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Prevalence of and Risk Factors for Abdominal Bleeding in Patients with External Duodenal Fistula

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Background: Abdominal bleeding is a severe complication of duodenal fistula, but few studies have focused on this problem. The purpose of the present study was to investigate the prevalence of and risk factors for intra-abdominal bleeding in patients with external duodenal fistula.

Material/Methods: From January 2014 to December 2016, medical records of 97 patients with external duodenal fistula were retrospectively reviewed and analyzed. The prevalence and risk factors for intra-abdominal bleeding were evaluated.

Results: The prevalence of abdominal bleeding in patients with external duodenal fistula was 31.9% (95%CI: 22.5–41.4%). A total of 31 patients had intra-abdominal bleeding. Results revealed that acute kidney failure (OR: 8.462, 95% CI: 1.921–37.28, p=0.005) and retroperitoneal infection (OR: 5.373, 95% CI: 1.504–19.197, p=0.010) were associated with abdominal bleeding.

Conclusions: The prevalence of abdominal bleeding in patients with external duodenal fistula was 31.9%, and acute kidney failure and retroperitoneal infection were found to be risk factors for intra-abdominal bleeding.

MeSH Keywords: Intestinal Fistula • Metrorrhagia • Prevalence • Risk Factors

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Background

External duodenal fistula is a complication of gastric and kidney surgeries, pancreatitis, and inflammatory bowel disease (IBD). The reported overall morbidity and mortality related to duodenal fistula ranged from 38% to 75% and 7% to 40%, respectively [1,2].

A few studies have focused on the intra-abdominal bleeding associated with external duodenal fistula, which found that intra-abdominal bleeding accounted for about 10% of complications [3,4]. The mortality from intra-abdominal bleeding with abdominal infection was approximately 50%, which led to hemorrhagic shock, rectal perforation, and renal injury [5,6]. Duodenal juice is a mixture of gastric and pancreatic juice and bile, and is more corrosive than juices in the small intestine and colon. Furthermore, the duodenum is surrounded by numerous vessels, that, in theory, gives this site the highest risk for bleeding, with enterocutaneous fistula having the worst prognosis [7–9]. The purpose of the present study was to investigate the prevalence of and risk factors for abdominal bleeding in patients with enterocutaneous duodenal fistula.

Material and Methods

Study sesign

This was a retrospective study performed at the Intestinal Fistula Treatment Center, Department of General Surgery, Jinling Hospital, Nanjing, China. From January 2014 to December 2016, patient medical records with external duodenal fistula were reviewed and screened out. All patients were transferred in from other hospitals to treat their duodenal fistula.

Patients in our center with external duodenal fistula were included in the study. The exclusion criteria of the patients were: (1) age <17 years old, (2) patients with iatrogenic abdominal bleeding, and (3) patients without complete clinical data (Figure 1). The prevalence of external duodenal fistula was investigated. According to whether the bleeding occurred after admission, patients were divided into a bleeding group and a non-bleeding group. The risk factors for bleeding were evaluated. The research project protocol was approved by the Ethics Committee of the institution, where the work was performed. All patients provided an informed consent form prior to being included in the study.

Therapeutic principles

After admission, the treatment procedure followed the SOWATS treatment guideline proposed by Visschers RG, et al. [10]. The SOWATS treatment guidelines include: Sepsis control (the method for sepsis control was puncture and drainage or laparotomy); Optimization of the nutritional state, including the total parenteral nutrition during the transitional period and enteral nutrition (EN) used during the stabilization period; Wound care; Anatomy; Timing of deterministic surgery (3–6 months after the hospital admission); and Surgical strategy.

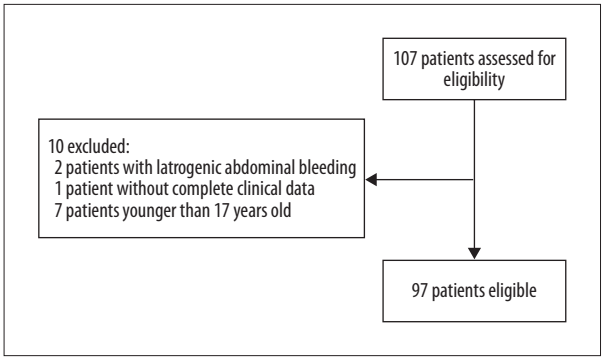

Figure 1. Flow of patient selection.

