

Perioperative Blood Transfusion and Postoperative Outcome in Patients with Crohn's Disease Undergoing Primary Ileocolonic Resection in the “Biological Era”

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Abstract

Background Perioperative blood transfusion has been shown to be associated with inflammatory response and immunosuppression. Patients receiving blood transfusion may have an increased risk for developing postoperative morbidities. The impact of blood transfusion on the postoperative recurrence of Crohn's disease (CD) has been controversial. The aim of this study was to assess the effect of blood transfusion on postoperative outcomes in CD in the current biological era.

Methods This historical cohort study involved data collection and analysis of CD patients who underwent the index ileocolonic resection in our institution between 2000 and 2012. Postoperative complications were compared between the transfused and nontransfused patients. The effects of perioperative blood transfusion on postoperative complications and disease recurrence were analyzed with both univariate and multivariate analyses.

Results A total of 318 patients were included in the study, and 52 of them (16.5 %) received perioperative blood transfusion. Blood transfusion was found to be associated with an increased risk of postoperative infectious and noninfectious complications both in univariate ($P<0.001$ for each) and multivariable analyses (infectious complications: odds ratio [OR]=8.73, 95 % confidence interval [CI] 2.85–26.78, $P<0.001$; noninfectious complications: OR=3.64, 95 % CI 1.30–10.18; $P=0.014$). In addition, the Cox regression model indicated that blood transfusion was associated with both surgical (hazard ratio [HR]=3.43, 95 % CI 1.92–6.13; $P<0.001$) and endoscopic (HR=2.08, 95 % CI 1.38–3.14; $P<0.001$) CD recurrence following the index surgery.

Conclusion Adverse outcomes after perioperative blood transfusion for the primary ileocolonic resection for CD resemble findings in surgery for other diseases. The presumed immunosuppressive effect of blood transfusion did not confer any protective effect on disease recurrence.

Keywords Blood transfusion · Bowel resection · Crohn's disease · Complications · Recurrence

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Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CD	Crohn's disease
CI	Confidence interval
EBL	Estimated blood loss
EIM	Extra-intestinal manifestations
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICR	Ileocolonic resection
OR	Odds ratio

SBO	Small bowel obstruction
SD	Standard deviation
SSI	Surgical site infection
TNF	Tumor-necrosis factor
UTI	Urinary tract infection
WBC	White blood cell

Introduction

The majority of patients with Crohn's disease (CD) require at least one bowel resection surgery during their disease course, due to the natural progress from inflammatory to stricturing and/or penetrating phenotype.^{1–3} Patients with CD have a higher incidence of postoperative complications than non-CD patients.^{4–7} In addition, surgery is typically not curative for CD.^{1–8} Most patients would develop disease recurrence at or near the site of anastomosis, with some becoming symptomatic, and the majority of them eventually require further surgical resection.^{9,10}

Blood transfusion remains a common practice in a surgical setting.¹¹ Transfused allogeneic blood has long been considered as being immunosuppressive and/or inductive for inflammatory response.^{12,13} It is speculated that allogeneic blood transfusion can predispose recipients to a large amount of foreign antigens in the circulation.^{14,15} The association between perioperative transfusion of allogeneic blood products and adverse outcomes (e.g., postoperative infectious complications and early cancer recurrence) has been demonstrated in patients undergoing various surgical operations for malignancies.^{16–24}

CD is a chronic inflammatory disorder which results from a complex interplay of genetic, environmental, microbial, and immunological factors.^{2,25,26} Aberrant innate and adaptive immune responses play a key role in the onset and perpetuation of intestinal inflammation and relapse of disease.^{27,28} Biological therapy, particularly the use of anti-tumor-necrosis factor (TNF) agents, has become a standard practice for patients with moderate to severe CD or ulcerative colitis (UC). Those agents have strong immunosuppressive effects, which may be associated with postoperative infectious complications^{29,30} and disease recurrence.^{31,32} We speculated that perioperative blood transfusion may have an adverse impact on the development of postoperative complications and/or disease recurrence. In fact, the effect of allogeneic blood transfusion on postoperative outcomes has been explored pre-“biological era”, and the results are conflicting.^{33–38} It is not clear whether the perioperative dual immunosuppression with anti-TNF and blood transfusion increases the risk for postoperative morbidities and disease recurrence, in the current era of the wide use of biological agents. The aim of this study was to examine the effect of perioperative allogeneic blood transfusion on

postoperative complications and recurrence of CD in a cohort of patients undergoing the first ileocolonic resection (ICR).

