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Original Research Article

Peri-operative blood transfusion and risk of infectious complications following intestinal-cutaneous fistula surgical repair: A retrospective nationwide analysis

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ABSTRACT

Background: Peri-operative blood transfusion (BT) may lead to transfusion-induced immunomodulation. We aimed to investigate the association between peri-operative BT and infectious complications in patients undergoing intestinal-cutaneous fistulas (ICF) repair.

Methods: We queried the ACS-NSQIP 2006–2017 database to include patients who underwent ICF repair. The main outcome was 30-day infectious complications. Univariate and multivariable logistic regression analyses were performed to assess the predictors of post-operative infections.

Results: Of 4,197 patients included, 846 (20.2%) received peri-operative BT. Transfused patients were generally older, sicker and had higher ASA (III–V). After adjusting for relevant covariates, patients who received intra and/or post-operative (and not pre-operative) BT had higher odds of infectious complications compared (OR = 1.22, 95% CI 1.01–1.48). Specifically, they had higher odds of organ-space surgical site infection (OR = 1.61, 95% CI 1.21–2.13), but not other infectious complications.

Conclusions: Intra and/or post-operative (and not pre-operative) BT is an independent predictor of infectious complications in ICF repair.

Introduction

Infectious complications occur in about 36% of patients undergoing intestinal-cutaneous fistula (ICF) repair and are associated with worse long-term outcomes such as failure of spontaneous fistula closure.[1,2] In addition, sepsis is the leading cause of death in ICF patients.[3,4] Patients undergoing ICF repair often have multiple risk factors for developing postoperative infectious complications, including the complexity of the surgical procedures performed, in addition to patient specific factors that may increase the risk for these complications, such as preoperative anemia, malnutrition, and immunosuppression state.[5,6]

Patients with ICFs commonly require blood transfusions (BT). There are many reasons this population may be anemic, including acute blood loss anemia, nutritional deficits, and anemia of chronic disease. However, BT has been shown to have negative effects on surgical outcomes. BT has been associated with increased rates of cancer recurrence, as well as increased rates of post-operative bacterial infections in both adult and pediatric surgical populations.[7–13] This is thought to be related to transfusion-induced immunomodulation (TII), in which BT has adverse effects on the recipient's immune response.[14] Therefore, efforts have been made to reduce the use of BT perioperatively. However, the effect of perioperative BT on surgical outcomes in patients undergoing surgical repair of ICFs remains unknown.

As patients with ICFs are likely to receive a BT, we have a critical need to understand the effects of transfusions in patient undergoing surgical repair of ICFs. Therefore, we aimed to investigate the association between peri-operative BT and post-operative infectious complications in patients undergoing ICF repair. Additionally, we aimed to evaluate whether there is a difference in infectious outcomes in patients receiving a pre-operative BT compared to those who only received an intra and/or post-operative BT.

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Methods

Study population, setting and design

We conducted a retrospective cohort study using the American College of Surgeon National Surgical Quality Improvement Program (ACS-NSQIP) database. ACS-NSQIP is a nationwide database with data on surgical outcomes collected prospectively at participating centers for quality improvement purposes. As of 2017, 708 hospitals provided their data for the ACS-NSQIP database.[15] We included adult patients (≥18-year-old) who underwent ICF surgical repair between 2006 and 2017. ICF was defined as an abnormal connection between the skin and the small bowel or large bowel. ICF repair was identified using Current Procedural Terminology (CPT) code '44640'. Both patients undergoing ICF repair as a primary or secondary procedure were included. Patients were excluded from the final cohort if they had a diagnosis of any other type of fistula, including rectovaginal fistula, colovesical fistula, vesicovaginal fistula, and perianal fistula. To limit post-operative complications from non-ICF repair, patients were also excluded if they underwent certain surgical procedures concomitantly with ICF repair. These procedures were: resection of rectum; creation, resection, or revision of ileoanal reservoir; any gastric procedure except for gastrostomy tube; repair or resection of duodenum; any procedure of the anus; any hepatobiliary procedure except for cholecystectomy and liver biopsy; any pancreatic procedure; any repair of the bladder; and excision of any tumor.

