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Risk factor and outcome for intra-abdominal bleeding in patients with enterocutaneous fistula

Lei Wu, MD[a], Jianan Ren, MD, FACS[a,*], Qinjie Liu, MD[b], Gefei Wang, MD[a], Xiuwen Wu, MD[a], Guosheng Gu, MD[a], Guanwei Li, MD[a], Kun Guo, MD[a], Zhiwu Hong, MD[a], Qiongyuan Hu, MD[c], Huajian Ren, MD[a], Jieshou Li, MD[a]

Abstract

Intra-abdominal bleeding is a major and lethal complication in patients with enterocutaneous fistula (ECF) while few studies are involved in this aspect. In the present study, we aimed to investigate the risk factors and assessed the outcome for intra-abdominal bleeding in patients with ECF.

A retrospective study was performed from October 2013 to October 2015. Medical records of 67 ECF patients with intra-abdominal bleeding and 134 ECF patients without intra-abdominal bleeding matched as controls were reviewed and analyzed. Logistic regression was performed to evaluate the risk factor of intra-abdominal bleeding in patients with ECF. Outcomes such as mortality, hospital durations, and cost were compared between ECF patients with or without intra-abdominal bleeding.

A total of 67 ECF patients suffered intra-abdominal bleeding during hospitalization. In the logistic regression, duodenum fistula (odds ratio [OR]: 3.899, 95% confidence interval [CI]: 1.204–12.634, $P=0.023$), hemorrhage history (OR: 15.846 95% CI: 5.779–43.448, $P<0.001$), and acute kidney injury (OR: 6.350 95% CI: 2.033–19.836, $P=0.001$) were independent risk factors for intra-abdominal bleeding in patients with ECF. In addition, the bleeding patients showed a significantly higher mortality rate, prolonged total parenteral nutrition days, hospital and intensive care unit durations, more complications, and increased cost.

We revealed the 3 risk factors for intra-abdominal bleeding among ECF patients. Besides, intra-abdominal hemorrhage was associated with a poor prognosis in patients with ECF.

Abbreviations: AKI = acute kidney injury, ALI = acute liver injury, APACHE II = acute physiology and chronic health evaluation II, CRRT = continuous renal replacement therapy, ECF = enterocutaneous fistula, ICU = intensive care unit, TPN = total parenteral nutrition.

Keywords: enterocutaneous fistula, intra-abdominal bleeding, outcome, risk factors

1. Introduction

Enterocutaneous fistula (ECF) is an abnormal communication between small or large intestine and skin, which allows the contents of the stomach or intestine to leak through an opening on the skin. Most ECF occur after surgical procedures. Other causes include trauma, inflammatory bowel diseases, and others.[1–4] Although the morbidity of ECF is low, the mortality is comparatively high, and the managements are extremely difficult.[5] In last century, Edmunds et al[4] had reported that the global mortality rate for fistula was up to 43.3%. With the improvement in the aspects of sepsis control, metabolic, surgical, and medical care, the mortality rate has decreased to 5–25% in recent years,[6–9] even though it is still a big challenge for surgeons all around the world, which always makes them frustrated when dealing with it.

Complications account for the mortality and the complexity of ECF patients. Edmunds et al[4] identified the classic triad of complications of ECF as sepsis, malnutrition, and fluid or electrolyte abnormalities. Early correction of fluid and electrolyte abnormalities and the provision of nutrition have been realized by surgeons in minimizing or avoiding these complications altogether, while, in a few patients with ECF, intra-abdominal bleeding can be difficult to deal with and can easily aggravate the disease, leading to a death.

However, compared to malnutrition, sepsis, and other complications, few literatures paid attention to intra-abdominal bleeding in ECF patients.[10] Some literatures mentioned bleeding in the context of arterioenteric fistula or ilioenteric fistula.[11,12] There was rarely literature discussing the rate, the etiology, the risk factors, and the prognosis of intra-abdominal bleeding in ECF patients, leaving less experience to deal with this sort of patients and making early preventive interventions a tough problem.

