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Incidence and risk factors for incisional surgical site infection in patients with Crohn's disease undergoing bowel resection

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Abstract

Background: Patients with Crohn's disease (CD) are often reported to be at a high risk for incisional surgical site infection (SSI). The aim of this study was to identify the risk factors associated with post-operative incisional SSI in CD patients after bowel resection.

Method: CD patients undergoing bowel resection between 2007 and 2015 were enrolled. Demographic and clinical features related to post-operative incisional SSI were analysed using both univariate and multivariate logistical analyses.

Results: Of all eligible patients ($n = 159$), 123 (77.4%) were male, with a mean age at surgery of 33.4 ± 11.8 years. A total of 35 (22.0%) CD patients developed post-operative incisional SSI. Post-operative incisional SSI was more likely to happen in patients who had penetrating type of disease ($P = 0.018$), underwent bowel resection for the indication of chronic fistula ($P = 0.005$) and had an intra-operative finding of fistula ($P = 0.001$). A greater proportion of patients with post-operative incisional SSI were found to have anemia ($P = 0.019$) but elevated levels of white blood cells ($P = 0.027$), neutrophils ($P = 0.006$) as well as an elevated percentage of neutrophils ($P = 0.005$). Multivariate logistic regression analysis showed that anemia (odds ratio [OR]: 3.31, 95% confidence interval [CI]: 1.05–10.46, $P = 0.041$), an elevated percentage of neutrophils (OR: 2.85, 95% CI: 1.23–6.59, $P = 0.014$) and an intra-operative finding of fistula (OR: 3.76, 95% CI: 1.53–9.21, $P = 0.004$) were significantly associated with the risk for post-operative incisional SSI.

Conclusions: Anemia, elevated percentage of neutrophils and intra-operative finding of fistula are predictors for the development of post-operative incisional SSI in CD patients undergoing bowel resection. Favorable pre-operative nutrition status and low inflammatory status may lessen the incidence of post-operative incisional SSI.

Key words: Crohn's disease; incisional surgical site infection; risk factors; bowel resection

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Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the intestines, most commonly involving the ileocecal region. Despite the advancement in medical management, such as 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators and biologics, up to 70% of CD patients will eventually require surgery for refractory disease or its complications [1–3]. Further, the presence of inflammation, abscesses, friable tissue and impaired healing make surgery more challenging in patients with CD [4].

Surgical site infection (SSI) was defined as superficial skin and deep soft-tissue infection, intra-abdominal abscess, anastomotic leak and mucocutaneous separation of the stoma [5]. According to the Centers for Disease Control and Prevention's (CDC) classification, SSI mainly consisted of incisional and organ/space SSI. A previous study demonstrated that the mechanisms as well as risk factors for incisional and organ/space SSI are different [6]. The frequency of incisional SSI in CD patients undergoing intestinal surgery generally has been reported to range somewhere from 3% to 38% in various reports, with a number of risk factors identified [7–12]. Incisional SSI is one of the most common complications following intestinal resection for CD and is associated with increased length of stay, increased cost and a negative impact on quality of life [13–16]. Therefore, identifying risk factors for incisional SSI is of great importance from both economic and epidemiologic perspectives.

Patients undergoing bowel resection for CD symbolize a high-risk cohort for incisional SSI. Potential risk factors, such as malnutrition, chronic immunosuppression, abdominal abscesses or peritonitis, anemia, intestinal obstruction and high incidence of emergent surgery predispose them to incisional SSI [17]. It is generally believed that the accompanying conditions in CD patients, such as poor nutritional status and administration of immunosuppressive agents, are associated with a high incidence of incisional SSI. In addition to impaired host defense, the presence of contaminated or dirty/infected wounds related to CD, such as pre-operative abscesses or peritonitis, also contributes to the likelihood of incisional SSI [18].

In this study, we retrospectively investigated the correlations between common clinicopathological variables and the risk for incisional SSI in CD patients who underwent bowel resection in our institution, to evaluate the diagnosis-specific risk factors for incisional SSI.

Methods

Patients

After Institutional Review Board (IRB) approval, a retrospective analysis was performed with the data from our prospectively accrued CD database. Demographics, clinicopathological variables, surgery-related details and outcomes were all prospectively maintained in the database. Consecutive CD patients between 2007 and 2015 who underwent bowel resection at the Department of Colorectal Surgery in the Sixth Affiliated Hospital, Sun Yat-sen University, were included. Both paper charts and electronic medical records were carefully reviewed when necessary.