Patients and Methods

Patient Identification

All consecutive eligible patients with CD at the Department of Colorectal Surgery, the Cleveland Clinic Foundation, between 2000 and 2012, were included in the study. The diagnosis of CD was based on a combined assessment of clinical, endoscopic, histologic, radiographic, and operative features. The historical cohort study was based on a prospectively collected, Institutional Review Board-approved CD database.

Inclusion and Exclusion Criteria

Inclusion criteria were patients with (1) underlying CD; (2) having the primary ileocecal or ICR with ileocolonic anastomosis, with or without a temporary diverting ileostomy; and (3) regular follow-up at our institution for more than 1 year. Exclusion criteria were patients with incomplete resections (i.e., residual disease left in situ), strictureplasty, follow-up less than 1 year, or UC with ileorectal anastomosis. Patients with the first ICR performed outside institutions or those having a prior history of CD-related bowel surgery were also excluded.

Clinical Variables

A standardized chart was used to retrieve patient data. For each patient, the following data were extracted from the our prospectively maintained CD database: gender, age, duration of disease, CD phenotype according to the Montreal Classification, body mass index (BMI) at the time of surgery, smoking status, perianal disease, family history of CD, extra-intestinal manifestation (EIM), preoperative white blood cell (WBC) counts and serum albumin level, hemoglobin level at the time of operation, medications (corticosteroids, immunomodulators, and anti-TNF biologics) 3 months preoperatively, postoperative prophylaxis (5-aminosalicylic acids, immunosuppressive agents, and anti-TNF biologics), postoperative complications, and postoperative endoscopic and surgical CD recurrence. Additionally, operative data including estimated blood loss (EBL), the American Society of Anesthesiologists (ASA) fitness grade, indication for surgery, urgency of surgery (emergent vs elective), surgical approach (open vs laparoscopic), anastomotic configuration (end-to-end vs side-to-side vs others), type of anastomosis (hand-sewn vs stapled), operative time, intraoperative findings (fistula and abscess), and construction of a temporary or a permanent stoma were also collected.

Special attention was given to the information of perioperative blood transfusion. Perioperative blood transfusion was defined as transfusion of red blood cell concentrate during the period from admission to hospital discharge after ICR.

Study Outcomes

The primary outcome was the 30-day postoperative infectious and noninfectious morbidities. Infectious complications included anastomotic leaks, intra-abdominal abscess, fascial dehiscence, sepsis, surgical site infection (SSI), and urinary tract infection (UTI). Noninfectious complications included postoperative ileus, small bowel obstruction (SBO), thromboembolism, and dehydration. Ileus was defined as the absence of bowel function on postoperative day 5 or the need for insertion of a nasogastric tube for abdominal decompression, nausea, or vomiting after the start of a liquid diet, after exclusion of mechanical bowel obstruction found.³⁹ SBO was defined as the presence of obstructive symptoms associated with radiographic findings consistent with mechanical intestinal obstruction.⁴⁰⁻⁴¹

The secondary outcome was the postoperative endoscopic and surgical recurrence of CD. Endoscopic recurrence was defined as a Rutgeerts score ≥ 2 .⁴²⁻⁴³ Surgical recurrence was defined as the necessity of subsequent surgical bowel resection for recurrent CD.