The purpose of the present study was to investigate the potential risk factors for intra-abdominal bleeding in patients with ECF and to assess the prognosis of the ECF patients with intra-abdominal bleeding.

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[a] Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, [b] Department of General Surgery, Jinling Hospital, Nanjing Medical University, [c] Medical School of Southeast University, Nanjing, China.

[*] Correspondence: Jianan Ren, Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, 305 East Zhongshan Road, Nanjing 210002, Jiangsu Province, China (e-mail: JiananR@gmail.com)

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2. Methods

2.1. Patients and definitions

This was a retrospective study performed at Jinling Hospital, Medical School of Nanjing University. Patients diagnosed with ECF who admitted to the Department of General Surgery of Jinling Hospital during the study period between October 2013 and October 2015 were screened for potential recruitment. Inclusion criteria were ECF patients aged 18 to 75 years, who were first time admitted to our hospital. Those patients were excluded who were in pregnancy, with hematologic system diseases, bleeding at admission, died or discharged less than 48 hours after admission. For patients who were admitted more than once, only the first admission was evaluated. To identify any potential factors that may predispose the ECF patients to suffer hemorrhage and to avoid overmatching, we selected randomly the controls from the patients according to the following factors: same hospital, same time period, with the diagnosis of ECF, and without an intra-abdominal bleeding. One hundred and thirty-four ECF patients met the criteria and were matched as a control, with a ratio of 2:1. The study was approved by the institutional review board of Jinling Hospital.

2.2. Standard of therapy

As a national treatment center for fistulas, all patients with ECF admitted to our hospital were first treated according to the following procedures: primarily assessed by an attending doctor; receiving antibiotics to control sepsis and somatostatin to suppress secretion of digestive juice; undergoing fistulography, and sump drainage was placed to control sepsis and promote the formation of fistulous tract; supported by total parenteral nutrition (TPN) to ameliorate nutrition condition; treated for complications such as sepsis, malnutrition, and fluid or electrolyte abnormalities. Thereafter, there would be a reassessment of the patients when they were in a medically stable condition. Most of them would be transferred to an affiliated hospital of Jinling hospital for nutrition support and physical exercise for about 3 months, preparing for the surgery if spontaneous closure of ECF assisted by fibrin glue was not achieved.[13] A few patients would receive a surgery immediately if needed when they were first admitted to our hospital. This procedure followed the SOWATS treatment guideline[14] and was in accordance with treatment approach advocated in earlier reports.[15–17]

2.3. Data collection

After admission, the demographic characteristics (including age, gender, height, weight, acute physiology and chronic health evaluation II [APACHE II] score, etiology, etc.) of each patient were collected and recorded. The location and complexity of fistula were evaluated by fistulography. Within the first 24 hours after admission, patients were given routine blood tests and biochemical tests. Besides, the information of dealing procedures for the bleeding was evaluated. Outcome assessments included mortality, intensive care unit (ICU) and hospital durations, TPN days, incidence of septic shock, mechanical ventilation and continuous renal replacement therapy (CRRT), and whether patients had spontaneous cure treatment or surgery during the first admission.

2.4. Statistical analysis

The statistical analysis was performed using SPSS 20.0 statistical software (IBM Analytics, Armonk, NY). Categorical data are presented as numbers and percentages. Continuous data are presented as mean ± standard deviation. Student t test was used for analyzing continuous variables, whereas the χ^2 test was used for analyzing 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. The method of enter was used in the multivariate analysis. Statistical significance was considered as $P < 0.05$ (2-tailed).

3. Results

3.1. Baseline characteristics

A total of 634 patients were primarily admitted to the hospital with the diagnosis of ECF. Among these patients, 67 suffered the intra-abdominal bleeding event during hospitalization, with the incidence of intra-abdominal bleeding 10.6%. One hundred and thirty-four who did not suffer intra-abdominal bleeding events were selected randomly and matched as a control in the ratio of 2:1. The baseline characteristics of ECF patients with or without intra-abdominal bleeding were displayed in Table 1. Comparing these 2 groups, there were no significant differences in age, body mass index, etiology, and basic diseases (such as heart disease, hypertension, or diabetes) ($P > 0.05$). Although patients in the

Table 1

Baseline characteristics of the enterocutaneous fistula patients with/without intra-abdominal bleeding.