Inclusion and exclusion criteria

Patients were included if they met the following criteria: (i) diagnosed with Crohn's disease, (ii) underwent bowel resection at our institution and (iii) had a minimum follow-up period of 30 days

after bowel resection. Exclusion from the study included: (i) surgical procedure of enterostomy instead of bowel resection and (2) only had closure of loop ileostomy or colostomy.

Definition of variables

Demographic and clinicopathological variables were defined as the following. The disease type (non-stricturing and non-perforating, stricturing or perforating types) was determined according to the Montreal classification criteria; duration from diagnosis to surgery—the time interval from the date of CD diagnosis to the date of bowel resection; current smoking—patients still using cigarettes prior to bowel resection; ex-smoking—cessation of smoking 6 months prior to bowel resection; history of bowel resection—patients received one or more bowel resection surgeries; significant comorbidities—congestive heart failure, coronary bypass surgery, chronic obstructive pulmonary diseases, renal function insufficiency, non-gastrointestinal cancer, stroke and liver failure; extra-intestinal manifestations—including the presence of arthralgia or arthropathy, pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis (PSC), CD-related ocular lesions, thromboembolic events; autoimmune disorders—adult-onset asthma, type 1 diabetes, rheumatoid arthritis, autoimmune thyroid diseases (including Grave's disease and Hashimoto's thyroiditis), psoriasis, systemic lupus erythematosus, autoimmune hemolytic anemia, vitiligo, celiac disease, pernicious anemia, idiopathic thrombocytopenic purpura and multiple sclerosis; prior use of biologic therapy with infliximab, adalimumab or certolizumab was classified based on timing of last dose: >3 months, between 1 and 3 months, and <1 month; elevated erythrocyte sedimentation rate—erythrocyte sedimentation rate more than 20 mm/h; elevated C-reactive protein—C-reactive protein level higher than 10 mg/L (dry chemical method) or 3 mg/L (hypersensitive method); anemia—hemoglobin less than 120 g/L in blood routine test; elevated white blood cell—white blood cell counts more than $10 \times 10^9/L$ in blood routine test; elevated neutrophils—neutrophil counts more than $7.5 \times 10^9/L$ in blood routine test; elevated percentage of neutrophils—the percentage of neutrophils in white blood cells more than 75% in blood test; low lymphocytes—lymphocyte counts less than $0.8 \times 10^9/L$ in blood routine test; elevated platelets—platelet counts more than $300 \times 10^9/L$ in blood routine test; low albumin—serum albumin level lower than 35 g/L in blood test.

Outcome measurement

Incisional SSIs were diagnosed by physicians according to the definitions provided by the Centers for Disease Control and Prevention (CDC) NNIS system [12]. Incisional SSI is defined as an infection that occurs within 30 days after the operation and involves the skin/subcutaneous tissue and deep soft-tissue infection of the incision. The criteria for diagnosis of incisional SSI include at least one of the following signs or symptoms: redness, heat, pain or tenderness, localized swelling and purulent drainage [19].

Statistical analysis

Descriptive statistics were computed for all variables. These included means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous factors and frequencies for categorical factors. Comparisons of the distribution of clinicopathological characteristics between the patients with or without incisional SSI were made by using the two-tailed t-test

(or Wilcoxon rank sum test as alternative) for continuous variables and chi-square test (or the Fisher exact test as alternative) for categorical variables. Multivariate analyses of risk factors associated with the incisional SSI were constructed using logistic regression analysis. All statistical analyses were performed with the SPSS software (version 16; SPSS, Chicago, IL). *P*-value less than 0.05 was considered statistically significant.

Results

Patient demographics

A total of 159 CD patients undergoing bowel resection between 2007 and 2015 were enrolled, including 35 patients (22.0%) with incisional SSI and 124 (78.0%) without. Of all eligible patients, 123 patients (77.4%) were male and 36 patients (22.6%) were female, with a mean age at CD diagnosis of 31.0 ± 11.9 years old and a median duration from CD diagnosis to bowel resection of 0.6 (0.1–0.9) years. Thirty-eight patients (23.9%) had L1/L2 (ileal/colonic) disease, 119 (74.8%) had L3 (ileocolic) disease and 7 (4.4%) had L4 (upper gastrointestinal) involvement. With respect to disease behavior, 63 (39.6%) patients had B1/B2 (non-stricturing and non-penetrating/stricturing) disease while 94 (59.1%) had B3 (penetrating) disease (Table 1).