The treatment was divided into 2 stages. In the first stage, examinations were completed as soon as possible after admission. Intraperitoneal or retroperitoneal infection was diagnosed after CT scans, and puncture and drainage or laparotomies were planned to treat the infections. Enteral nutrition was provided through a nasojejunal tube. The fistula locations were investigated using radiography of the gastrointestinal tract. Surgery was performed during the second stage.

Definitions

The diagnosis of abdominal bleeding was not difficult. Abdominal bleeding caused by duodenal fistula was signaled by a series of clinical manifestations, including massive bleeding from an abdominal drain, tachycardia, and hemodynamic instability. Organ failure was defined as a score of >2 using the Marshall scoring system [11]. According to this scoring system, acute hepatic failure (AHF) was defined as having a total bilirubin >60 μmol/L [11]. Respiratory failure was defined as having a PaO2/FiO2 <200mmHg [11]. Acute kidney failure (AKF) was defined as having a creatinine >200 μmol/L [11] (or if the patient had continuous renal replacement therapy (CRRT), on admission). According to the location of the effusion, exudation, and necrosis, using CT, retroperitoneal or intraperitoneal infection was diagnosed.

Data collection

Data on demographic characteristics (including age, sex, and body mass index [BMI]), imaging examinations, and etiology were collected on admission. The laboratory examination results and the acute physiology and long-term health evaluation (APACHE) II score were recorded within the first 24 h of

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Table 1. Characteristics of the patients between the 2 groups.

Variable	Bleeding group (n=31)	Nonbleeding group (n=66)	p
Age, yeas, mean ±SD	49.63±16.86	45.52±15.59	0.245
Male, n (%)	13 (41.96%)	21 (25.76%)	0.108
BMI, kg/m^2, mean ±SD	22.41± 4.60	22.17± 3.79	0.785
Pulse rate, median (IQR)	95 (82–110)	88 (81–110)	0.226
Temperature, median (IQR)	37.3 (36.6–38.0)	36.7 (36.5–37.1)	**0.004**
Enteral nutrition support#, n (%)	3 (9.68)	9 (13.64)	0.581
Previous bleeding, n (%)	4 (12.90)	5 (8.20)	0.399
Time interval from fistula onset to admission, days, median (IQR)	30 (10–53)	26 (16–44)	0.904
Time interval from admission to bleeding, days, median (IQR)	5 (3–10)	N/A	N/A
APACHE II score	13.29±4.22	8.98±4.16	**<0.001**
Retroperitoneal infection, n (%)	19 (61.29)	11 (16.67)	**<0.001**
Intraperitoneal infection, n (%)	28 (90.32)	62 (93.94)	0.521
Co-morbidities, n (%)			
Hypertensio	5 (16.13)	7 (10.61)	0.441
Diabetes mellitus	3 (9.68)	10 (15.15)	0.541
Chronic nephritis	1 (3.23)	2 (3.03)	0.959
Virus hepatitis	2 (6.45)	3 (4.55)	0.692
AHF, n (%)	9 (29.03)	6 (9.84)	0.029
AKF, n (%)	13 (41.94)	5 (7.58)	**<0.001**
Respiratory failure, n (%)	5 (16.13)	7 (10.61)	0.441

Intestinal nutrient solution was fed through the nasointestinal tube and the speed >20 ml/hour. AHF – acute hepatic failure; AKF – acute kidney failure; APACHE II – acute physiology and chronic health evaluation II; BMI – body mass index.

admission. Respiratory function, kidney function, and hepatic function were evaluated according to the oxygen index, creatinine levels, and total bilirubin levels, respectively.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 20.0 for Windows (IBM Analytics, Armonk, NY). A *t* test and a Mann-Whitney U test were used to compare continuous variables. Fisher's exact test was used to compare categorical variables. To identify the potential risk factors for bleeding, all variables with a value P<0.05 in the univariate analyses were enrolled into a multivariate logistic regression analysis. A P value of <0.05 was regarded as statistical significance.

