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Associations between multiple immunosuppressive treatments before surgery and surgical morbidity in patients with ulcerative colitis during the era of biologics

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Abstract

Purpose It is unclear whether immunomodulators or biologics, with the exception of corticosteroids, can be risk factors for postoperative infectious complications of ulcerative colitis (UC). Moreover, many immunosuppressive therapies including some biologics are used mainly to treat UC, and many patients are on multi-agent immunosuppressive therapy at the time of surgery. Therefore, we evaluated the influence of pre-operative multiple immunosuppressive agents on the occurrence of surgical site infection (SSI) in UC during the era of biologics.

Methods We reviewed surveillance data from 301 patients who underwent surgery between January 2015 and April 2018. The incidences of SSI and possible risk factors among patients receiving different immunosuppressive therapies were compared and analyzed.

Results The incidence of incisional SSI was 6.6%, and that of organ/space SSI was 7.0%. Doses of corticosteroids were significantly decreased because of the recent shift toward the use of biologics. The types and numbers of immunosuppressive agents did not significantly correlate with each incidence. Age ≥ 65 years (odds ratio (OR) 3.0), total prednisolone dose $\geq$ 9000 mg (OR 2.7), and perioperative blood transfusion (OR 3.6) were shown to be independent risk factors for incisional SSI, whereas duration of surgery ≥ 252 min (OR 3.8), urgent/emergent surgery (OR 2.9), and perioperative blood transfusion (OR 2.6) were identified as independent risk factors for organ/space SSI.

Conclusions Although no correlation between pre-operative immunosuppressive therapies, except for corticosteroids, was found, selection bias may have occurred due to treatment before surgery. However, biologics, calcineurin inhibitors, and thiopurines did not affect surgical morbidity in UC.

Keywords Ulcerative colitis · Surgical site infection · Anti-tumor necrosis factor-α · Immunosuppressive therapy

Introduction

Recently, several agents, including calcineurin inhibitors (CNIs), thiopurines, and anti-tumor necrosis factor alpha

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(anti-TNF-α) antibodies, have replaced corticosteroids as treatments for refractory, severe, and extended ulcerative colitis (UC). Corticosteroids are thought to be an independent risk factor for postoperative complications represented by surgical site infection (SSI), including wound infection, abdominal/pelvic abscess, or anastomotic leakage. However, Nelson et al. [1] reported in 2014 that CNI or infliximab (IFX) use with corticosteroids just before surgery for refractory UC was not associated with postoperative complications. Kimura et al. [2] also reported that immunosuppressive drugs have had little effect on the risk of postoperative complications during surgery for UC in a nationwide study in Japan. However, other reports suggested that anti-TNF-α therapy has been shown to be an independent risk factor for anastomotic leakage or septic

complications [3, 4], although in 2010, a meta-analysis conducted after the above reports did not demonstrate any association between anti-TNF-α therapy and postoperative complications [5]. In 2010, we evaluated the incidence of SSI and associations with pre-operative status, including several therapies; however, there were no significant associations between SSI and pre-operative thiopurine, CNI, or anti-TNF-α antibody use, except with corticosteroid use, in surgery for UC [6]. Today, the usage rates of thiopurine, CNIs, and anti-TNF-α antibodies are drastically increasing over corticosteroid usage. Moreover, several immunosuppressive agents are often concomitantly used, especially in patients with severe and refractory UC. Although we previously reported that multi-agent immunosuppression could not affect postoperative complications after UC surgery, no similar reports have shown this finding, and evidence is still lacking [7].

Because the effects of anti-TNF-α therapy on postoperative complications in UC surgery are still controversial and therapies for refractory UC are now shifting to biologics from corticosteroids, we are going to re-evaluate the incidence of SSI during UC surgery and the predictive factors for SSI that could be associated with pre-operatively administered agents or immunosuppressed status due to multiple agents before surgery during the era of biologics.

Methods

Patients

We prospectively obtained surveillance data that included the patient's background, characteristics of UC, treatment for UC, surgical details, and SSI starting from April 2006 at the Department of Inflammatory Bowel Disease at Hyogo College of Medicine, and we reviewed these data for a retrospective evaluation. Only patients with a confirmed diagnosis of UC by endoscopy and histology were included in the initial selection. Patients who were surgically treated with total colectomy and ileostomy, total proctocolectomy (TPC) with end-ileostomy, or ileal-pouch anal anastomosis (IPAA) with or without ileostomy as an initial surgery were included in this study. A total of 301 consecutive patients with UC who underwent open or laparoscopic-assisted surgery between January 2015 and April 2018 were included in this study. Laparoscopic-assisted IPAA was introduced in April 2017 at our institution. Its indication is limited to patients with mild/moderate colitis in this series.