We identified patients who underwent a small bowel resection (CPT codes: 44110, 44120, 44121, 44125, 44130, 44202, 44203), ileostomy/jejunostomy including revision (44310, 44312, 44314), enterorrhaphy (44602, 44603), colectomy (44139, 44140, 44141, 44143: 44144: 44145, 44146, 44147, 44150, 44155, 44160, 44204, 44205, 44206, 44207, 44208, 44210, 44213, 44227), colostomy (44345, 44346), drainage of intra-abdominal abscess (49020, 49021, 49060), ventral hernia repair (49560, 49561, 49565, 49566, 49568, 49654, 49655), myocutaneous/fasciocutaneous flaps (15734), and debridement of abdominal wall (11005, 11008).

Study variables and outcomes

Peri-operative BT was defined based on two ACS-NSQIP variables as at least 1 unit of packed red blood cell transfusion as follows: 1. *Pre-operative*: within 72 h before surgery, 2. *Intra-operative and/or post-operative*: anytime during surgery and/or within 72 h after surgery. The main outcome was 30-day post-operative infectious complications. These include superficial, deep, and organ-space surgical site infection (SSI), wound dehiscence, pneumonia, urinary tract infection (UTI), and sepsis (including septic shock). Pre-operative anemia was defined as hematocrit less than 40% in male patients and less than 36% in females. We defined 30-day recurrence using the International Classification of Diseases, 9th Revision (ICD-9) (569.81, 998.6 and 537.4) and ICD-10 (K63.2) codes from readmission and reoperation variables. To account for frailty, we used the 5-item modified Frailty Index (mFI-5).[16] The 5 variables composing mFI-5 are diabetes mellitus (DM), hypertension (HTN), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and functional dependence at baseline. Functional dependence was defined as a patient's partial or total assistance from another person to perform activities of daily living 30 days prior to surgery, including but not limited to dressing, bathing, toileting, eating, and ambulating.[17] Each variable of the mFI-5 received a value of 0.2. The mFI-5 was calculated by multiplying number of variables present by 0.2. The maximum mFI-5 score is 1 (0.2 multiplied by 5). If the patient had a missing component of the mFI-5 we considered that component to be equal to zero and we did not include it in the denominator.

The study outcome was 30-day post-operative infectious complications. These include surgical site infection (SSI), including superficial, deep, and organ-space SSI as well as wound dehiscence, urinary tract infection (UTI), pneumonia, and sepsis.

Statistical analyses

Patient characteristics and other potential predictors of post-operative infection were compared between those who received peri-operative BT and those who did not using univariate analysis: for categorical variables chi-squared or Fisher's exact tests were used as appropriate; and for continuous variables, means were compared using *t*-test or Wilcoxon rank sum test. Multivariable logistic regression analyses were performed to assess the predictors of overall post-operative infectious complications and for each specific infectious complication. Covariates were included in the models if their p-value was <0.2 in the univariate analysis. All statistical analyses were performed using StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.

Results

Patient characteristics

Of the 4,197 patients that underwent ICF repair, 846 (20.2%) received peri-operative BT; 743 (87.8%) of them received intra and/or post-operative BT only, 43 (5.1%) received pre-operative BT only, and 60 (7.1%) received both. For those who received at least intra and/or post-operative BT (n = 803), 799 (99.5%) received one unit of RBCs, while three patients received two units and one patient received three units. Compared to non-transfused patients (Table 1), peri-operative BT patients were older (median [interquartile range, IQR] = 59 [49, 68] vs 57 [46, 67], $p < 0.001$), more likely to be female (516 [61.0%] vs 1,744 [52.1%], $p < 0.001$), had lower body mass index (BMI) [median (IQR) 27.1 (22.4, 32.8) vs 27.9 (23.2, 33.7), $p = 0.003$], had higher ASA (III–V) classes ($p < 0.001$) and mFI-5 (0.2–0.8) scores ($p = 0.002$). Transfused patients were more likely to also have dirty or infected surgical wounds (379 [44.8%] vs 1,179 (35.2%), $p < 0.001$).

In terms of baseline comorbidities, peri-operative BT patients were more likely to be functionally dependent and comorbid. For example, they were more likely to have diabetes, congestive heart failure, significant weight loss, chronic kidney disease (requiring dialysis), ascites, ventilatory dependence, metastatic cancer, and bleeding disorder. Moreover, pre-operative anemia, hypoalbuminemia, pre-operative wound infection, and sepsis were more likely in the peri-operative BT cohort, all $p < 0.05$.