Variable	Bleeding group (n = 67)	Nonbleeding group (n = 134)	P
Age, y	50.3 ± 15.4	48.0 ± 16.7	0.11
Sex, male, %	58 (86.6)	94 (71.6)	0.034
BMI, kg/m^2	20.7 ± 3.4	20.4 ± 3.7	0.747
Time interval from fistula onset to admission, d	32.2 ± 41.4	78.0 ± 134.6	<0.01
Anatomy of fistula, no., %			
Stomach	5 (7.5)	6 (4.5)	0.38
Duodenum	22 (32.8)	24 (17.9)	0.018
Small intestine	31 (46.3)	72 (53.7)	0.318
Large intestine	9 (13.4)	32 (23.9)	0.083
Number of fistula, no., %			0.01
Single fistula	46 (68.7)	118 (81.3)	
Multiple fistula	21 (31.3)	16 (11.9)	
Primary disease, no., %			
Trauma	25 (37.3)	29 (21.6)	0.018
Postoperative of benign abdominal disease	22 (32.8)	65 (48.5)	0.035
Malignancy	17 (25.4)	34 (25.4)	1
IBD	3 (4.5)	6 (4.5)	1
Hemorrhage history			
Before admission, no., %	51 (76.1)	25 (18.7)	<0.01
Abdominal infection	55 (82.5)	88 (65.7)	0.015
APECHE II score	10.2 ± 6.0	5.8 ± 5.1	0.094
MAP. MMHG	85.6 ± 13.5	87.0 ± 11.6	0.098
AKI, no., %	47 (70.1)	31 (23.1)	<0.01
ALI, no., %	36 (53.7)	20 (14.9)	<0.01
Co-morbidities, no, %			
Heart-disease	1 (1.5)	4 (3.0)	0.522
Hypertension	10 (14.9)	18 (13.4)	0.773
Diabetes mellitus	5 (7.5)	6 (4.5)	0.38

AKI = acute kidney injury, ALI = acute liver injury, APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, IBD = inflammatory bowel disease, MAP = mean arterial pressure.

Table 2

Laboratory examinations at admission.

Variable	Bleeding group (n = 67)	Nonbleeding group (n = 134)	P
WBC, $\times 10^9$ cells/L	14.0 ± 18.0	8.9 ± 6.0	0.11
CRP, mg/L	100.0 ± 66.3	51.2 ± 56.2	0.036
PCT, μg/L	5.5 ± 10.9	1.4 ± 4.3	<0.01
HB, g/L	88.3 ± 19.2	103.7 ± 21.4	0.297
ALB, g/L	27.9 ± 6.4	33.3 ± 6.6	0.578
RBC, $\times 10^9$ cells/L	4.1 ± 10.0	4.9 ± 16.3	0.855
PLT, $\times 10^9$ cells/L	202.0 ± 141.7	281.8 ± 116.2	0.772
PT, s	15.5 ± 4.0	13.2 ± 2.8	0.051
INR, s	1.3 ± 0.3	1.1 ± 0.2	0.138
TB, mmol/L	70.5 ± 71.5	27.5 ± 38.2	<0.01
ALT, U/L	44.9 ± 54.8	33.3 ± 25.4	0.112
AST, U/L	47.4 ± 54.8	24.8 ± 18.4	0.05
CR, mmol/L	97.0 ± 80.1	65.6 ± 56.8	<0.01
BUN, mmol/L	11.9 ± 9.7	6.7 ± 7.4	0.03

ALB = albumin, ALT = alanine aminotransferase, AST = aspertate aminotransferase, BUN = blood urea nitrogen, CR = creatinine, CRP = C-reactive protein, HB = hemoglobin, INR = international normalized ratio, PCT = procalcitonin, PLT = blood platelet, PT = prothrombin time, RBC = red blood cell, TB = total bilirubin, WBC = white blood cell.

