to results of this study, the rate of distant abdominal fluid collections was 80%, including concomitant significant collections around the surgical side. In the same study, no significant difference in the rate of diagnosis of POPF was present between the patients with and without distant fluid collections.

The current study is retrospective in design, which makes it impossible to standardize the parameters, radiologists, and patient selection. This is the main limitation of the study. However, the radiologists were not aware of the risk for POPF in each patient. Additionally, the number of patients was limited, which made it difficult to perform more detailed statistical analysis. In this study, the accepted definition of POPF included the presence of amylase-rich fluid on or after POD 3. According to the study design, this definition can brings to mind the question: "In this study, was the US performed on some patients with abdominal drainage of amylase rich fluid?" The answer is "No." Patients who had a definitive diagnosis of POPF before the first US examination were excluded. Additionaly, POPF has a long clinical course. Therefore, we do not believe that this is a weakness in our study.

In conclusion, transabdominal US has low sensitivity (28% to 36%) for the early diagnosis of POPF after PD. Nevertheless, it can be used for first-line evaluation in the first week after PD to exclude patients at low risk of POPF, as it has a relatively high specificity (74% to 85%). The specificity of transabdominal US will slightly increase to 85% if there is no leukocytosis or hyperamilasemia in POD 1, or peripancreatic or perianastomotic fluid collections larger than 2 cm in diameter with or without fever.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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