Data collection

The patients were divided for analysis according to the number of administered immunosuppressive agents or location of the SSI. The patient demographics and characteristics were

recorded at admission or perioperatively. Possible risk factors for SSI were analyzed, namely, male gender; age at surgery; disease severity; corticosteroid use; immunomodulator use (thiopurines, including azathioprine (AZA) and 6-mercaptopurine (6-MP), or CNIs, including tacrolimus and cyclosporine A); anti-TNF-α antibody use including infliximab (IFX), adalimumab (ADA), or golimumab (GOL); the number of immunosuppressive therapy agents, which included single, double, or triple agents; pre-operative prednisolone (PSL) at a dose of ≥ 40 mg; total administered PSL dose ≥ 9000 mg; pre-operative oral antibiotic prophylaxis use; types of surgery including rectal (REC) or colonic surgery (COLN), open surgery, or prolonged surgery (≥ 252 min); amount of intra-operative blood loss ≥ 330 mL; perioperative blood transfusion; wound class ≥ 3; American Society of Anesthesiologists (ASA) score ≥ 3; serum albumin (Alb) level < 2.5 g/dL; pre-operative lymphocytes; low Onodera's prognostic nutritional index (O-PNI) score, calculated by Alb $\times 10 +$ lymphocyte count $\times 0.005$, which could indicate the prognosis for morbidity and mortality after UC surgery [8]; postoperative blood sugar (BS) level ≥ 165 mg/dL; body mass index (BMI) ≥ 22.7 kg/m^2; urgent/emergent surgery; and ostomy creation.

The interquartile values in this study were used as the cutoffs for the continuous valuables. The total administered PSL dose was calculated based on the previously administered steroid dose, which was converted to PSL after the initial diagnosis. The median and 75th percentile values of the daily PSL dose were both 10 mg/day. The SSI risk was decreased for patients with PSL doses of less than 40 mg/day, as previously reported by Heuschen et al. [9]. Therefore, a PSL dose of 40 mg/day was used as the cut-off value in this series. Only 5 patients had a BMI higher than 30 kg/m^2, which is generally suggested as a risk factor for SSI [10]. We used the 75th percentile BMI value as the cut-off, although this value was extremely low in our series (22.7 kg/m^2).

Disease severity at initial surgery was defined as mild, moderate, severe, or fulminant according to definition of Truelove and Witts, which was based on the stool frequency, the presence of fever, anemia, and tachycardia, and the erythrocyte sedimentation rate [11]. Anti-TNF-α antibody use was considered to be any infusion in the 12 weeks prior to surgery. The use of corticosteroids was defined to encompass patients who had used corticosteroids within 1 month prior to surgery or perioperatively. CNI or AZA/6-MP use was defined to include patients who used immunomodulators 72 h before surgery, regardless of the dosage.

Outcome measurement

SSIs were diagnosed and recorded according to their location. Generally, incisional SSIs included wound infection, while organ/space SSIs included abdominal or pelvic abscess,

including anastomotic leakage [12]. To compare the factors associated with SSI, we used the wound classification system of the National Nosocomial Infection Surveillance (NNIS) [12]. SSI was diagnosed by designated staff on our infection-control team who were trained in applying surveillance methods and determining SSI based on definitions stated in guidelines issued by the NNIS system of the Centers for Disease Control and Prevention (CDC) [13]. The criterion for a diagnosis of SSI was an infection that occurred within 30 days after the operation.

Statistical analysis

Categorical variables were compared using a chi-squared test or Fisher's exact test. Continuous variables are expressed as the median and range and were compared using the Mann-Whitney U test. The level of statistical significance was set at $p < 0.05$. Univariate analyses of categorical data and each individual factor were also conducted. All variables with a p value of less than 0.2 in the univariate analysis were subsequently entered into a stepwise logistic regression model. SPSS ver. 15.0 (SPSS Inc., Tokyo, Japan) was used to perform all analyses.

Ethical consideration

All study protocols were approved by the institutional review board at Hyogo College of Medicine, and informed consent for permission to use patient data was required prior to admission.

Results

A total of 301 patients with UC were surgically treated during the study period. The patient demographics and characteristics are shown in Table 1. PSL, CNIs, and anti-TNF-α antibodies were administered to 117/301 (38.9%), 119/301 (39.5%), and 146/301 (48.5%) patients, respectively. Among patients treated with anti-TNF-α antibodies, 124 patients received IFX, 53 patients received ADA, and 6 patients received GOL. The 75th percentile for total amount of PSL administered and pre-operative PSL dose were 9000 mg and 10 mg, respectively. REC, which included 207 IPAAs and 25 TPCs, was performed in 232/301 (77.1%) patients as an initial surgery. A total of 15 patients underwent IPAA without ileostomy. Nine patients underwent laparoscopic-assisted IPAA with ileostomy.