Table 3

Logistic regression of risk factors for intra-abdominal bleeding in patients with enterocutaneous fistula.

Variable	OR	95% CI	P
Sex	0.909	0.282–2.937	0.874
Time interval from fistula onset to admission	0.997	0.989–1.004	0.389
Duodenum fistula	3.899	1.204–12.634	0.023
Trauma	0.750	0.205–2.747	0.664
Postoperative of benign abdominal disease	0.367	0.108–1.241	0.107
Multiple fistula	2.326	0.707–7.649	0.165
Hemorrhage history before admission	15.846	5.779–43.448	<0.001
Abdominal infection	0.524	0.165–1.669	0.274
AKI	6.350	2.033–19.836	0.001
ALI	2.001	0.495–8.087	0.330
CRP	1.006	0.997–1.014	0.192
PCT	1.012	0.942–1.086	0.751
TB	1.001	0.992–1.010	0.815
CR	1.005	0.994–1.017	0.340
BUN	0.942	0.858–1.035	0.216

AKI = acute kidney injury, ALI = acute liver injury, BUN = blood urea nitrogen, CR = creatinine, CRP = C-reactive protein, PCT = procalcitonin, TB = total bilirubin, WBC = white blood cell.

bleeding group had higher APACHE II scores and levels of mean arterial pressure, they did not show a significant difference ($P > 0.05$). The days from diagnosis of fistula to transfer into this hospital in the bleeding group were significantly shorter than in the control group ($P < 0.01$). Besides, significant differences were found between 2 groups regarding the location of duodenum ($P = 0.018$), more complexity in the number of fistula ($P = 0.01$), a male predominance ($P = 0.034$), a hemorrhage history within 2 weeks before admission ($P < 0.01$), and intra-abdominal infection ($P = 0.015$). Patients with intra-abdominal hemorrhage had a significant worse kidney function and liver function when admitted to this hospital, with acute kidney injury (AKI) ($P < 0.01$) and acute liver injury (ALI) ($P < 0.01$).

The comparison of routine blood tests and biochemical tests during the first 24 hours of admission was shown in Table 2. The patients who suffered intra-abdominal hemorrhage during hospitalization appeared significantly higher in white blood cell, C-reactive protein, procalcitonin, total bilirubin, aspertate aminotransferase, creatinine, and blood urea nitrogen.

3.2. Risk factors predicting intra-abdominal bleeding in ECF patients

To identify the potential risk factors for intra-abdominal bleeding of the ECF patients, we took a logistic regression analysis (Table 3). It revealed that duodenum fistula (OR: 3.899, 95% CI: 1.204–12.634, $P = 0.023$), hemorrhage history before admission to this hospital (OR: 15.846, 95% CI: 5.779–43.448, $P < 0.001$), and AKI (OR: 6.350, 95% CI: 2.033–19.836, $P = 0.001$) were 3 independent risk factors of bleeding in ECF patients.

3.3. Clinical feature and management of intra-abdominal bleeding in ECF patients

Owing to the complexity of bleeding in ECF patients, it could be difficult to define the precise bleeding source sometimes. The most common site of bleeding occurred in external drainage catheters, among which single drainage tube and sump drainage each accounted for 43% (29) and 36% (24). Bleeding around the fistula orifice and digestive tract accounted for 8% (5) and 13% (9). Table 4 shows initial bleeding sites and the managements of the bleeders, as well as their outcomes. As for managements, conservative treatment was chosen preferentially, which contained a series of measurements, such as abdominal packing, fluid infusion, hemostatic drugs, blood transfusion, and vasoactive drugs. Other 3 managements were adopted separately if the conservative treatment could not work, or the bleeding was swift and violent. Thirty-six (54%) patients with bleeding took conservative treatment, among whom, 31 (86%) patients had bleeding stopped and 5 (14%) patients died of hemorrhagic shock. Other 31 (46%) patients needed a further step to stop the bleeding. A total of 53 (79%) patients successfully stopped bleeding, whereas 31 (46%) patients died. Among them, 14 (21%) patients died of hemorrhagic shock and 16 (24%) died of a secondary septic shock or multiple organ dysfunction syndrome (MODS).