Results

Population and prevalence of abdominal bleeding

A total of 107 patients with external duodenal fistula were treated at our center. Of the 107 patients, abdominal bleeding occurred in 2 patients due to punctures of the viscera or blood vessels, 1 patient did not have complete clinical data, and 7 patients were younger than 17 years of age.

A total of 97 patients were ultimately included in this study (Figure 1). There were 34 males (35.05%) and 63 females (64.95%). There were 31 patients in the bleeding group and 66 patients in the non-bleeding group. The prevalence of abdominal bleeding overall was 31.9% (95%CI: 22.5–41.4%). The prevalence of abdominal bleeding in patients with

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Table 2. Characteristics of the fistulas between the 2 groups.

Variable	Bleeding group (n=31)		Nonbleeding group (n=66)		p
Anatomy of fistula, n (%)					
Stump	8	(25.81)	20	(30.30)	0.649
Bulb	2	(6.45)	10	(15.15)	0.225
Descending portion	20	(64.52)	34	(51.52)	0.229
Horizontal part of duodenum	1	(3.23)	2	(3.03)	1.000
Etiology, n (%)					
Primary repair	9	(29.03)	24	(36.36)	0.477
Perforated ulcer	2	(6.46)	4	(6.06)	1.000
Trauma	7	(22.58)	20	(30.30)	0.429
Billroth II gastrectomy	8	(25.81)	20	(30.30)	0.649
Perforated ulcer	1	(3.23)	2	(3.30)	1.000
Trauma	1	(3.23)	3	(4.55)	0.761
Gastric cancer	6	(19.35)	15	(22.73)	0.707
Excision of duodenum tumor	1	(3.23)	4	(6.06)	0.556
Biliary tract surgery	4	(12.90)	3	(4.55)	0.205
Acute necrotic pancreatitis	5	(16.13)	9	(13.64)	0.745
Kidney surgery	4	(12.90)	6	(9.09)	0.565
Combined with colonic fistula, n (%)	11	(35.48)	17	(25.76)	0.303
Combined with intestinal fistula, n (%)	3	(9.68)	8	(12.12)	0.723

intraperitoneal fistula (stump or bulb fistula, n=40) was 25.0% (95%CI: 11.0–39.0%). The prevalence of abdominal bleeding in patients with extraperitoneal fistula (descending portion or horizontal part of the fistula, n=57) was 36.8% (95%CI: 23.9–49.8%) and there was no significant difference in prevalence of abdominal bleeding between the 2 types (intraperitoneal fistula and extraperitoneal fistula; p=0.218)

Assessment of organ function

A total of 18 cases were diagnosed as AKF, 13 in the bleeding group (2 cases with CRRT on admission and 11 cases with creatinine >200 μmol/L) and 5 in the non-bleeding group (all the 5 with creatinine >200 μmol/L; 41.94% *vs.* 7.58%, p<0.001). Once admitted, 15 cases had AHF: 9 in the bleeding group and 6 in the non-bleeding group (29.03% *vs.* 9.84%, p=0.029). No obvious difference in the incidence of respiratory failure were found between the 2 groups (16.13% (n=5) *vs.* 10.61% (n=7), p=0.441).

Risk factors for abdominal bleeding in patients with duodenal fistula

The characteristics of patients (general health condition and assessment of organ damage in patients at the time of admission) and the fistulas (locations and the etiologies of duodenal fistula) between the 2 groups are shown in Tables 1 and 2. The results of routine blood and biochemical tests and inflammatory index examinations are shown in Table 3. Characteristics of the 97 were significantly different patients between the bleeding group and the non-bleeding group in 8 aspects: body temperature of patients on admission, APACHE II score, retroperitoneal infection incidence, C reactive protein (CRP), platelets (PT), albumin (ALB), and incidence of AHF and AKF. Multi-logistic regression analysis was used to identify the risk factors for intra-abdominal bleeding shown in Table 4. We found that that AKF (OR: 8.462, 95% CI: 1.921–37.28, P=0.005) and retroperitoneal infection (OR: 5.373, 95% CI: 1.504–19.197, P=0.010) were the independent risk factors for abdominal bleeding.