Patient backgrounds distinct from the numbers of immunosuppressive agents are shown in Table 2. Age at initial surgery was significantly lower in patients with three agents, including PSL, CNIs, and anti-TNF-α antibody ($p < 0.01$). Urgent/emergent surgery was significantly less common in patients

Table 1 Patients' backgrounds

Risk factors	No. of all patients $n = 301$
Age (years)	50.3 (36–65)
Gender (male:female)	183:118
BMI (kg/m^2)	20.3 (18.2–22.7)
Pre-operative serum Alb (g/dL)	3.4 (2.5–4.1)
Pre-operative lymphocyte	1168.7 (708–1628)
O-PNI	40.7 (31.5–48.1)
PSL administration	117 (38.9)
Total given PSL dose (mg)	3000 (1000–9000)
Pre-operative PSL (mg/day)	10 (0–10)
Immunosupressant administration	186 (61.8)
AZA/6-MP	121 (40.2)
CNI	119 (39.5)
aTNF administration	146 (48.5)
Infliximab administration	124 (41.2)
Adalimumab administration	53 (17.6)
Golimumab administration	6 (2.0)
PSL + CNI + aTNF	17 (5.6)
CNI + aTNF	58 (19.3)
PSL + CNI	28 (9.3)
PSL + aTNF	25 (8.3)
ASA score ≥ 3	65 (21.6)
Oral antiprophylaxis use	146 (48.5)
Type of surgery(REC:COLN)	232:69
Wound class ≥ 3	16 (5.3)
Timing of surgery (urgent, emergent)	84 (27.9)
Laparoscopic-assisted surgery	9 (3.0)
Ostomy creation	286 (95.0)
Surgical indication (cancer/dysplasia)	80 (26.6)
Disease severity (severe, fulminant)	125 (41.5)
Duration of surgery (min)	207 (191–252)
Intra-operative blood loss (mL)	200 (120–330)
Perioperative blood transfusion	43 (14.2)
Postoperative blood sugar (mg/dL)	139 (120–165)

BMI body mass index, *Alb* albumin, *O-PNI* Onodera's Prognostic Nutritional Index, *PSL* prednisolone, *AZA* azathioprine, *6-MP* 6-mercapto purine, *CNI* calcineurin inhibitor, *aTNF* anti-tumor necrosis factor-α antibody, *ASA* American Society of Anesthesiologist, *COLN* colonic surgery, *REC* rectal surgery

Continuous variables are indicated as median and interquartile range

Categorical data are numbers with percentages in parentheses

with no or one agent(s) ($p = 0.04$). Patients with no agents or AZA/6-MP administration alone had many more surgical indications of cancer/dysplasia ($p < 0.01$). However, ostomy creation was significantly less common in the none or thiopurine alone group than in other groups with multiple agents ($p < 0.01$). Similarly, severe or fulminant disease was significantly lower in patients with no agents or thiopurine alone than in other groups ($p < 0.01$).

Table 2 Backgrounds distinct from immunosuppressive agents

Administrated agents	None or thiopurine alone	One (PSL/CNI/aTNF)	Two (CNI + PSL/CNI + aTNF/aTNF + PSL)	Three(PSL + CNI + aTNF)	p value
Patient numbers	66(21.9)	107(35.5)	111(36.9)	17(5.6)	
Age (median years and IQR)	53.2(40.2–65.2)	52.6(43.9–63.8)	44.9(28.4–60.1)	40.2(33.1–65.0)	< 0.01
ASA score ≥ 3	10(15.2)	23(21.5)	27(24.3)	5(29.4)	0.60
Oral antiprophylaxis use	30(45.5)	61(57.0)	48(43.2)	7(46.7)	0.25
Type of surgery REC	44(66.7)	86(80.4)	87(78.4)	15(88.2)	0.20
Type of surgical procedure (IPAA:TPC:TC)	(32:9:22)	(76:10:21)	(84:6:24)	(15:0:2)	0.07
Wound class ≥ 3	4(6.1)	5(4.7)	6(5.4)	1(5.9)	0.86
Timing of surgery (urgent, emergent)	15(22.7)	23(21.5)	43(38.7)	4(23.5)	0.04
Laparoscopic surgery	0(0)	3(2.8)	5(4.5)	1(5.9)	0.66
Ostomy creation	45(68.2)	91(85.0)	100(90.1)	16(94.1)	< 0.01
Surgical indication (cancer/dysplasia)	42(63.6)	34(31.8)	4(3.6)	0(0)	< 0.01
Disease severity (severe, fulminant)	14(21.2)	44(41.1)	62(55.9)	5(29.4)	< 0.01
Overall SSI	8/66(12.1%)	15/107(14.0%)	16/111(14.4%)	2/17(11.8%),	0.99
Incisional SSI	2/66(3.0%)	9/107(8.4%)	7/111(6.3%)	2/17(11.8%),	0.73
Organ/space SSI	6/66(9.1%)	6/107(5.6%)	9/111(8.1%)	0/17(0%)	0.84