Outcomes

Overall, patients with peri-operative BT had higher in-hospital and 30-day complications (Table 2). They had higher hospital length of stay (median [IQR] 19 [11, 32] vs 9 [6, 16] days, $p < 0.001$), spent more time in the operation room (median [IQR] 284 [193, 397] vs 189 [116, 275] minutes, $p < 0.001$) and were more likely to be discharged to a nursing facility (150 [23.7%] vs 231 [11.5%)], $p < 0.001$). Generally, post-operative infectious complications were higher in the peri-operative BT cohort compared to non-transfused group (412 [48.7%] vs 1080 [32.2%], $p < 0.001$). More specifically, they had higher organ-space SSI (141 [16.7%] vs 284 [8.5%], $p < 0.001$), wound dehiscence (56 [6.6%] vs 151 [4.5%] $p = 0.011$), pneumonia (71 [8.4%] vs 145 [4.3%], $p < 0.001$), UTI (58 (6.9%) vs 148 [4.4%], $p = 0.003$) and sepsis (including septic shock) [241 (28.5%) vs 509 (15.2%), $p < 0.001$).

Table 1
Comparison of patient and surgery characteristics and comorbidities between patients with and without peri-operative blood transfusion in enterocutaneous fistula surgical repair cohort.

Variable	Without peri-operative blood transfusion, n (%)	With peri-operative blood transfusion, n (%)	*p*-value
Total number of patients	3351 (79.8)	846 (20.2)	
Age, median (IQR)	57 (46, 67)	59 (49, 68)	< **0.001**
Age categories			
<20	23 (0.7%)	4 (0.5%)	**0.007**
20–40	548 (16.4%)	97 (11.5%)	
40–60	1318 (39.3%)	339 (40.1%)	
60–80	1313 (39.2%)	362 (42.8%)	
>80	149 (4.4%)	44 (5.2%)	
Female	1744 (52.1)	516 (61.0)	< **0.001**
Race			
White	2693 (80.4)	655 (77.4)	**0.015**
Asian, Hawaiian or Pacific Islander	39 (1.2)	13 (1.5)	
African American	20 (0.6)	4 (0.5)	
American Indian or Alaska Native	316 (9.4)	112 (13.2)	
Unknown	283 (8.4)	62 (7.3)	
BMI categories			
Underweight	154 (4.7)	61 (7.3)	**0.002**
Normal weight	956 (28.9)	267 (32.0)	
Overweight	918 (27.7)	202 (24.2)	
Obese	1281 (38.7)	305 (36.5)	
BMI, median (IQR)	27.9 (23.2, 33.7)	27.1 (22.4, 32.8)	**0.003**
Current smoker within 1 year	775 (23.1)	169 (20.0)	0.050
Alcohol drinking (> 2 drinks/day in 2 weeks before admission)	19 (1.3)	1 (0.5)	0.36
ASA classes	34 (1.0)	2 (0.2)	< **0.001**
ASA I	34 (1.0)	2 (0.2)	< **0.001**
ASA II	1041 (31.1)	117 (13.9)	
ASA III	2049 (61.2)	586 (69.6)	
ASA IV	222 (6.6)	136 (16.2)	
ASA V	1 (<1)	1 (0.1)	
mFI-5			
0	1638 (48.9%)	360 (42.6%)	**0.002**
0.2	1106 (33.0%)	284 (33.6%)	
0.4	468 (14.0%)	148 (17.5%)	
0.6	119 (3.6%)	46 (5.4%)	
0.8	18 (0.5%)	7 (0.8%)	
1.0	2 (0.1%)	1 (0.1%)	
mFI-5, median (IQR)	0.2 (0, 0.2)	0.2 (0, .2)	< **0.001**
Emergency vs elective surgery	151 (4.5)	51 (6.0)	0.065
Surgical wound class			
Clean	43 (1.3)	8 (0.9)	< **0.001**
Clean-contaminated	1178 (35.2)	238 (28.1)	
Contaminated	951 (28.4)	221 (26.1)	
Dirty or infected	1179 (35.2)	379 (44.8)	
Baseline comorbidities			
Diabetes on oral agents or insulin	540 (16.1)	172 (20.3)	**0.004**
Hypertension requiring medications	1319 (39.4)	343 (40.5)	0.530
Severe COPD	244 (7.3)	65 (7.7)	0.690
On steroid for any chronic condition	364 (10.9)	98 (11.6)	0.550
Ascites	13 (0.4)	11 (1.3)	**0.002**
CHF in 30 days before surgery	29 (0.9)	16 (1.9)	**0.010**
Functionally dependent prior to surgery	349 (10.5)	155 (18.5)	< **0.001**
Ventilator dependent	24 (0.7)	12 (1.4)	**0.048**
Weight loss >10% in last 6 months	238 (7.1)	94 (11.1)	< **0.001**
Bleeding disorders	182 (5.4)	94 (11.1)	< **0.001**
Cancer metastasis	100 (3.0)	41 (4.8)	**0.007**
AKI before surgery	9 (0.3)	7 (0.8)	**0.018**
On renal dialysis before surgery	30 (0.9)	27 (3.2)	< **0.001**
Wound infection before surgery	1602 (47.8)	511 (60.4)	< **0.001**
Sepsis before surgery	301 (9.0)	150 (17.8)	< **0.001**
Pre-operative anemia	1968 (62.0)	720 (86.6)	< **0.001**
Low serum albumin before surgery	682 (27.4)	383 (51.4)	< **0.001**