Statistical Analysis

Descriptive statistics were presented as mean \pm standard deviation (SD) for continuous variables and frequency distributions for categorical variables. The Mann–Whitney *U* test, Student's *t* test, chi-squared test, and Fisher's exact probability test were used as appropriate. To adjust confounding factors, we performed multivariate analysis using logistic regression model. Independent variables for multivariate analysis included those with a significant influence in univariate analysis as well as those previously reported as influencing the risk of postoperative complications (odds ratio [OR], 95 % confidence interval [CI]). Survival data were graphically described by Kaplan–Meier curves. Recurrence-free survival differences between the groups were tested with the log-rank test. A Cox regression model was constructed in which incorporated all significant variables in the univariate along with those previously reported risk factors in the literature. Hazard ratios (HR) with 95 % CI were calculated accordingly. All *P* values were two-sided. A *P* value of <0.05 was considered statistically significant.

Results

During the study period, 318 eligible patients were included in this study. Overall, 52 (16.4 %) patients received blood transfusion (the transfused group), and the remaining 266 (83.7 %) did not (the nontransfused group). Of the 52 transfused patients, 6 (11.5 %), 13 (25.0 %), and 33 (63.5 %) received preoperative, intraoperative, and postoperative blood transfusion, respectively.

Baseline Characters

The demographic characteristics are listed in Table 1. The mean age of the whole cohort was 36.3 ± 14.1 years. There were 137 male patients (43.1 %). The mean disease duration was 7.9 ± 8.9 years. The preoperative use of anti-TNF biologics was documented in 40.4 % of the transfused patients and in 21.8 % of the nontransfused patients ($P=0.006$). Patients in the transfused group had lower preoperative levels of albumin ($P=0.001$) and hemoglobin than that in the nontransfused group ($P<0.001$). There was no difference in gender, age, disease duration, or disease phenotype. BMI, smoking status, concomitant perianal disease, family history of CD, EIM, preoperative WBC count, the postoperative use of anti-TNF biologics, and the use of corticosteroids or immunosuppressive agents before or after surgery. There were 24 patients in the cohort had a preoperative interval from admission to surgery ≥ 7 days, with 9 of 52 (17.3 %) in the transfused group and 15 of 266 (5.6 %) in the nontransfused group ($P=0.009$).

The surgery-related variables are presented in Table 2. Ninety-one of 218 procedures (28.6 %) were performed for medical refractory CD, 111 (34.9 %) for stricturing CD, 105 (33.0 %) for penetrating CD, and 11 (3.5 %) for other indications. A total of 159 (50.0 %) patients were operated laparoscopically, and ICR was urgently performed in 18 (5.7 %). Patients in the transfused group had a higher volume of EBL ($P<0.001$), a higher frequency of ASA classification score of ≥ 3 ($P=0.005$), a greater chance of intraoperative finding of fistula ($P<0.001$), and a more prolonged operative time ($P=0.002$), than those in the nontransfused group. More patients in the transfused group had temporary stoma than those in the nontransfused group ($P=0.001$). In addition, a significant difference was observed in indication for surgery ($P=0.004$) between the two groups. However, no significant difference was found in the requirement of emergent surgery, laparoscopic surgery, type of anastomosis, anastomotic configuration, or intraoperative abscess, between the two groups.

The 30-Day Postoperative Complications

Overall, 98 patients (30.8 %) had complications within 30 days after the surgery. Sixty-one patients had infectious