Comparison of characteristics between the patients with and without incisional SSI

A higher frequency of patients who developed incisional SSI were found to have penetrating disease (77.1% vs 54.9%, $p=0.018$). Patients with incisional SSI were more likely to have anemia (88.6% vs 68.5%, $p=0.019$), but an elevated white blood cell level (28.6% vs 12.9%, $p=0.027$), an elevated neutrophil level (31.4% vs 12.1%, $p=0.006$) and an elevated percentage of neutrophils (45.7% vs 21.8%, $p=0.005$) (Table 1). As for surgery-related features, more patients with incisional SSI underwent surgery indicated for the presence of chronic fistula (74.3% vs 47.6%, $p=0.005$) and had an intra-operative finding of fistula (77.1% vs 46.8%, $p=0.001$) compared with those without (Table 2). There were no statistically significant differences between patients with/without incisional SSI in other clinicopathological features.

Risk factors for incisional SSI

A multivariate logistic regression model was constructed to identify the risk factors associated with incisional SSI in CD patients who underwent bowel resection, which revealed that anemia (OR: 3.31, 95% CI: 1.05–10.46, $P=0.041$), intra-operative finding of fistula (OR: 3.76, 95% CI: 1.53–9.21, $P=0.004$) and elevated percentage of neutrophils (OR: 2.85, 95% CI: 1.23–6.59, $P=0.014$) were independent risk factors related to the development of post-operative incisional SSI (Table 3).

Discussion

Incisional SSI is defined as surgical site infection limited to the skin and subcutaneous tissues. The incidence of incisional SSI in patients with CD undergoing bowel resection ranges from 11% to 27% in various reports [20–22]. Patients with CD represent a high-risk cohort probably due to their relative immune-compromised and poor nutritional state [17]. Given that post-operative incisional SSI is relatively common in CD patients after bowel resection, which is associated with longer durations of hospitalization, lower levels of patient satisfaction as well as

increased treatment costs, awareness of risk factors for incisional SSI might promote effective preventive strategies [23]. In the current study, the incidence of incisional SSI was 22.0% (35/159), comparable to previous investigations. Anemia, elevated percentage of neutrophils and intra-operative finding of fistula were determined to be significant predictors for post-operative incisional SSI. In a previous study, Kanazawa *et al.* found that an operating time of >180 minutes, penetrating type and handsewn anastomosis were main risk factors for post-operative intra-abdominal septic complications [24]. In addition, other risk factors formerly reported include low albumin levels, weight loss, pre-operative thiopurine therapy, pre-operative steroid use, poor nutritional status and presence of abscesses at the time of surgery [25–27]. Hence, anemia and elevated percentage of neutrophils can be considered as newly verified risk factors for incisional SSI.

Pre-operative anemia has been reported to significantly increase the incidence of post-operative infectious complications and anastomotic complications after ileoanal pouch procedures [28]. A number of studies demonstrated that perioperative blood transfusion caused by anemia was an independent risk factor for post-operative SSI [29–32]. In our study, a greater proportion of patients with post-operative incisional SSI were found to have anemia. Possible explanations are as follows. First, patients with anemia typically require perioperative transfusion. Consequently, the side effects of transfusion-related immunosuppression on SSI could be a confounding factor [32]. Second, anemia can lead to impaired tissue oxygenation, causing reduced collagen synthesis as well as impaired primary defense mechanism of oxidative killing by neutrophils.

Several pieces of research have revealed that a high white blood cell or neutrophil count predicted a high incidence of post-operative infectious complications including SSI [33, 34]. Araki *et al.* showed that a higher pre-operative white blood cell or neutrophil count and a lower pre-operative lymphocyte count were risk factors for SSI [33]. Besides, Moyes *et al.* confirmed that elevated pre-operative white blood cell counts were independently associated with an increased risk of developing post-operative infection, such as incisional SSI [34]. Likewise, we found that patients with high pre-operative neutrophil percentages were more likely to develop post-operative incisional SSI. We hypothesized that high pre-operative neutrophil percentages indicated an intense systemic inflammatory response, leading to the occurrence of incisional SSI.

Yamamoto *et al.* found that intra-abdominal abscess or fistula was associated with an increased risk of SSI [25]. Kanazawa *et al.* confirmed these findings using a larger population [24]. In our study, intra-operative finding of fistula was a significant independent risk factor for post-operative incisional SSI in patients with CD. It is well known that intra-abdominal abscess and fistula could exacerbate the inflammatory status and contaminate the abdominal incision, which would seriously endanger the incision healing. Even though the finding of internal fistula during operation is a frequent situation in patients with CD, our results underlined the need for careful pre-operative assessment.