IQR interquartile range, *ASA* American Society of Anesthesiologist, *REC* rectal surgery, *IPAA* ileal-pouch anal anastomosis, *TPC* total proctocolectomy, *TC* total colectomy, *SSI* surgical site infection, *PSL* prednisolone, *CNI* calcineurin inhibitor, *aTNF* anti-tumor necrosis factor-α antibody

Data are numbers with percentages in parentheses unless otherwise indicated

The incidences of overall, incisional, and organ/space SSI were 41/301 (13.6%), 20/301 (6.6%), and 21/301 (7.0%), respectively. Regarding the rates of SSIs according to the surgical procedure, the incidences of overall, incisional, and organ/space SSI were 22/192 (11.5%), 12/192 (6.3%), and 10/192 (5.2%), respectively, in patients who received IPAA with ileostomy. For patients who received IPAA without ileostomy, the incidences of overall, incisional, and organ/space SSI were 2/15 (13.3%), 0/15 (0%), and 2/15 (13.3%). For patients who underwent TPC, the incidences of overall, incisional, and organ/space SSI were 8/25 (32.0%), 4/25 (16.0%), and 4/25 (16.0%), respectively. For patients who underwent colectomy and ileostomy, the incidences of overall, incisional, and organ/space SSI were 9/69 (13.0%), 4/69 (5.8%), and 5/69 (7.2%), respectively. Organ/space SSIs occurred in 2 patients who underwent laparoscopic-assisted IPAA, and no patient had an incisional SSI. No significant differences were found in the incidence of SSI among surgical procedures.

The incidences of SSIs according to the number of immunosuppressive treatments are shown in Table 2. No significant differences in the incidence of SSI were found according to the number of immunosuppressive agents.

The results of the univariate analysis for overall SSI are shown in Table 3. Age at initial surgery ≥ 65 years, urgent/emergent surgery, duration of surgery ≥ 252 min, amount of blood loss during surgery ≥ 330 mL, and perioperative blood transfusion were found to be significant risk factors for overall SSI. In addition, the following nine factors were included in

the multivariate logistic regression analysis: age ≥ 65 years, pre-operative serum Alb < 2.5 g/dL, anti-TNF-α antibody use, ASA score ≥ 3, wound class ≥ 3, urgent/emergent surgery, duration of surgery ≥ 252 min, amount of blood loss during surgery ≥ 330 mL, and perioperative blood transfusion.

The results of the univariate analysis for incisional SSI are shown in Table 4. Age at initial surgery ≥ 65 years and perioperative blood transfusion were found to be significant risk factors only for incisional SSI. In addition, the following six factors were included in the multivariate logistic regression analysis: age ≥ 65 years, total amount of PSL administered ≥ 9000 mg, ASA score ≥ 3, surgical indication of cancer/dysplasia, amount of blood loss during surgery ≥ 330 mL, and perioperative blood transfusion.

The results of the univariate analysis for organ/space SSI are shown in Table 5. Pre-operative PSL dose ≥ 40 mg/day, urgent/emergent surgery, duration of surgery ≥ 252 min, and perioperative blood transfusion were found to be significant risk factors for organ/space SSI. In addition, the following eight factors were included in the multivariate logistic regression analysis: pre-operative serum Alb < 2.5 g/dL, pre-operative PSL dose ≥ 40 mg/day, anti-TNF-α antibody use, ASA score ≥ 3, urgent/emergent surgery, duration of surgery ≥ 252 min, amount of blood loss during surgery ≥ 330 mL, and perioperative blood transfusion.

The results of the stepwise logistic regression model are shown in Table 6. Perioperative blood transfusion (OR 3.17, 95% CI 1.45–6.93, $p = 0.004$) and duration of surgery

Table 3 Univariate analysis for risk factors associated with overall SSI

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 260$	No. of patients with SSI $n = 41$	p value	Odds ratio (95%CI)
Age (years)					
≥ 65	72	57	15	0.04	2.06(1.02–4.14)
Gender					
Male	183	158	25	0.98	0.99(0.51–1.95)
BMI (kg/m^2)					
≥ 22.7	77	66	11	0.84	1.08(0.51–2.27)
Pre-operative serum Alb level (g/dL)					
< 2.5	68	55	13	0.14	1.73(0.84–3.56)
Pre-operative lymphocyte					
< 708	56	48	8	0.87	1.07(0.47–2.46)
O-PNI					
< 31.5	75	63	12	0.49	1.29(0.62–2.69)
PSL administration					
Yes	117	98	19	0.29	0.70(0.36–1.36)
Total given PSL (mg)					
≥ 9000	77	65	12	0.56	1.24(0.60–2.57)
Pre-operative PSL (mg/day)					
≥ 40	33	27	6	0.42	1.48(0.57–3.84)
Immunosuppressant administration					
Yes	186	159	27	0.59	0.82(0.41–1.65)
AZA/6-MP administration					
Yes	121	108	13	0.26	1.53(0.76–3.09)
CNI administration					
Yes	119	101	18	0.54	0.81(0.42–1.58)
aTNF administration					
Yes	146	130	16	0.19	0.64(0.33–1.25)
No	155	130	25		
PSL + CNI + aTNF					
Yes	17	15	2	0.82	0.84(0.18–3.81)
CNI + aTNF					
Yes	58	51	7	0.70	0.84(0.35–2.01)
PSL + CNI					
Yes	28	22	6	0.21	1.86(0.70–4.89)
PSL + aTNF					
Yes	25	22	3	0.81	0.85(0.24–2.99)
ASA score					
≥ 3	65	52	13	0.09	1.86(0.90–3.83)
Oral antiprophylaxis use					
Yes	146	127	19	0.77	1.11(0.57–2.14)
Type of surgery					
REC	232	200	32	0.87	1.67(0.48–2.36)
Wound class					
≥ 3	16	12	4	0.18	2.23(0.68–7.29)
Timing of surgery					
Emergent	84	67	17	0.04	2.04(1.03–4.03)
Laparoscopic surgery					
Yes	9	8	1	0.82	0.79(0.10–6.47)