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Table 3. Results of laboratory examination.

Variable	Bleeding group (n=31)	Nonbleeding group (n=66)	p
WBC, (10^9 cells/L), median (IQR)	10.80 (7.20–12.80)	9.20 (5.90–12.70)	0.477
CRP, mg/L, median (IQR)	128.10 (43.50–170.00)	31.50 (7.98–87.63)	<0.001
PLT, (10^9 cells/L), mean ±SD	200.23±68.05	237.12±97.87	0.061
PT, s, mean ±SD	13.93±1.40	13.23±1.23	0.015
APTT, s, mean ±SD	35.10±6.95	33.87±8.03	0.47
ALB, g/L, mean ±SD	30.41±5.16	33.19±6.18	0.032
ALT, U/L, median (IQR)	27.00 (21.00–50.00)	31.00 (22.00–55.00)	0.787
ALP, U/L, median (IQR)	94.00 (74.00–155.00)	115.60 (84.00–163.50)	0.181
AST, U/L, median (IQR)	30.00 (20.00–50.00)	30.00 (20.00–50.00)	0.798
TB, μmol/L, mean ±SD	56.86±65.34	25.57±28.59	0.015
CR, μmol/L, mean ±SD	131.69± 95.79	58.56±24.54	<0.001

ALB – albumin; ALT – alanine aminotransferase; ALP – alkaline phosphatase; APTT – activated partial thromboplastin time; AST – aspertate aminotransferase; CR – creatinine; CRP – C-reactive protein; PLT – bloodplatelet; PT – prothrombin time; TB – total bilirubin; WBC – white blood cell.

Table 4. Logistic regression of risk factors for intra-abdominal bleeding.

Variable	OR	CI	p
Temperature	1.220	0.487–3.056	0.671
APECHE II score	1.021	0.863–1.208	0.806
Retroperitoneal infection	5.373	1.504–19.197	0.010
CRP	1.007	0.996–1.017	0.159
PT	1.154	0.665–2.040	0.622
ALB	0.946	0.828–1.0582	0.421
AKI	8.462	1.921–37.28	0.005
AHI	2.172	0.464–10.171	0.325

AKI – acute kidney injury; AHI – acute hepatic injury; ALB – albumin; APECHE II – acute physiology and chronic health evaluation; CRP – C-reactive protein; PT – prothrombin time.

Definitive surgeries and prognoses

A total of 14 patients died during the treatments, and all died before definitive surgeries were performed. The mortality rate of the bleeding group was 38.71% (n=12), which was higher than that in the non-bleeding group (3.03%, n=2, p<0.001).

Two patients in the bleeding group and 21 patients in the non-bleeding group achieved spontaneous closure of the duodenal fistula (p=0.005). The surgical procedures for the duodenal fistula included the primary repair of duodenal fistula for most locations expect for the bulb fistula, for which a Billroth II gastrectomy was performed. The length of hospital stay (LOS) of survivors in the bleeding group was 110 (72–176) days, which was longer than it in the non-bleeding group (85 (62–114) days, p=0.045).

Discussion

Duodenal fistula is a complication of gastric resections or surgeries of the biliary tract, duodenum, pancreas, and kidney [4], which account for 3–14% of all enterocutaneous fistulas [1]. Little research has focused on the intra-abdominal bleeding in duodenal fistula cases. However, intra-abdominal bleeding in patients with enterocutaneous fistula and acute pancreatitis was a fatal complication, with mortality rates as high as 46% and 50%, respectively [5,9]. Duodenal juice is more corrosive than fluid in the small intestinal and colon, and most of the fistulas had an output of over 1000 ml/day. Additionally, the duodenum has more vessels compared with the small intestine and colon. The incidence of bleeding seemed to be higher in duodenal fistulas than in small intestinal and colonic fistulas [6–8,12], and the prognosis was poorer. As a result, the bleeding caused by duodenal fistulas should be taken seriously. Therefore, our present research is of great significance.