*BMI: body mass index; mFI-5: modified Frailty Index-5; COPD: chronic obstructive pulmonary disease; CHF: congestive heart failure; AKI: acute kidney injury.

Patients who received peri-operative BT had higher risk of non-infectious complications within 30 days of surgery compared to non-transfused patients. For example, they had higher risk of deep vein thrombosis (35 [4.1%] vs 54 (1.6%), $p < 0.001$), pulmonary embolism (14 [1.7%] vs 22 [0.7%], $p = 0.005$), stroke (6 [0.7%] vs 6 [0.2%], $p = 0.010$), myocardial infarction (10 [1.2%] vs 12 [0.4%], $p = 0.003$), cardiac arrest requiring cardiopulmonary resuscitation (15 [1.8%] vs 19 [0.6%], $p < 0.001$), and acute kidney injury (38 [4.5%] vs 51 [1.5%], $p < 0.001$). Moreover, those patients were more likely to return to the operation room (103 [16.5%] vs 170 [9.2%], $p < 0.001$), required unplanned intubation (78 [9.2%] vs 120 [3.6%], $p < 0.001$), and required to be on the ventilator for more than 2 days (117 (13.8%) vs 155 [4.6%], $p < 0.001$). Finally, they had a higher 30-day mortality rate (41 [4.8%] vs 54 [1.6%], $p < 0.001$) and 30-day re-

Table 2
Comparison of patient outcomes between patients with and without peri-operative blood transfusion in enterocutaneous fistula surgical repair cohort.

Variable	Without peri-operative blood transfusion, n (%)	With peri-operative blood transfusion, n (%)	p-value
Length of total hospital stay, median (IQR)	9 (6, 16)	19 (11, 32)	< **0.001**
Total operation time (minutes), median (IQR)	189 (116, 275)	284 (193, 397)	< **0.001**
Discharge disposition to a nursing home facility	231 (11.5%)	150 (23.7%)	< **0.001**
30-day infectious complications			
Superficial SSI	337 (10.1%)	68 (8.0%)	0.076
Deep SSI	160 (4.8%)	51 (6.0%)	0.140
Organ-space SSI	284 (8.5%)	141 (16.7%)	< **0.001**
Wound dehiscence	151 (4.5%)	56 (6.6%)	**0.011**
Pneumonia	145 (4.3%)	71 (8.4%)	< **0.001**
UTI	148 (4.4%)	58 (6.9%)	**0.003**
Sepsis (including septic shock)	509 (15.2%)	241 (28.5%)	< **0.001**
Any infectious complication	1080 (32.2%)	412 (48.7%)	< **0.001**
Other 30-day complications			
DVT	54 (1.6%)	35 (4.1%)	< **0.001**
PE	22 (0.7%)	14 (1.7%)	**0.005**
AKI	51 (1.5%)	38 (4.5%)	< **0.001**
Stroke	6 (0.2%)	6 (0.7%)	**0.010**
Cardiac arrest that requires CPR	19 (0.6%)	15 (1.8%)	< **0.001**
MI	12 (0.4%)	10 (1.2%)	**0.003**
Return to the operation room	170 (9.2%)	103 (16.5%)	< **0.001**
Unplanned intubation	120 (3.6%)	78 (9.2%)	< **0.001**
Ventilator >48 h	155 (4.6%)	117 (13.8%)	< **0.001**
Mortality	54 (1.6%)	41 (4.8%)	< **0.001**
30-day re-admission	298 (8.9%)	82 (9.7%)	0.470
30-day re-operation	195 (5.8%)	117 (13.8%)	< **0.001**
30-day ICF recurrence	20 (0.6%)	6 (0.7%)	0.710