Table 1 Demographic and clinical characteristics

	All patients (<i>n</i> =318)	Transfusion (<i>n</i> =52)	No transfusion (<i>n</i> =266)	<i>P</i> value
Male gender	137 (43.1)	26 (50.0)	111 (41.7)	0.29
Age at surgery (years)	36.3±14.1	37.3±16.5	36.1±13.6	0.57
Disease duration (years)	7.9±8.9	8.4±9.4	7.8±8.8	0.63
Disease behavior				0.24
B1	36 (11.3)	6 (11.5)	30 (11.3)	
B2	124 (39.0)	15 (28.9)	109 (41.0)	
B3	158 (49.7)	31 (59.6)	127 (47.7)	
BMI	25.9±8.2	26.1±9.5	25.9±7.9	0.85
Smoking status				0.62
Never	182 (57.2)	27 (51.9)	155 (58.3)	
Former	54 (17.0)	11 (21.2)	43 (16.2)	
Current	82 (25.8)	14 (26.9)	68 (25.6)	
Perianal disease	59 (18.6)	11 (21.2)	48 (18.1)	0.70
Family history of CD	68 (21.4)	10 (19.2)	58 (21.8)	0.72
EIM	38 (12.0)	4 (7.7)	34 (12.8)	0.36
Preoperative WBC (×10 ⁹ /L)	8.7±3.7	8.2±3.7	8.8±3.7	0.34
Preoperative albumin (g/dL)	3.7±0.6	3.4±0.7	3.8±0.6	0.001
Preoperative hemoglobin (g/dL)	12.4±1.9	11.3±2.3	12.7±1.7	<0.001
Preoperative medications				
Steroids	201 (63.2)	28 (53.9)	173 (65.0)	0.16
Immunosuppressive agents	75 (23.6)	12 (23.1)	63 (23.7)	0.99
Biologics	79 (24.8)	21 (40.4)	58 (21.8)	0.006
Postoperative medications				
5-Aminosalicylic acid	87 (27.4)	18 (34.6)	69 (25.9)	0.23
Immunosuppressive agents	93 (29.3)	14 (26.9)	79 (29.7)	0.74
Biologics	33 (10.4)	5 (9.6)	28 (10.5)	0.99

Data are presented as mean±SD or number (percentage)

complications and 62 had noninfectious complications. There were statistically significant differences in the frequency of 30-day overall postoperative morbidities ($P=0.001$), infectious complications ($P<0.001$), and noninfectious complications ($P<0.001$) between the two groups. Although the frequency of specific infectious complications, such as SSI and UTI, was not significantly different between the two groups, patients in the transfused group had an increased frequency of anastomotic leak ($P<0.001$), intra-abdominal abscess ($P=0.001$), fascial dehiscence ($P<0.001$), and sepsis ($P=0.031$). In addition, a significant difference was observed in ileus ($P=0.007$) and thrombotic events ($P=0.007$) despite a similar rate of dehydration or SBO between the two groups (Table 3). The reoperation rate was 26.9 % in the transfused group and 3.0 % in the nontransfused group ($P<0.001$). The indications for reoperation were as follows: 16 (72.7 %) for anastomotic leak, 2 (9.1 %) for intra-abdominal bleeding, 2 (9.1 %) for small bowel obstruction, and 2 (9.1 %) for sepsis. The length of hospital stay was 12.7±10.0 days in the transfused group

and 5.9±4.0 days for the nontransfused group ($P<0.001$). The readmission rate in was 25.0 % in the transfused group and 13.9 % in the nontransfused group ($P=0.059$) (Table 3). There was no significant difference between patients receiving 1 to 2 units ($n=27$) and those receiving transfusion ≥ 3 units ($n=25$) in respect to all complications ($P=0.11$), infectious ($P=0.26$), or noninfectious ($P=0.26$), and readmission ($P=0.75$), reoperation ($P=0.061$), and length of hospital stay ($P=0.062$).

Multivariate analyses were performed to identify the risk factors for perioperative infectious or noninfectious complications (Table 4). We found that blood transfusion ($P=0.001$), the preoperative use of immunomodulators ($P=0.046$) or biologics ($P=0.014$), and older age at surgery ($P=0.022$) were independent risk factors for postoperative overall morbidities. We also found that transfusion ($P<0.001$), the preoperative use of immunomodulators ($P=0.015$) or anti-TNF biologics ($P=0.02$), and a high preoperative WBC count ($P=0.042$) were associated with an increased risk for postoperative