Table 3 (continued)

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 260$	No. of patients with SSI $n = 41$	p value	Odds ratio (95%CI)
Ostomy creation					
Yes	286	247	39	0.97	1.03(0.22–4.72)
Surgical indication					
Cancer/dysplasia	80	69	11	0.97	0.99(0.47–2.07)
Disease severity					
Severe, fulminant	125	102	23	0.74	1.12(0.58–2.18)
Duration of surgery (min)					
≥ 252	68	53	15	0.02	2.25(1.12–4.55)
Intra-operative blood loss (mL)					
≥ 330	67	52	15	0.020	2.31(1.14–4.67)
Perioperative blood transfusion					
Yes	43	30	13	0.001	3.56(1.67–7.61)
Postoperative blood sugar (mg/dL)					
≥ 165	77	67	10	0.85	0.93(0.43–1.99)

BMI body mass index, *Alb* albumin, *O-PNI* Onodera's Prognostic Nutritional Index, *PSL* prednisolone, *AZA* azathioprine, *6-MP* 6-mercapto purine, *CNI* calcineurin inhibitors, *aTNF* anti-tumor necrosis factor-α antibody, *ASA* American Society of Anesthesiologist, *COLN* colonic surgery, *REC* rectal surgery

≥ 252 min (OR 2.20, 95% CI 1.06–4.56, $p = 0.03$) were identified as an independent risk factor for overall SSI; age $\geq$ 65 years (OR 3.02, 95% CI 1.19–7.62, $p = 0.02$), total amount of PSL ≥ 9000 mg (OR 2.71, 95% CI 1.05–6.97, $p = 0.04$), and perioperative blood transfusion (OR 3.46, 95% CI 1.25–9.56, $p = 0.01$) were identified as independent risk factors for incisional SSI, whereas duration of surgery ≥ 252 min (OR 3.84, 95% CI 1.46–10.15, $p = 0.007$), urgent/emergent surgery (OR 2.92, 95% CI 1.11–7.70, $p = 0.03$), and perioperative blood transfusion (OR 2.63, 95% CI 1.36–7.65, $p = 0.01$) were identified as independent risk factors for organ/space SSI.

Discussion

Anti-TNF-α antibodies have become one of the leading treatments for achieving remission of UC. Although controversial issues remain, they seem to hold a mild risk for infectious complications even after surgery [6]. Although a meta-analysis of 13 studies including 2933 patients indicated a negative association between anti-TNF therapy and postoperative complications [5], some studies suggested that pelvic sepsis, including anastomotic leakage, was significantly increased during IPAA in patients who were administered anti-TNF-α antibodies before surgery [4, 14, 15]. Immunosuppressive treatments that include not only anti-TNF-α antibodies but also AZA/6-MP or CNIs can increase the risks for SSIs. Although several

reports are published evaluating immunosuppressed status and perioperative complications, most studies have a low quality of evidence because they were retrospective study designs at a single institution with small sample sizes [1–6, 14, 15]. Moreover, they were evaluated with mixed conditions, such as different surgical procedures, disease severity, malnutrition, or anemia. However, randomized controlled trials to prove the associations between pre-operative immunosuppressive agents and surgical complications cannot be performed due to ethical concerns, because the treatment strategy for UC cannot be decided on the basis of surgical complications but rather on the characteristics of colitis.