SSI: surgical site infection; UTI: urinary tract infection; DVT: deep vein thrombosis; PE: pulmonary embolism; AKI: acute kidney injury; CPR: cardiopulmonary resuscitation; MI: myocardial infarction.

operation rate (117 [13.8%] vs 195 [5.8%], p < 0.001). However, there was no difference between the transfused and non-transfused cohorts in terms of 30-day re-admission (82 [9.7%] vs 298 [8.9%], p = 0.470) and 30-day recurrence (6 [0.7%] vs 20 (0.6%), p = 0.710).

In a sub-analysis, patients who underwent small bowel ICF repair and received peri-operative BT were more likely to develop infectious complications more specifically organ-space SSI (41 [16.9%] vs 82 [10.6%], p = 0.009), wound dehiscence (19 [7.8%] vs 35 [4.5%], p = 0.047), and sepsis/septic shock (72 [29.6%] vs 156 [20.2%], p = 0.002) compared to those who did not receive BT (Table 3). Similarly, those who had colonic ICF takedown and received peri-operative BT were more likely to develop post-operative infections particularly deep SSI (14 [8.4%] vs 26 [4.3%], p = 0.037), organ-space SSI (30 [18.0%] vs 54 [9.0%], p = 0.001), pneumonia (12 [7.2%] vs 14 [2.3%], p = 0.002), UTI (11 [6.6%] vs 15 [2.5%], p = 0.010), and sepsis/septic shock (50 [29.9%] vs 78 [13.0%], p < 0.001) compared to non-transfused group.

After adjusting for relevant covariates including demographics, comorbidities (including frailty and preoperative anemia) and operative details (Table 4), peri-operative BT did not seem to influence post-operative infectious complications (OR = 1.16, 95% CI 0.96–1.40, p = 0.132). However, intra- and/or post-operative (and not pre-operative) BT was an independent determinant for infectious complications (OR = 1.22, 95% CI 1.01–1.48, p = 0.039) [Table 5]. Therefore, we looked at the association between intra- and/or post-operative BT and each specific post-operative infectious complication (Table 6). Intra- and/or post-operative BT group had higher odds of organ-space SSI (OR = 1.61, 95% CI 1.21–2.13, p = 0.001), but not deep SSI (OR = 1.03, 95% CI 0.69–1.54, p = 0.897), wound dehiscence (OR = 1.32, 95% CI 0.65–2.72, p = 0.65–2.72), UTI (OR = 0.82, 95% CI 0.56–1.21, p = 0.325) or sepsis (OR = 0.82, 95% CI 0.80–1.84, p = 360). Intra- and/or post-operative BT was associated with lower odds of superficial SSI (OR = 0.68, 95% CI 0.49–0.95, p = 0.023).

Table 3
Univariate analysis comparing post-operative infectious complications in patients who received perioperative blood transfusion vs those who did not, following intestinal-cutaneous small bowel or colonic fistula surgical repair.

Variable	Small bowel procedures			Colonic procedures		
	Without peri-operative blood transfusion, n (%)	With peri-operative blood transfusion, n (%)	p-value	Without peri-operative blood transfusion, n (%)	With peri-operative blood transfusion, n (%)	p-value
Total number of patients	771 (76.0%)	243 (24.0%)	–	601 (78.3%)	167 (21.7%)	–
Superficial SSI	77 (10.0%)	23 (9.5%)	0.810	60 (10.0%)	14 (8.4%)	0.540
Deep SSI	50 (6.5%)	13 (5.3%)	0.520	26 (4.3%)	14 (8.4%)	**0.037**
Organ-space SSI	82 (10.6%)	41 (16.9%)	**0.009**	54 (9.0%)	30 (18.0%)	**0.001**
Wound dehiscence	35 (4.5%)	19 (7.8%)	**0.047**	17 (2.8%)	9 (5.4%)	0.110
Any SSI	176 (22.8%)	79 (32.5%)	**0.002**	118 (19.6%)	48 (28.7%)	**0.011**
Pneumonia	41 (5.3%)	19 (7.8%)	0.150	14 (2.3%)	12 (7.2%)	**0.002**
UTI	43 (5.6%)	19 (7.8%)	0.200	15 (2.5%)	11 (6.6%)	**0.010**
Sepsis (including septic shock)	156 (20.2%)	72 (29.6%)	**0.002**	78 (13.0%)	50 (29.9%)	< **0.001**
Any infectious complications	279 (36.2%)	127 (52.3%)	< **0.001**	174 (29.0%)	80 (47.9%)	< **0.001**