In univariate analysis, penetrating disease was a risk factor for post-operative incisional SSI, whereas no significant differences were found in multivariate analysis. Since the patients with an intra-operative finding of fistula were almost all penetrating/B3 type of disease, these two features may have an overlapping effect on post-operative incisional SSI. In addition, patients with a history of bowel resection, location of CD as ileocolon/L3 and number of anastomosis ≥ 1 were found to have an

Table 1. Patient characteristics

Characteristic	All cases (N = 159)	Patients without wound infection (N = 124)	Patients with wound infection (N = 35)	P-value
Age at CD diagnosis, year	31.0±11.9	30.8±12.4	31.5±9.8	0.78
Age at surgery, year	33.4±11.8	33.3±12.4	33.6±9.7	0.88
Duration from diagnosis to surgery, year	0.6(0.1–2.9)	0.6(0–2.8)	0.4(0.1–3.1)	0.99
Male gender	123 (77.4)	94 (75.8)	29 (82.9)	0.38
Body mass index, kg/m ²	17.6±2.9	17.5±2.8	18.0±3.2	0.42
Ex or current smoker	5 (3.1)	4 (3.2)	1 (2.9)	1.0
History of any drug allergy	29 (18.2)	23 (18.5)	6 (17.1)	0.85
History of bowel resection	49 (30.8)	34 (27.4)	15 (42.9)	0.081
Significant comorbidity	27 (17.0)	22 (17.7)	5 (14.3)	0.63
History of diagnosis of UC or IC	4 (2.5)	3 (2.4)	1 (2.9)	1.0
Extra-intestinal manifestations	10 (6.3)	6 (4.8)	4 (11.4)	0.23
Location of CD				0.056
L1/L2	38 (23.9)	34 (27.6)	4(11.8)	
L3	119 (74.8)	89 (72.4)	30 (88.2)	
Upper GI involvement	7 (4.4)	7 (5.7)	0 (0.0)	0.35
Perianal disease	51 (32.1)	42 (33.9)	9 (25.7)	0.36
Disease behavior				0.018
B1/B2	63 (39.6)	55 (45.1)	8(22.9)	
B3	94 (59.1)	67 (54.9)	27 (77.1)	
Pre-operative use of biologics—ever	24 (15.0)	17 (13.7)	7 (20.0)	0.36
Pre-operative use of biologics—3 m	15 (9.4)	10 (8.1)	5 (14.3)	0.32
Pre-operative use of biologics—1 m	9 (5.7)	6 (4.8)	3 (8.6)	0.41
Pre-operative use of immunosuppressants_ever	58 (36.5)	44 (35.5)	14 (40.0)	0.62
Pre-operative use of immunosuppressants—3 m	40 (25.2)	31 (25.0)	9 (25.7)	0.93
Pre-operative use of immunosuppressants—1 m	35 (22.0)	29 (23.4)	6 (17.1)	0.43
Pre-operative use of steroids—ever	48 (30.2)	34 (27.4)	14 (40.0)	0.15
Pre-operative use of steroids—3 m	20 (12.6)	13 (10.5)	7 (20.0)	0.15
Pre-operative use of steroids—1 m	19 (11.9)	12 (9.7)	7 (20.0)	0.14
Pre-operative use of 5-ASA—ever	89 (56.0)	70 (56.5)	19 (54.3)	0.82
Pre-operative use of 5-ASA—3 m	46 (28.9)	37 (29.8)	9 (25.7)	0.64
Pre-operative use of 5-ASA—1 m	37 (23.3)	30 (24.2)	7 (20.0)	0.6
Pre-operative use of antibiotics—ever	35 (22.0)	28 (22.6)	7 (20.0)	0.75
Pre-operative use of antibiotics—3 m	28 (17.6)	23 (18.5)	5 (14.3)	0.56
Pre-operative use of antibiotics—1 m	27 (17.0)	22 (17.7)	5 (14.3)	0.63
Elevated erythrocyte sedimentation rate	91 (57.2)	74 (76.3)	17 (89.5)	0.36
Elevated C-reactive protein	90 (56.6)	73 (71.6)	17 (85.0)	0.21
Anemia	116 (73.0)	85 (68.5)	31 (88.6)	0.019
Elevated white blood cell	26 (16.4)	16 (12.9)	10 (28.6)	0.027
Elevated neutrophils	26 (16.4)	15 (12.1)	11 (31.4)	0.006
Elevated percentage of neutrophils	43 (27.0)	27 (21.8)	16 (45.7)	0.005
Low lymphocytes	35 (22.0)	31 (25.0)	4 (11.4)	0.087
Elevated platelet	63 (39.6)	45 (36.3)	18 (51.4)	0.11
Low albumin	53 (33.3)	38 (32.8)	15 (44.1)	0.22

Data are presented as mean ± standard deviation or number (percentage).

CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis; GI, gastrointestinal; B1, non-stricturing and non-penetrating; B2, stricturing; B3, penetrating; L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper GI. 5-ASA, 5-aminosalicylic acid.

obvious tendency to develop post-operative incisional SSI, although statistically significant differences were not reached ($P = 0.081, 0.056$ and 0.087 , respectively), which slightly differed with the conclusion found by Rutgeerts et al. and Eshuis et al. [35, 36]. This might result from the retrospective design and the relatively small cohort in our study. It still remains controversial for the relationship between emergent surgery and incisional SSI in previous studies [17, 18, 33]. We found that emergent surgery in CD did not influence the post-operative incisional SSI in our study. The small number of patients ($n = 6$) with emergent surgery included in this study might account for this.

The influence of malnutrition as well as immunosuppressive status on the occurrence of post-operative incisional SSI remains controversial at present. Some studies showed that low pre-operative serum albumin, pre-operative administration of steroids as well as immunosuppressive agents, including anti-TNF α agents and immunomodulators, were not associated with the incidence of post-operative incisional SSI [17, 25, 37–40]. Results in our study were in line with above studies. No significant increase in the occurrence of post-operative incisional SSI for patients with hypoalbuminemia as well as pre-operative application of steroids, biologics and immunomodulators was identified ($P = 0.22, 0.15, 0.36$ and 0.62 , respectively).

Table 2. Surgery-related features

Characteristic	All cases (N = 159)	Patients without wound infection (N = 124)	Patients with wound infection (N = 35)	P-value
Chronic fistula as the indication for surgery	85	59 (47.6)	26 (74.3)	0.005
Emergent surgery	6	5 (4.0)	1 (2.9)	1.0
Laparoscopic surgery	30	26 (21.0)	4 (11.4)	0.2
Type of anastomosis				0.5
Handsewn	27	22 (24.7)	5 (18.5)	
Stapled	89	67 (75.3)	22 (81.5)	
Number of anastomosis, n (%)				0.087
0	35	31 (25.0)	4 (11.4)	
≥1	124	93 (75.0)	31 (88.6)	
Stoma creation	51	40 (32.3)	11 (31.4)	0.93
Intra-operative finding of fistula	85	58 (46.8)	27 (77.1)	0.001
Intra-operative finding of abscess	47	33 (26.6)	14 (40.0)	0.13
Intra-operative finding of perforation	7	6 (4.8)	1 (2.9)	1.0
Intra-operative finding of phlegmon	47	32 (25.8)	15 (42.9)	0.051
Intra-operative finding of small bowel obstruction	69	55 (44.4)	14 (40.0)	0.65
Intra-operative finding of fibrostenosis	90	73 (58.9)	17 (48.6)	0.28
Length of hospitalization, days	14 (11–22)	12.5 (10–17)	24 (18–36)	<0.001

Data are presented as median (interquartile range) or number (percentage).

Table 3. Multivariate analysis of risk factors associated with wound infection in patients with Crohn's disease

Characteristics	Odds ratio	95% Confidence interval	P-value
Anemia (yes vs no)	3.31	1.05–10.46	0.041
Intra-operative finding of fistula (yes vs no)	3.76	1.53–9.21	0.004
Elevated percentage of neutrophils (yes vs no)	2.85	1.23–6.59	0.014

As a single-center retrospective study, our study was inherently limited by its small sample size as well as some inevitable bias, such as selection bias and information bias [41]. In addition, specifics of the operative procedure, such as wound class and blood glucose level, which may have a profound impact on post-operative incisional SSI rates, are currently not captured by our database [17]. Finally, it is quite difficult to adjust for every possible variable, which introduces the typical selection bias in our studies [41]. Consequently, a prospective multi-center study with a large cohort is warranted.

Our study identified that anemia, an intra-operative finding of fistula and an elevated percentage of neutrophils were risk factors associated with post-operative incisional SSI in CD patients after bowel resection. Despite these findings needing to be confirmed by further investigation, we might be able to manage patients with CD more efficiently with the knowledge of these risk factors.

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