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In the present study, 97 patients with external duodenal fistula were included, and the prevalence of bleeding was 31.9%, which was much higher than those published in other articles. In addition, there was no significant difference in prevalence of abdominal bleeding between the intraperitoneal fistulas and extraperitoneal fistulas; (25% *vs.* 36.8%; p=0.218). However, in the present study, the incidence of retroperitoneal infection in the bleeding group was higher than that in the non-bleeding group (61.29% *vs.* 16.67%; p<0.001). The location of the fistula might not have contributed to the abdominal bleeding and retroperitoneal infection, and more attention should be paid to retroperitoneal infection. The relationship between retroperitoneal infection and the abdominal bleeding prevalence could be the subject of future study.

The AKF and the retroperitoneal infections were the 2 risk factors for the intra-abdominal bleeding in duodenal fistulas. AKF was a common complication of sepsis [13]. In the treatment of AKF caused by sepsis, the timing of CRRT was not clear [14,15], and little research has concentrated on the correlation between creatinine and coagulation function. More studies about hyper-creatinine and bleeding are needed, and arbitrary conclusions should not be made. However, the controversy over the increased risk for bleeding in CRRT and the recent studies focusing on the relationship between renal failure and platelet function would make sense.

Hemodialysis can partially decrease creatinine level and improve acid-base balance, which is indispensable for patients with AKF. However, the heparin used in CRRT could reduce coagulation function, and although citrate can reduce bleeding incidences better than heparin, serum calcium was decreased even further, making bleeding risks still higher in patients needing CRRT compared with patients that do not require CRRT. In addition, some studies on platelet function even suggested that platelet dysfunction, the multifactorial defect of interaction between vessel walls and circulating cells in kidney disease, was able to increase the risk of bleeding [16,17], while the detailed pathophysiological process is complex and it is not completely understood [18]. Moreover, hemodialysis can even contribute to bleeding by the continuously activating platelets, which led to a reduction in platelet numbers and cytokine activation [18–21]. In summary, patients with AKF have a higher risk of bleeding.

Most of the duodenum lies in the retroperitoneum. As a result, the retroperitoneal infections are likely a manifestation of poor infection control, meaning that a large amount of duodenal fluid cannot drain adequately. Since many retroperitoneal vessels surround the duodenum, duodenal fluid that does not drain properly can harm and destroy the vascular tissues. This retention of fluid is responsible for the formation of pseudoaneurysms, vascular and intestinal erosions, and consequent hemorrhages, and may be similar to the abdominal bleeding seen in patients with necrotizing pancreatitis [22]. Therefore, there is a higher risk of bleeding in patients with retroperitoneal infection.

The present study has certain limitations. First, as the study was retrospective, selection bias exists. Second, hepatic failure could have contributed to the coagulation dysfunction and related bleeding. The criteria for AHF was defined as patients with a score of >2 using the Marshall scoring system, or in other words, as patients with a total bilirubin >60 μm/L. However, in patients with duodenal fistula, intestinal fluid loss and intestinal function damage due to poor control of infections has made support of successful enteral nutrition (EN) implementation a difficult task [23]. Lack of EN for extended time periods and the use of somatostatin lead to hyperbilirubinemia [24,25], which can be relieved after EN support [24,25]. In the present study, there were only 12 patients with EN support at the time of admission. The hyperbilirubinemia probably was related to failed EN support and use of somatostatin. Under these circumstances there may be some deviations in the diagnosis of liver failure according to the Marshall score (cutoff point=60 μm/L). Duodenal fistula combined with bleeding was relatively rare and to the best of our knowledge this study is the first to investigate the risk factors for bleeding in this population. We found that AKF and retroperitoneal infections are predictors of intra-abdominal bleeding.

Conclusions

In the present study, the prevalence of abdominal bleeding in patients with external duodenal fistula was 31.9%. AKF and retroperitoneal infection were revealed to be 2 risk factors for intra- abdominal bleeding in cases of duodenal fistula.

Conflict of interest

None.

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