Table 2 Operative information

	All patients (n=318)	Transfusion (n=52)	No transfusion (n=266)	P value
EBL (mL)	180.0±189.0	315.3±326.7	151.0±128.1	<0.001
ASA ≥3	63 (19.8)	18 (34.6)	45 (16.9)	0.005
Indication for surgery				0.004
Medical refractory	91 (28.6)	10 (19.2)	81 (30.5)	
Stricture/obstruction	111 (34.9)	25 (48.1)	86 (32.3)	
Penetrating disease	105 (33.0)	12 (23.1)	93 (35.0)	
Others	11 (3.5)	5 (9.6)	6 (2.3)	
Emergent surgery	18 (5.7)	4 (7.7)	14 (5.3)	0.51
Laparoscopic surgery	159 (50.0)	27 (51.9)	132 (49.6)	0.76
Stapled anastomosis	243 (76.4)	36 (69.2)	207 (77.8)	0.099
Anastomotic configuration				0.52
End-to-end	85 (26.7)	19 (36.5)	66 (24.8)	
Side-to-side	140 (44.0)	23 (44.2)	117 (44.0)	
Other	93 (39.4)	16 (30.8)	77 (29.0)	
Temporary ileostomy	83 (26.1)	24 (46.2)	59 (22.2)	0.001
Intraoperative finding of fistula	141 (44.3)	31 (59.6)	110 (41.4)	<0.001
Intraoperative finding of abscess	79 (24.8)	13 (25.0)	66 (24.8)	0.26
Mean operative time (min)	127.8±65.9	164.3±103.7	119.9±51.9	0.002

Data are presented as mean±SD or number (percentage)

infectious complications. In addition, blood transfusion ($P=0.014$), older age at surgery ($P=0.027$), and EBL ($P=0.046$) were found to be independent risk factors for noninfectious complications. Further analysis with adjustment for potential confounding factors including intraoperative finding of fistula

or abscess, a longer operative time, and high EBL was performed. Our data showed that, even adjusted for those confounding factors, the perioperative blood transfusion remained to be associated with postoperative overall complications (OR=4.58, 95 % CI 1.43–14.65, $P=0.010$), infectious

Table 3 Postoperative outcome

	Transfusion (n=52)	No transfusion (n=266)	P value
All complications	27 (51.9)	71 (26.7)	0.001
Infectious complications	20 (38.5)	41 (15.4)	<0.001
Anastomotic leak	10 (19.2)	6 (2.3)	<0.001
Intra-abdominal abscess	10 (19.2)	13 (4.9)	0.001
Fascial dehiscence	6 (11.5)	2 (0.8)	<0.001
Sepsis	11 (21.2)	26 (9.8)	0.031
SSI	7 (13.5)	27 (10.2)	0.62
UTI	1 (1.9)	5 (1.9)	0.99
Noninfectious complications	20 (38.5)	42 (15.8)	<0.001
SBO	4 (7.7)	16 (6.0)	0.75
Ileus	13 (25.0)	28 (10.5)	0.007
Thrombotic events	5 (259.6)	4 (1.5)	0.007
Dehydration	2 (3.9)	7 (2.6)	0.64
Readmission	13 (25.0)	37 (13.9)	0.059
Reoperation	14 (26.9)	8 (3.0)	<0.001
Length of hospital stay (days)	12.7±10.0	5.9±4.0	<0.001

Data are presented as mean±SD or number (percentage)

Table 4 Multivariate analysis of factors associated with postoperative complications

Risk factors	OR	95 % CI	P value
Overall complications			
Transfusion	3.03	1.53 5.98	0.001
Preoperative biologic use	2.08	1.16 3.71	0.014
Preoperative steroid use	0.74	0.44 1.25	0.26
Preoperative immunomodulator use	1.83	1.01 3.30	0.046
ASA ≥ 3	0.67	0.34 1.31	0.24
Age at surgery	1.02	1.00 1.04	0.022
Intraoperative finding of fistula	0.62	0.36 1.07	0.086
Infectious complications			
Transfusion	8.73	2.85 26.77	<0.001
Preoperative biologic use	2.71	1.17 6.28	0.020
Preoperative steroid use	0.68	0.29 1.57	0.37
Preoperative immunomodulator use	3.03	1.24 7.38	0.015
ASA ≥ 3	0.60	0.20 1.82	0.37
Preoperative level of WBC	1.12	1.00 1.24	0.042
Noninfectious complications			
Transfusion	3.64	1.30 10.18	0.014
Age at surgery	1.03	1.00 1.07	0.027
EBL	1.00	1.00 1.01	0.046
BMI	1.05	0.99 1.10	0.073
Preoperative immunomodulator use	1.88	0.74 4.75	0.18
Disease behavior	0.56	0.28 1.10	0.092
Smoking status	1.37	0.85 2.23	0.20

complications (OR=6.19, 95 % CI 1.80–21.26, $P=0.004$), and noninfectious complications (OR=5.72, 95 % CI 1.72–19.02, $P=0.004$).