Table 4
Multivariable (logistic regression) analysis of potential determinants of post-operative infections following enterocutaneous fistula surgical repair.

Independent variable	OR	p value	95% CI
Age categories			
<20	Base (1.00)		
20-40	1.11	0.845	0.40–3.05
40-60	0.91	0.848	0.33–2.48
60-80	0.88	0.808	0.32–2.43
>80	0.50	0.207	0.17–1.47
Gender: female vs male	0.99	0.863	0.84–1.15
BMI categories			
Underweight	Base (1.00)		
Normal weight	0.89	0.502	0.63–1.25
Overweight	0.84	0.324	0.59–1.19
Obese	0.88	0.464	0.62–1.24
ASA classes			
ASA I	Base (1.00)		
ASA II	1.89	0.324	0.53–6.74
ASA III	2.43	0.171	0.68–8.61
ASA IV	2.75	0.125	0.75–10.02
ASA V	1.90	0.682	0.09–40.95
mFI-5	2.20	**0.001**	**1.37–3.52**
Baseline comorbidities			
Bleeding disorders	1.35	**0.042**	**1.01–1.79**
Cancer metastasis	0.98	0.939	0.67–1.46
On renal dialysis before surgery	1.28	0.429	0.69–2.37
Wound infection before surgery	1.13	0.114	0.97–1.33
Sepsis before surgery	1.19	0.148	0.94–1.51
Preoperative anemia	1.19	0.058	0.99–1.43
Weight loss (>10%) the last 6 months	0.85	0.252	0.65–1.12
Low serum albumin before surgery	1.41	< **0.001**	**1.19–1.68**
Type of surgery: emergency vs elective	1.43	0.046	1.01–2.03
Surgical wound class			
Clean	Base (1.00)		
Clean/Contaminated	1.36	0.458	0.60–3.05
Contaminated	1.89	0.124	0.84–4.26
Dirty/Infected	1.89	0.124	0.84–4.24
Total operation time, median (IQR)	1.00	< **0.001**	**1.00–1.00**
Peri-operative blood transfusion	1.16	0.132	0.96–1.40

ASA: American Society of Anesthesiologists; BMI: body mass index; mFI: modified Frailty Index.

Discussion

We used a nationwide database to identify the association between peri-operative blood transfusion and infectious complications. Post-operative infections are a significant driver of morbidity in patients with ICFs. There are many reasons why this population is at a greater risk of infectious complications. For example, several studies have shown preoperative anemia, malnutrition, immunosuppression, presence of bacteria in fistula tract, and preoperative enteral nutrition for less than 3 months to be associated with higher risk of infectious complications following ICF repair.[3,5,6,18,19] However, the relationships between peri-operative BT and these infectious complications has not been studied before.

Our results show that ICF patients who received peri-operative BT were older, with lower body mass index (BMI), and more likely to be frail with more comorbidities. On average, they had longer operative times and hospital stays. In multivariable analyses, we showed that intra- and/or post-operative BT was an independent determinant for post-operative infections. Pre-operative BT, however, was not found to influence the risk of infectious complications. Intra- and/or post-operative BT, in particular was found to be associated with organ-space SSI but not with other infectious complications.

Table 5
Multivariable (logistic regression) sub-analysis of potential determinants of post-operative infections (dependent outcome variable) following enterocutaneous fistula surgical repair.

Independent variable	OR	p value	95% CI
Intra- and or postop- transfusion	**1.22**	**0.039**	**1.01–1.48**
Pre-operative transfusion	0.75	0.199	0.48–1.16

Table 6
Multivariable logistic regression analyses for different post-operative infectious complications with *intra and/or post-operative* blood transfusion as one of the independent covariates.