We previously evaluated the incidence and risk factors for SSI in UC surgery during consecutive SSI surveillance between January 2010 and September 2012 [16] and between January 2012 and March 2014 [7]. The incidences of overall SSI were 47/196 (24.0%) and 37/181 (20.4%), respectively, which were significantly higher than that of this series ($p < 0.01$). PSL use just before surgery was 121/196 (61.7%) and 113/181 (62.4%), respectively, which was significantly higher than that in this series (38.9%, $p < 0.01$). Moreover, the median total amount of PSL administered and the preoperative PSL dose just before surgery were 8640 mg and 12 mg/day and 11,987 mg and 18.4 mg/day, respectively, which were also significantly higher than 3000 mg and 10 mg/day, respectively, in this series ($p < 0.01$). Regarding immunomodulators including AZA/6-MP and CNIs, their use

Table 4 Univariate analysis for risk factors associated with incisional SSI

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 281$	No. of patients with SSI $n = 20$	p value	Odds ratio (95%CI)
Age (years)					
≥ 65	72	62	10	0.01	3.20(1.29–7.88)
Gender					
Male	183	172	11	0.78	0.78(0.31–1.93)
BMI (kg/m^2)					
≥ 22.7	77	73	4	0.48	0.67(0.22–2.05)
Pre-operative serum Alb level (g/dL)					
< 2.5	68	62	6	0.50	1.41(0.52–3.78)
Pre-operative lymphocyte					
< 708	56	51	5	0.53	1.40(0.49–4.01)
O-PNI					
< 31.5	75	70	5	0.90	0.94(0.33–2.65)
PSL administration					
Yes	117	108	9	0.56	1.31(0.53–3.29)
Total given PSL (mg)					
≥ 9000	77	66	11	0.07	2.34(0.95–5.79)
Pre-operative PSL (mg/day)					
≥ 40	33	32	1	0.36	0.39(0.05–2.99)
Immunosuppressant administration					
Yes	186	171	15	0.22	1.91(0.68–5.41)
AZA/6-MP administration					
Yes	121	115	6	0.34	0.62(0.23–1.66)
CNI					
Yes	119	108	11	0.23	1.96(0.79–4.88)
aTNF administration					
Yes	146	137	9	0.75	0.86(0.35–2.14)
PSL + CNI + aTNF					
Yes	17	15	2	0.39	1.97(0.42–9.29)
CNI + aTNF					
Yes	58	54	4	0.93	1.05(0.34–3.27)
PSL + CNI					
Yes	28	25	3	0.37	1.81(0.50–6.59)
PSL + aTNF					
Yes	25	25	0	0.99	not estimable
ASA score					
≥ 3	65	59	6	0.10	2.25(0.85–5.98)
Oral antiprophylaxis use					
No	155	146	9	0.55	1.32(0.53–3.29)
Type of surgery					
REC	232	216	16	0.75	1.20(0.39–3.73)
Wound class					
≥ 3	16	14	2	0.34	2.12(0.45–10.05)
Timing of surgery					
Emergent	84	77	7	0.47	1.43(0.55–3.71)
Laparoscopic surgery					
Yes	9	9	0	0.99	not estimable

Table 4 (continued)

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 281$	No. of patients with SSI $n = 20$	p value	Odds ratio (95%CI)
Ostomy creation					
Yes	286	266	20	0.99	not estimable
Surgical indication					
Cancer/dysplasia	80	72	8	0.16	1.94(0.76–4.92)
Disease severity					
Severe, fulminant	125	117	8	0.89	0.93(0.37–2.36)
Duration of surgery (min)					
≥ 252	68	62	6	0.49	1.41(0.52–3.78)
Intra-operative blood loss (mL)					
≥ 330	67	59	8	0.08	2.31(0.91–5.82)
Perioperative blood transfusion					
Yes	43	37	6	0.045	2.83(1.02–7.81)
Postoperative blood sugar (mg/dL)					
≥ 165	77	72	5	0.85	0.90(0.32–2.55)

BMI body mass index, *Alb* albumin, *O-PNI* Onodera's Prognostic Nutritional Index, *PSL* prednisolone, *AZA* azathioprine, *6-MP* 6-mercapto purine, *CNI* calcineurin inhibitors, *aTNF* anti-tumor necrosis factor-α antibody, *ASA* American Society of Anesthesiologist, *COLN* colonic surgery, *REC* rectal surgery

was increased from 94/196 (48%) in a report in 2013 [16] and 105/181 (58.0%) in a report in 2015[7] to 186/301 (61.8%) in this series. Anti-TNF-α antibodies were administered to 22/196 (11.2%) patients in a report in 2013 [16] and 44/181 (24.3%) patients in a report in 2015 [7]. Anti-TNF-α therapy has gradually and significantly increased to 48.5% during the recent biologic era in this series ($p < 0.01$). In those two studies, either a higher total amount of PSL administered or a higher PSL dose just before surgery was selected as an independent risk factor for SSI. Decreasing the dose of PSL by proper usage and the evolution of additional immunosuppressive therapies, including immunomodulators and anti-TNF-α antibodies, might contribute to the decrease in SSIs resulting from a reduction in PSL dose.