Postoperative Recurrence of CD

The mean duration of follow-up was 6.1 ± 4.1 years after the index ICR, and there was no significant difference between the transfused (5.4 ± 1.2) and nontransfused patients (6.3 ± 4.1) ($P=0.16$). Blood transfusion was found to be associated with both endoscopic ($P<0.001$) and surgical recurrence ($P<0.001$) (Fig. 1). In addition to blood transfusion, univariate analysis showed that family history of CD ($P=0.033$) and concomitant perianal disease ($P=0.013$) were associated with a higher risk, while older age at surgery was associated with a lower risk ($P=0.001$) for endoscopic recurrence. The factors associated with postoperative surgical recurrence were the presence of family history of CD ($P=0.006$), EIM ($P=0.01$), and intraoperative finding of abscess ($P=0.016$). The impact of postoperative complications on postoperative recurrence was also explored, considering the result that blood transfusion was associated with postoperative complications. However, we found that postoperative complications were not associated with either endoscopic ($P=0.54$) or surgical recurrence ($P=0.22$). To investigate a possible dose-dependent association of blood transfusion with postoperative disease recurrence, we compared the cumulated recurrence in patients who received 1 to 2 units or ≥ 3 units. We found that a greater number of units transfused were not associated with an increased risk for endoscopic recurrence ($P=0.46$) or surgical recurrence ($P=0.69$).

Multivariate analyses were performed to identify the independent risk factors for postoperative recurrence (Table 5). Transfusion (HR=2.08, 95 % CI 1.38–3.14, $P<0.001$) and concomitant perianal disease (HR=1.71, 95 % CI 1.14–2.57, $P=0.01$) were identified as risk factors for endoscopic recurrence. Interestingly, we found that older age at surgery was a