3.4. Prognosis and outcome

Table 5 shows a variety of clinical variables concerning the outcome of ECF patients with/without intra-abdominal bleeding. Three (4.5%) patients received tried fibrin glue, and 1 (1.5%) patient received surgery in the bleeding group. But in the nonbleeding group, 26 (19.4%) patients tried fibrin glue, and 11 (8.2%) patients received definite surgery. During hospitalization, significantly more patients in the bleeding group underwent

Table 4

Management for the intra-abdominal bleeding in enterocutaneous fistula patients.

Bleeding control procedure	n	Bleeding stopped, %	Death, %
Conservative measures	36	31 (86)	13 (35)
DSA + conservative measures	12	6 (50)	8 (66.7)
Endoscopy + conservative measures	4	4 (100)	1 (25)
Operation + conservative measures	15	12 (80)	9 (60)
Total	67	53 (79)	31 (46.3)

DSA = digital subtraction angiography.

Table 5

Clinical course and outcome of enterocutaneous fistula patients with or without bleeding.

Variable	Bleeding group (n = 67)	Nonbleeding group (n = 134)	*P*
Mortality, no., %	31 (46.3)	10 (7.5)	<0.01
Hospital duration, d	30.7 ± 27.3	24.3 ± 17.6	0.022
ICU duration, d	14.1 ± 16.2	2.4 ± 4.7	<0.01
TPN, duration, d	21.7 ± 14.7	15.0 ± 11.3	0.05
Treatment with glue, no., %	3 (4.5)	26 (19.4)	0.05
Operation, no., %	1 (1.5)	11 (8.2)	0.058
Mechanical ventilation, no., %	32 (47.8)	9 (6.7)	<0.01
CRRT, no., %	12 (17.9)	4 (3)	<0.01
Septic shock, no., %	18 (26.9)	9 (6.7)	<0.01
MODS, no., %	7 (10.4)	4 (3)	0.028
Cost, thousand CNY	300.6 ± 200.4	153.6 ± 107.6	<0.01

CRRT = continuous renal replacement therapy, ICU = intensive care unit, MODS = multiple organ dysfunction syndrome, TPN = total parenteral nutrition.

mechanical ventilation (32, 47.8%), CRRT (12, 17.9%), MODS (7, 10.4%), and septic shock (18, 26.9%). The mortality was markedly lower in the nonbleeding group (31/67 [46.3%] vs 10/134 [7.5%], $P < 0.01$). Besides, compared with the nonbleeders, the bleeders had prolonged ICU and hospital durations, TPN days as well as the cost, which indicated a worse outcome.

4. Discussion

Intra-abdominal bleeding is a lethal complication of ECF. The death rate of intra-abdominal bleeding among patients with ECF was 46% in this study, which was comparatively high. However, there was little literature concerning the bleeding in ECF patients. Because ECF was an infrequent disease, there were comparative insufficient studies related. Most of the literatures paid their attention to the experience or the factors that affected the healing and mortality of ECF.[14,18,19] Some other literatures involving bleeding were about aorto-enteric fistula or cholecysto-duodenal fistula.[20,21] There was no literature investigating intra-abdominal bleeding in ECF patients directly. To our knowledge, this was so far the first study that investigated intra-abdominal bleeding in ECF patients, which included the risk factors, managements, and outcome.

In the present study, we respectively collected 201 patients with ECF. Comparing the basic characteristics and laboratory examinations, the bleeder held the following significant differences: more bleeders were man, time interval from fistula onset to admission was shorter, more bleeders were duodenum fistula and multiple fistulas, more patients had an etiology of trauma while less of postoperation of benign abdominal disease, more bleeders had a hemorrhage history, abdominal infection, AKI, ALI, and others. These consequences were consistent with our clinic experience. Logistic regression analysis evaluating the risk factors for intra-abdominal bleeding in patients with ECF demonstrated that duodenum fistula, hemorrhage history, and AKI were 3 independent influencing factors.