In this study, immunosuppressive therapies and their combinations were not associated with SSI, except for corticosteroids. Moreover, older age, prolonged surgery urgent/emergent surgery, and perioperative blood transfusion have been recognized as general risk factors for several diseases and surgeries [10, 12, 13, 17, 18]. A high amount of total corticosteroids administered was selected as an independent risk factor for incisional SSI in this study as similar to previous studies [7, 16]. Prolonged corticosteroid use is well known to lead to friability and atrophy of skin or subcutaneous tissue [19]. Therefore, it may be selected as a risk for incisional SSI.

In this study, we analyzed and evaluated data collected between January 2015 and April 2018, although SSI surveillance was started in April 2006. Many differences and biases

occurred over the 10 years of surveillance. For example, a so-called care bundle for preventing SSI, including changing of surgical instruments, devices, or suture materials (antibiotic-coated sutures), use of antimicrobial prophylaxis (oral and intravenous antibiotics), use of skin disinfectant before surgery, maintenance of body temperature during surgery, and perioperative glycemic control, differed according to the era [20–23]. Moreover, the decreasing incidence of incisional SSI in this series may be explained by size of the incisional wound. We gradually introduced mini-laparotomy for UC surgery. The standard length of the skin incision in the median lower abdomen was 8 to 15 cm in 2006 and was gradually shortened to 3 to 4 cm at the smallest in umbilical incision due to the development of laparoscopic-assisted surgery, energy devices, linear staplers, and auto sutures. Laparoscopic-assisted surgery was introduced in April 2017 only for elective surgical patients with mild or moderate disease activity and a low BMI. Therefore, further study is needed because our experience with laparoscopic-assisted surgery for UC is currently limited. Due to the above-mentioned reasons, we evaluated and analyzed data from January 2015 to April 2018 with similar SSI care bundle. Moreover, laparoscopic-assisted surgery was not chosen as a possible low risk factor for SSI because few cases were included in this series.

Multiple administration of immunosuppressive agents was not a significant risk factor for SSI. Notably, however, disease severity and patient age were lower in triple-agent administration. Multiple immunosuppression seemed to be used more

Table 5 Univariate analysis for risk factors associated with organ/space SSI

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 280$	No. of patients with SSI $n = 21$	p value	Odds ratio (95%CI)
Age (years)					
≥ 65	72	67	5	0.91	1.07(0.37–3.04)
Gender					
Male	183	169	14	0.57	1.31(0.51–3.36)
BMI (kg/m^2)					
≥ 22.7	77	70	7	0.32	1.62(0.62–4.23)
Pre-operative serum Alb level (g/dL)					
< 2.5	68	61	7	0.18	1.94(0.74–5.08)
Pre-operative lymphocyte					
< 708	56	53	3	0.67	0.76(0.22–2.69)
O-PNI					
< 31.5	75	68	7	0.29	1.69(0.65–4.40)
PSL administration					
Yes	117	107	10	0.29	1.63(0.66–4.04)
Total given PSL (mg)					
≥ 9000	77	74	3	0.27	0.49(0.14–1.73)
Pre-operative PSL (mg/day)					
≥ 40	33	28	5	0.046	3.01(1.02–8.91)
Immunosuppressant administration					
Yes	186	174	12	0.64	0.81(0.33–1.97)
AZA/6-MP					
Yes	121	114	7	0.51	0.73(0.29–1.86)
CNI					
Yes	119	112	7	0.55	0.75(0.29–1.92)
aTNF administration					
Yes	146	139	7	0.16	0.51(0.20–1.30)
PSL + CNI + aTNF					
Yes	17	17	0	0.99	not estimable
CNI + aTNF					
Yes	58	55	3	0.55	0.68(0.19–2.40)
PSL + CNI					
Yes	28	25	3	0.42	1.70(0.47–6.17)
PSL + aTNF					
Yes	25	22	3	0.31	1.96(0.53–7.15)
ASA score					
≥ 3	65	58	7	0.18	1.91(0.74–4.96)
Oral antiprophylaxis use					
Yes	146	138	8	0.37	0.63(0.26–1.58)
Type of surgery					
REC	232	216	16	0.92	0.95(0.33–2.69)
Wound class					
≥ 3	16	14	2	0.38	2.00(0.42–9.45)
Timing of surgery					
Emergent	84	74	10	0.04	2.53(1.03–6.20)
Laparoscopic surgery					
Yes	9	8	1	0.63	1.70(0.20–14.28)

Table 5 (continued)

Risk factors	No. of all patients $n = 301$	No. of patients without SSI $n = 280$	No. of patients with SSI $n = 21$	p value	Odds ratio (95%CI)
Ostomy creation					
Yes	286	267	19	0.30	0.44(0.09–2.08)
Surgical indication					
Cancer/dyaplasia	80	77	3	0.20	0.44(0.13–1.53)
Disease severity					
Severe, fulminant	125	115	10	0.56	1.30(0.54–3.17)
Duration of surgery (min)					
≥ 252	68	59	9	0.02	3.08(1.22–7.78)
Intra-operative blood loss (mL)					
≥ 330	67	60	7	0.16	1.98(0.76–5.19)
Perioperative blood transfusion					
Yes	43	36	7	0.010	3.39(1.28–8.96)
Postoperative blood sugar (mg/dL)					
≥ 165	77	72	5	0.95	0.97(0.34–2.76)