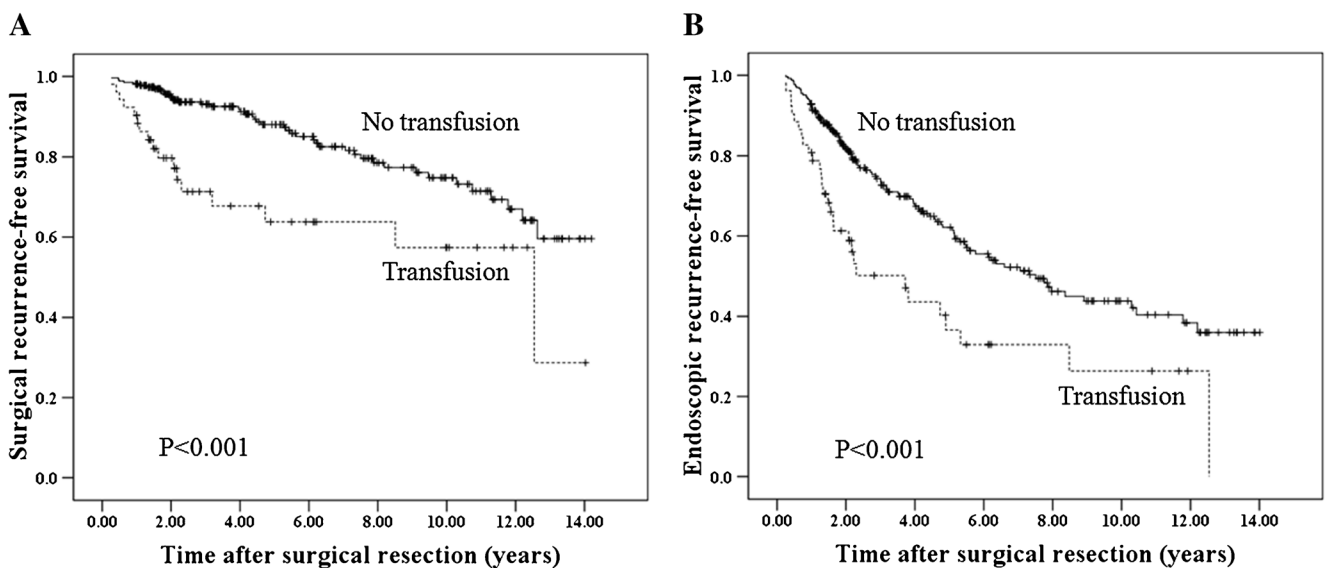


Fig. 1 Postoperative surgical recurrence-free survival (a) and endoscopic recurrence-free survival (b) in transfused and non-transfused patients

Table 5 Multivariate analysis of factors associated with postoperative recurrence

Risk factors	HR	95 % CI		P value
Surgical recurrence				
Transfusion	3.43	1.92	6.13	<0.001
Family history of CD	2.23	1.28	3.88	0.004
EIM	3.14	1.62	6.07	0.001
Intraoperative finding of abscess	2.64	1.29	5.39	0.008
Endoscopic recurrence				
Transfusion	2.08	1.38	3.14	<0.001
Family history of CD	1.42	0.96	2.10	0.079
Older age at surgery	0.55	0.38	0.81	0.002
Concomitant perianal disease	1.71	1.14	2.57	0.010

protective factor for postoperative endoscopic recurrence (HR=0.55, 95 % CI 0.38–0.81, $P=0.002$). Blood transfusion (HR 3.43, 95 % CI 1.92–6.13, $P<0.001$), family history of CD (HR 2.23, 95 % CI 1.28–3.88, $P=0.004$), EIM (HR=3.14, 95 % CI 1.62–6.07, $P=0.001$), and an intraoperative finding of abscess (HR=2.64, 95 % CI 1.29–5.39, $P=0.008$) were found to be factors associated with postoperative surgical recurrence.

Discussion

In this study, we attempted to determine whether perioperative blood transfusion was associated with adverse postoperative outcomes in patients undergoing the primary ICR for CD in the current “biological era.” We analyzed the data from our prospectively maintained registry and found that the overall 30-day postoperative morbidity rate was as high as 30 %. We also found that blood transfusion was associated with an increased risk for postoperative infectious complications, which is consistent with findings in the literature in patients undergoing non-CD alimentary tract surgeries.^{24,44,45} In addition, patients receiving blood transfusion had a higher rate of non-infectious complications than those without blood transfusion, which is also in concordance with previous reports in non-CD surgeries.^{46,48} Our data also showed that perioperative blood transfusion was associated with an increased risk for postoperative endoscopic as well as surgical recurrence of CD.

The association between blood transfusion and postoperative infectious complications has been demonstrated by multiple reports in patients undergoing surgery for alimentary tract malignancies.^{18,49–52} A study of 169 patients undergoing bowel resection for CD showed that the risk of postoperative septic complications was related to the number of units of blood transfused.³³ The increased postoperative infectious complications observed in patients receiving blood transfusion may result from the increased inflammatory response or

immunosuppression from transfused red blood cells.^{12,13} The findings of our study suggest that patients receiving perioperative blood had an increased frequency of postoperative infectious complications, independent of other known preoperative risk factors, such as surgical indications, family history of IBD, and the use of immunomodulators or anti-TNF biologics. Anti-TNF agents have increasingly been used in patients with CD. The adverse impact of these immunosuppressive medications on surgical outcomes has been debated and the effect of preoperative use of biologics on postoperative infectious complications in CD or UC has been controversial.^{6,29,53,54} In this study, we again found that the preoperative use of anti-TNF biologics was associated with postoperative complications. Importantly, we demonstrated that blood transfusion was a risk factor for postoperative complications in addition to the preoperative use of biologics.