Outcome (dependent) variable	OR	*p*-value	95% CI
Superficial SSI	**0.68**	**0.023**	**0.49–0.95**
Deep SSI	1.03	0.897	0.69–1.54
Organ-space SSI	**1.61**	**0.001**	**1.21–2.13**
Wound dehiscence	1.32	0.473	0.65–2.72
Pneumonia	1.08	0.671	0.75–1.57
UTI	0.82	0.325	0.56–1.21
Sepsis (including septic shock)	1.21	0.36	0.80–1.84
Any infectious complication	**1.22**	**0.039**	**1.01–1.48**

In our study, 51.4% of those who received peri-operative BT had pre-operative hypoalbuminemia compared to only 27.4% of those who did not ($p < 0.001$). In addition, hypoalbuminemia was a significant predictor of infectious complications in the multivariable logistic regression analysis (OR = 1.4, 95% CI 1.2–1.7). However, albumin is a negative acute phase reactant and therefore it is difficult to show that malnutrition (which is commonly indicated by low albumin) is a contributing factor to development of infectious complications in those patients.[20,21] Despite that, malnutrition is likely to have played a role but this needs to be confirmed through other more accurate measures of nutritional status.

Our findings are in line with other studies that confirmed the association between peri-operative blood transfusion and infectious complications in non-ICF patients.[22–26] For example, Lan et al. found peri-operative BT to be associated with higher risk of infectious complications including SSI (of all types), pneumonia, UTI and sepsis/septic shock compared to non-transfused group in patients undergoing surgery for Crohn's disease in their univariate analysis.[25] However, they did not run a multivariable analysis to assess if the association remained in each infectious complication. Bernard et al. showed that intra-operative BT was associated with worse outcomes including SSI, pneumonia, and sepsis/septic shock in general surgery patients after adjusting for patient and operative characteristics in their multivariable logistic regression analysis.[26]

Although the exact mechanism of this association has not been proven yet, the most believed theory is TII. Studies[27,28] have shown several immunomodulators, mainly interleukin-6, are highly expressed after surgery in patients who receive peri-operative BT. TII is also believed to play a role in lower rejection rates of renal allotransplantation and increased recurrence rates of solid tumors in patients who received peri-operative BT.[29]

Our study has some important strengths including the nationwide nature of the ACS-NSQIP database which provides a reasonably large sample size and therefore makes the results more representative to the population. Our study is the first and largest study evaluating the association between peri-operative BT and post-operative infections in ICF patients undergoing surgery. We have adjusted for confounding factors including baseline comorbidities, such as pre-operative anemia and operative details such as operative time, wound class, and type of surgery. Finally, we performed sub-analyses to first determine the relationship between the timing of BT in relation to surgery and post-operative infections and second to determine the exact association between intra/post-operative BT and each specific infectious complication.

The study has some limitations too. The ACS-NSQIP database does not provide information about intra-operative adverse events

especially those that require BT. However, we used the available operative details as proxy of intra-operative events. Similarly, residual confounders may have remained even after adjusting for available baseline characteristics and operative details in the multivariable analysis. The composite "intra/post-operative" BT variable in this database did not allow us to investigate whether intra-operative or post-operative BT is associated with post-operative infectious complications. As most of ICF surgical patients included in this cohort required one unit of BT, we could not assess the dose-dependency between BT and post-operative infectious complications. ACS-NSQIP database only contains 30-day outcomes, therefore we could not extrapolate the results to infectious complications that occurred beyond this time window. The differences in the fistula characteristics are largely unaccounted for in this study as the NSQIP dataset does not provide that level of granularity. Lastly, as with any retrospective studies using large datasets, establishing causality between BT and infectious complications is impossible and it is not the purpose of this study.

Conclusions

We have shown that intra and/or post-operative BT, and not pre-operative BT, is an independent predictor of infectious complications in ICF patients requiring repair. Adopting a judicious approach when ICF patients require BT around the time of surgery and correcting pre-operative anemia may help in mitigating these risks.

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Ethical approval

This study was approved by our Institutional Review Board. Data Use Agreement (DUA) was also signed to comply with ACS-NSQIP's regulations.

Declaration of competing interest

We declare no competing interest.

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