BMI body mass index, *Alb* albumin, *O-PNI* Onodera's Prognostic Nutritional Index, *PSL* prednisolone, *AZA* azathioprine, *6-MP* 6-mercapto purine, *CNI* calcineurin inhibitors, *aTNF* anti-tumor necrosis factor-α antibody, *ASA* American Society of Anesthesiologist, *COLN* colonic surgery, *REC* rectal surgery

Table 6 multivariate logistic regression analysis for risk factors associated with SSI in patients with ulcerative colitis

	Risk factors	p value	Odds ratio (95%CI)
Overall SSI	Pre-operative serum Alb < 2.5 g/dL	0.67	0.81(0.30–2.15)
	Transfusion	0.004	3.17(1.45–6.93)
	Age $\geqq$ 65 years	0.06	1.99(0.96–4.12)
	aTNF administration	0.72	0.88(0.42–1.82)
	ASA score $\geqq$ 3	0.89	0.94(0.39–2.29)
	Wound class $\geqq$ 3	0.22	2.34(0.59–9.20)
	Urgent/emergent surgery	0.22	1.75(0.72–4.25)
	Intra-operative blood loss $\geqq$ 330 mL	0.50	1.33(0.58–3.03)
	Duration of surgery $\geqq$ 252 min	0.03	2.20(1.06–4.56)
Incisional SSI	Age $\geqq$ 65 years	0.02	3.02(1.19–7.62)
	Surgical indication (cancer/dysplasia)	0.20	2.03(0.69–5.94)
	Total given PSL $\geqq$ 9000 mg	0.04	2.71(1.05–6.97)
	Intra-operative blood loss $\geqq$ 330 mL	0.40	1.56(0.56–4.35)
	Transfusion	0.01	3.46(1.25–9.56)
	ASA score $\geqq$ 3	0.52	1.45(0.47–4.49)
Organ/space SSI	Pre-operative PSL $\geqq$ 40 mg/day	0.37	1.74(0.52–5.89)
	Pre-operative serum Alb < 2.5 g/dL	0.64	1.35(0.38–4.74)
	Duration of surgery $\geqq$ 252 min	0.007	3.84(1.46–10.15)
	aTNF administration	0.64	0.78(0.28–2.19)
	Urgent/emergent surgery	0.03	2.92(1.11–7.70)
	ASA score $\geqq$ 3	0.75	0.82(0.25–2.74)
	Intra-operative blood loss $\geqq$ 330 mL	0.97	1.03(0.34–3.13)
	Transfusion	0.01	2.63(1.36–7.65)

*Selected final steps in stepwise logistic regression analysis

SSI surgical site infection, *CI* confidence interval, *Alb* albumin, *ASA* American Society of Anesthesiologist, *aTNF* anti-tumor necrosis factor-α antibody

often with younger patients who can physically afford to try additional treatments. Moreover, long-standing mild inflammation is known to be a risk factor for colitis-associated cancer/dysplasia in UC [24]. Therefore, IPAA without ileostomy was more frequently performed in patients with cancer/dysplasia whose disease severity was mild even without immunosuppressive treatments, which was the major limitation of this study because the patients had several conditions, treatments, or surgical procedures together in all analyses.

The limitations of this study are indicated below. First, this study was a retrospective analysis at a single institution. Second, as mentioned above, there were several differences in patient backgrounds. Patients whose colitis was closer to a severe or fulminant condition did not have time to try using several agents, and those whose condition was worsening were not selected for additional medical treatments, especially elderly patients. There was major selection bias in several patients about the number of immunosuppressive agents used. Third, whether an immunosuppressive agent could have an effect postoperatively after stopping that particular agent is still unknown. IFX can reportedly remain in the body for 12 weeks after the last administration [25]. Although thiopurines and CNIs could be washed out through the body within several days after stopping, it is unknown whether the immunosuppressive status can be reversed within those several days. Fourth, vedolizumab and tofacitinib were not available in Japan during this study period, and thus, there were no patients who were using these agents. Fifth, mini-laparotomy or laparoscopic-assisted surgery is generalized even in UC, similar to colorectal cancer. This factor can greatly affect SSI and should be evaluated in further study during the same surgical procedures. Sixth, the definition of urgent surgery was not strict in this series and could be influenced by each patient's condition or background.

In conclusion, anti-TNF-α therapy or immunosuppression with multiple agents did not affect SSI in patients with UC in the recent era of biologics. Although a major selection bias for using pre-operative treatments exists, the general condition, including malnutrition and anemia, can be affected more by surgical morbidity than by the use of several agents.

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