Duodenum juice is a mixture of gastric juice, bile, pancreatic juice, which is more corrosive than small or big intestinal fluid. Besides, there were more vessels located around duodenum, such as gastroduodenal artery, cystic artery, superior mesenteric artery, and others. It was easy for duodenum fluid to corrode these vessels or tissue around it and caused a bleeding, which had been mentioned in some case reports.[20,22,23] A hemorrhage history meant that the patient had experienced a loss of blood and had a high possibility of receiving excessive fluid resuscitation and component blood transfusion, which would cause a loss or a dilution of blood coagulation factor, leaving this sort of patient with a potential coagulation disorder.[24,25] When exposed to corrosive intestinal juice, the vessels ever damaged or not were easier to bleed again. So, the improvement of coagulation function in this sort of patient would prevent hemorrhage in a certain degree, which included the early use of cryoprecipitation for fibrinogen and thrombin.[26]

AKI was a frequent and serious complication of sepsis and was associated with mortality rates up to 50–60%, depending on severity.[27,28] As sepsis was a frequent complication of patient with ECF, there would be a large portion of ECF patients accompanied with AKI. These had been studied that clinical bleeding was a major manifestation of renal failure in the predialysis era.[28] The mechanism of bleeding in uremic condition was not clear yet.[27] Multifactorial defect of the interaction between vessel walls and circulating cells seemed to be one of the most popular theories.[29,30] Besides, there were studies that proved AKI was an independent risk factor for massive bleeding in Infected Necrotizing Pancreatitis.[31] Also, comparison of the patients with and without hemorrhage showed that the bleeder held a significant higher value of creatine and urea nitrogen, the indicators for renal function. From this aspect, sepsis control, as a way to improve renal function, might help prevent bleeding in ECF patients.

Dealing with intra-abdominal bleeding can be always a big challenge, especially in patients with ECF. In this study, although 53 (79%) patients stopped hemorrhage, 31 (46.3%) patients died eventually, of which more than half (17, 25.4%) died of a secondary septic shock or MODS. Because of a poor physiological status, which was a result of sepsis, malnutrition, and fluid or electrolyte abnormalities or hemorrhage, surgery should be the last choice for the management of bleeding. Although resort to surgery, the concept of damage control surgery should also be kept in mind for the reason that long and traumatic surgery would be a disaster for the intra-abdominal bleeding patients with ECF.[32] According to the concept of damage control resuscitation, permissive hypotension would be beneficial. Full blood would be good at improving the coagulation disorder. Combining high-dose fresh frozen plasma, cryoprecipitate, and platelet therapy with a high total fibrinogen load appeared to produce a consistent improvement in coagulation.

We admitted that there were some limitations in this study. First, due to the retrospective nature of this study, there existed some selection bias for the study. Second, this study was performed at a single tertiary-care medical center. Therefore, it had been a long time from the fistula onset to transformed to this hospital. So, it might complicate the results. Besides, an important data that the fistula output was not calculated in this study, because of the use of somatostatin once the patient admitted to the hospital, which could suppress the secret of intestinal juice. Lastly, the number of the bleeders was relatively small, and the control group did contain all the nonbleeder of the same time, which might affect the precision of the results. However, we thought that it would still leave hemorrhage history before admission and AKI as valuable tools for predicting intra-abdominal bleeding.

In conclusion, we found that duodenum fistula, history of hemorrhage, and AKI were 3 independent risk factors for intra-abdominal bleeding in patients with ECF. In addition, ECF patients with intra-abdominal hemorrhage were always associated with a poor prognosis, which had a higher mortality, organ

dysfunction, hospital stay, and costs. Further studies with a larger population would be needed to investigate the intra-abdominal bleeding risk and management in patients with ECF.

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