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The association between bowel resection and the risk of nontyphoidal salmonella infection: a nationwide propensity score-matched cohort study

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Nontyphoidal salmonella (NTS) infection has a high mortality rate. Bowel resections affect gut microbiota and immune function, and the association between bowel resection and NTS infection in human beings has not been addressed. We conducted a nationwide propensity score (PS)-matched cohort study to clarify this association. Data from the Longitudinal Health Insurance Database of Taiwan were used to establish a case-cohort with bowel resections from 2000 to 2013. Informed consent was waived by the Institutional Review Board of China Medical University Hospital (CMUH104-REC2-115) because all personal identifying information used had been de-identified. Each case was matched with one control without any bowel resection according to age, gender, index date, and propensity score (PS). Cumulative incidences of and hazard ratios (HRs) for NTS infection development were analyzed. The incidence of NTS infection was greater in patients with a bowel resection than in the control group (2.97 vs. 1.92 per 10,000 person-years), with an adjusted hazard ratio (aHR) of 1.64 (95% CI = 1.08–2.48). The incidence of NTS infection increased significantly for cases with small bowel resections and right hemicolectomies. Age (31–40 and > 50 years), hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and autoimmune diseases were significant risk factors of NTS infection. Stratification analysis revealed that patients without comorbidities were prone to NTS infection after bowel resections. The increased risk of developing NTS infection could be related to the bowel resection. Specific age groups and comorbidities also contribute to increased risk of NTS infection.

Nontyphoidal salmonella (NTS) infection is an important issue. The incidence of invasive NTS was 7.5 cases per 100,000 people worldwide in 2017¹. The main risk factors of hosts include extreme age, immunocompromised status and immunomodulator use^{2,3}. NTS bacteremia usually results in higher rate of mortality in patients with underlying diseases⁴.

Our gut mucosal immune system can keep pathobionts in check, restrict microbial overgrowth, and react to invading microorganisms that breach the intestinal chemical and physical barriers⁵. Several bacteria have some

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controlling effects on *S. enterica*, such as *Bifidobacterium thermophilum* and *Lactobacillus casei*^{6,7}. Argüello et al. discovered that manipulating certain taxa of microbiota could decrease salmonella infection for pigs⁸.

In human beings, bowel resection strongly influences gut microbiota and intestinal healing⁹. In the small intestine, the main reported bacterial species included Bacilli (Firmicutes), Streptococcaceae (Firmicutes), Actinobacteria, Clostridium and Bacteroides⁵. Phyla Bacteroidetes and Firmicutes can dominate the mucosa-associated bacteria from the distal small intestine and the colon⁵. Specialized bacteria (e.g., Clostridium, Lactobacillus, or Enterococcus) able to adhere to mucus (as a nutrient source) and different species in feces (belonging to Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus, and Ruminococcus) were identified⁵. Kunz et al. indicated that gastrectomy could lead to *S. enteritis*. This might result from relative or absolute achlorhydria, decreased hydrogen ion concentration, rapid emptying of food into the small intestine and the colon and altered bacterial flora¹⁰.

However, currently the association between bowel resection (except the stomach) and NTS infection was still not clarified. The present nationwide propensity score (PS)-matched cohort study was carried out in Taiwan to evaluate the risk of NTS infection after bowel resection.

Materials and methods

Data source and ethics statement. We extracted the claims-based data from the Longitudinal Health Insurance Database 2000 (LHID), which is a dataset included in Taiwan's National Health Insurance Research Database (NHIRD). The NHIRD contains patients' characteristics, medical information, total expenditure, and diagnoses coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. Taiwan's National Health Insurance (NHI) programme is administered by the government and covers more than 99% of the 23.4 million population of Taiwan¹¹. Data for the LHID were collected by systematically and randomly sampling from the NHIRD; this database includes the data of one million individuals. Information on demographic data, inpatient and outpatient cares, date of clinic visit or hospitalization, and prescriptions were available in the database for the period from 1997 to 2013. The NHRI reported no significant differences between the patients in the LHID and those in the original NHIRD¹². The studies involving human participants were reviewed and approved by the Institutional Review Board of China Medical University Hospital (approval number CMUH104-REC2-115). Written informed consent for participation was not required for this study in accordance with national legislation and institutional requirements. Our research adhered strictly in accordance with relevant guidelines/regulations.

Study subjects and design. A bowel resection-related case group was established, including patients aged 18 years and over who had received a bowel resection (small bowel, large bowel, or both) from 2000 to 2013. We included the cases identified by the procedure codes of 45.6 (small bowel resection), 45.73 (right hemicolectomy), 45.74 (transverse colon resection), 45.75 (left hemicolectomy), 45.76 (sigmoidectomy), 45.8 (total colectomy), or 45.9 (bowel anastomosis). We defined the index date as the operation date. We excluded patients with appendectomy/gastrectomy/cholecystectomy, any kind of cancer, human immunodeficiency virus infection, index dates out of the study period, diagnosis of NTS, or missing gender or aged under 18 before index dates (Fig. 1). The outcome was the development of NTS (ICD-9-CM codes: 003.xx) after the index date.