Reported risk factors for postoperative recurrence of CD include younger age at the onset of disease, smoking, family history of IBD, type of anastomotic configuration, gender, and submucosal plexitis in proximal resection margins on histopathology.^{55–58} The main finding of our study was that there was an association between blood transfusion and postoperative endoscopic as well as surgical recurrence in CD patients after initial ICR. In an early study including 60 patients who underwent small bowel resection, Williams et al. reported that transfused patients had a significantly lower recurrence rate, suggesting that the immunosuppressive effect of blood transfusion may modify the progression of CD.^{24,37} In a separate study of 79 patients, Peters et al. found that perioperative blood transfusion was associated with a decreased rate of recurrence of CD.³⁸ The protective effect of perioperative blood transfusion on the postoperative recurrent CD was further confirmed in parous women.^{59,60} In contrast, a UK study of 197 patients undergoing right hemi-colectomy showed that perioperative blood transfusion had no impact on the development of recurrent CD.^{34,35} Hollaar et al. published the results of a pooled analysis with 622 patients by evaluating the effect of perioperative blood transfusion on the recurrence of CD.⁶¹ In the study, the investigators found comparable rate of disease recurrence of CD between transfused and nontransfused patients. Therefore, the reported results on the association between perioperative blood transfusion and postoperative CD recurrence have been inconsistent in the literature.^{34,35,37,38} One of the main causes for the discrepancy may be due to the heterogeneity of the studied populations. In the present study, we found that there was an association between blood transfusion and postoperative endoscopic recurrence as well as surgical recurrence in a relatively homogeneous CD patient population after the index ICR, although there was a lack of dose-dependent association between transfusion and disease recurrence.

The exact mechanisms of the adverse impact of perioperative complication and disease recurrence in CD are not clear.

The first notice of the link between the transfusion of blood or blood products and immune suppression dates back to 1970s.⁶² The whole constellation of transfusion-associated immune response have been referred as transfusion-related immune modulation effect.¹¹ Theoretically, CD patients undergoing surgical resection may benefit from the transfusion-related immune modulation.^{63–65} In addition to its downregulation of host's immune response,^{15–66–69} blood transfusion also has been shown to have proinflammatory effects which may trigger the perpetuation of chronic inflammation in the host. Other explanation for the implications of blood transfusion in the disease recurrence is based on the fact that CD may be an immune defective disease as suggested by some authors.^{70–71} It is speculated that a constitutionally compromised immune response may be related to the granuloma formation and chronic inflammation in CD, and one of the contributing factors is the extensive use of immunosuppressive agents.^{72–74} The transfusion-related immunosuppression can aggravate the aberrant immune response in patients with CD, which may subsequently facilitate the disease recurrence. However, we did not detect the dose-dependent association between transfusion and CD recurrence, implying that the effect of blood transfusion may be an “all-or-none” phenomenon. This is in contrast to the reported dose-dependent association between the volume of blood transfusion and cancer recurrence or survival rate in patients with malignancies.^{75–77}

Our study has several clinical implications. The risks and benefits of perioperative blood transfusion should be carefully balanced in CD patients undergoing the initial ICR. We found that more than 50 % patients had received 1 or 2 units of blood transfusion during the perioperative period. Of those patients, some could have benefited from the avoidance of transfusion exposure. Clinicians may refrain from over transfusion in CD patients undergoing bowel resection, especially with severe immunosuppression or poor nutrition status.

The main limitation to our study is its generalizability, as the study population was restricted to CD patients with the index ICR in a tertiary care center. The findings may not be applicable to CD patients with stricturoplasty, recurrent anastomotic stricture, and upper gastrointestinal tract CD. Secondly, the status of postoperative prophylaxis was not controlled and this might have affected outcomes. The main strength of our study, however, is that we were able to evaluate the association between blood transfusion and recurrent CD in a large historical cohort study. Furthermore, the study population is rather homogenous, as patients included in this study were those undergoing the first ICR. While the study design, minimizing confounding factors, it does affect the generalizability. Finally, the sample size may be not large enough to include all variables in the multivariable analyses, even though, this was the first study performed in the current biological era evaluating the association between transfusion and CD recurrence.

In conclusion, our study showed that patients with ICR for CD receiving perioperative blood transfusion are at a higher risk for postoperative complications as well as postoperative disease recurrence.

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