Propensity score matching and covariates. A matched control was assigned to each case (Fig. 1). We used the PS-matching method to account for baseline differences¹³. The observed covariates in the logistic regression model to generate the PS were hypertension (ICD9 codes: 401–405), diabetes (ICD9 code: 250), hyperlipidemia (ICD9 codes: 272), coronary artery disease (ICD9 codes: 410–414), cerebrovascular accident (430–438), chronic kidney disease (ICD9 code: 585), chronic obstructive pulmonary disease (COPD, ICD9 codes: 491, 492, 496), chronic liver disease (ICD9 code: 571.4), autoimmune diseases (including systemic lupus erythematosus, ICD9 code: 710.0; ankylosing spondylitis, ICD9 code: 720.0; rheumatoid arthritis, ICD-9-CM code: 714.0; Sjögren's syndrome, ICD-9-CM code: 710.2), psoriasis (ICD9 code: 696), vasculitis (ICD9 code: 446), and inflammatory bowel disease (IBD, including Crohn's disease, ICD9 codes: 555.x and ulcerative colitis, ICD9 codes: 556.x).

Statistical analysis. Chi-square test was used to determine the differences of baseline characteristics for categorical variables and Student's *t*-test was applied to examine continuous variables between case group (bowel resection) and the control group. Standardized mean difference (SMD) was used to assess the difference between the case group and the control group after PS matching; a value of <0.1 was considered negligible¹³. Incidence of NTS infection was estimated for both groups by the end of 2013. We used the Kaplan–Meier method to measure fractions free of NTS infection during the follow-up period in the two groups and used the log-rank test to examine the difference. Incidence rates (IRs) of NTS infection, per 10,000 person-years, were calculated for patients with or without bowel resections, gender, age group, occupation, and comorbidities. Cox proportional-hazards regression analysis was used to calculate the case group to the control group hazard ratio (HR) of NTS infection and 95% confidence interval (CI). Adjusted hazard ratio (aHR) was estimated after controlling for covariates. Gender-, age-, occupation-, and comorbidities-stratified analyses of NTS infection with or without bowel resection were conducted. All statistical analyses were performed using SAS software version 9.4 (SAS Institute INC., Carey, NC, USA). A two-tailed *p*-value below 0.05 was considered as significant.

Sensitivity analysis. According to Wu et al.¹⁴, a temporal association between the use of proton pump inhibitors and increased susceptibility to NTS was demonstrated, which would bias our results. Therefore, we

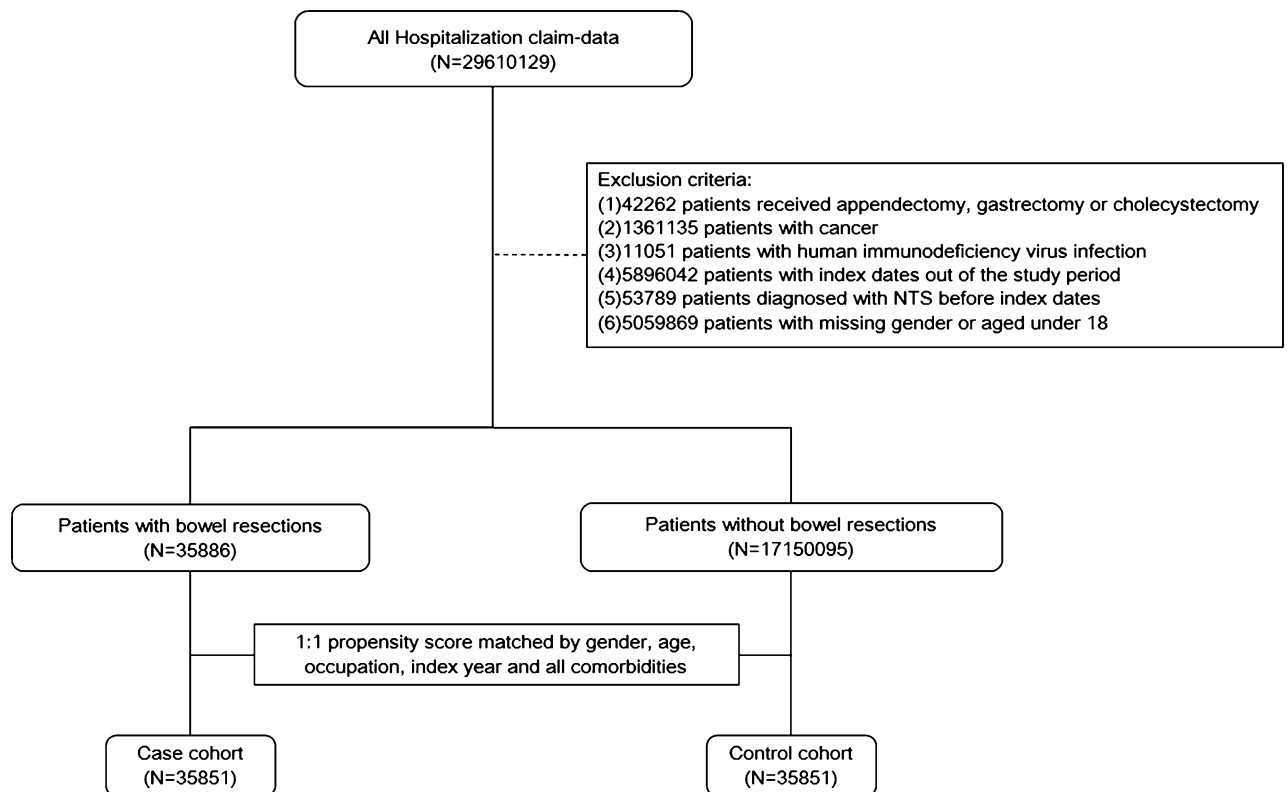


Figure 1. Study flowchart.

performed the sensitivity analysis by excluding peptic ulcer disease patients (ICD9 codes: 531, 532, 533, and 534) who had a high probability of taking proton pump inhibitors and PS matching.

Results

Demographic characteristics of patients. Our study population includes 35,851 cases and 35,851 controls. Table 1 shows that the male ratio and the mean age were 52% and 56.1 years in the case group, and 51% and 55.6 years in the control group, respectively. There was no significant difference in the baseline occupation and comorbidities. The overall median follow-up time was 4.53 years.

Cumulative incidence and risk of NTS infection. By the end of follow-up, the Kaplan–Meier analysis showed that the NTS infection was significantly more in the bowel resection group than in the control group ($p=0.03$) (Fig. 2). The IR of NTS infection was higher in the bowel resection group than in the control group (2.97 vs. 1.92 per 10,000 person-years), with an aHR of 1.64 (95% CI=1.08–2.48) for the bowel resection group (Table 2). Considering the location of bowel resection, the IR of NTS infection was higher in the small bowel resection group than in the control group (3.66 vs. 1.92 per 10,000 person-years), with an aHR of 1.96 (95% CI=1.20–3.19) for the small bowel resection group, and higher in the right hemicolectomy group than in the control group (3.32 vs. 1.92 per 10,000 person-years), with an aHR of 1.96 (95% CI=1.02–3.77) for the right hemicolectomy group. Besides, age (31–40 years, aHR of 4.71, 95% CI=1.05–21.1; > 50, aHR of 5.25, 95% CI=1.27–21.8), hypertension (aHR of 1.61, 95% CI=1.00–2.58), chronic kidney disease (aHR of 2.35, 95% CI=1.06–5.21), COPD (aHR of 2.18, 95% CI=1.18–4.02), and autoimmune disease (aHR of 3.83, 95% CI=1.4–10.47) also increased the risk of NTS infection significantly. Large bowel resection, left hemicolectomy, sigmoidectomy, total colectomy, and bowel anastomosis did not increase the NTS infection risk prominently.

Stratification analysis of nontyphoidal salmonella infection. The stratification analysis (Table 3) revealed that in those without comorbidities, compared with patients without bowel resections, patients who received bowel resections had significantly increased risk of NTS infection for those without hypertension (aHR of 2.34, 95% CI=1.3–4.22), diabetes (aHR of 2.11, 95% CI=1.29–3.46), hyperlipidemia (aHR of 1.91, 95% CI=1.22–2.98), coronary artery disease (aHR of 1.82, 95% CI=1.15–2.88), cerebrovascular accident (aHR of 1.59, 95% CI=1.03–2.46), chronic kidney disease (aHR of 1.56, 95% CI=1.01–2.39), COPD (aHR of 1.85, 95% CI=1.17–2.93), chronic liver disease (aHR of 1.62, 95% CI=1.05–2.48), vasculitis (aHR of 1.64, 95% CI=1.08–2.48), or IBD (aHR of 1.59, 95% CI=1.04–2.42). The significant association between bowel resection and NTS infection was not found in each age group of all patients, different genders, different occupations, patients without autoimmune disease or psoriasis, and patients with comorbidities.

Variables	Bowel resection				SMD
	No (n = 35,851)		Yes (n = 35,851)		
	n	%	n	%	
Gender					0.01
Female	17,522	49%	17,300	48%	
Male	18,329	51%	18,551	52%	
Age, year					
18–30	3418	10%	3229	9%	0.02
31–40	4788	13%	4659	13%	0.01
41–50	6382	18%	6344	18%	0.003
> 50	21,263	59%	21,619	60%	0.02
Mean, (SD)	55.6	(18.5)	56.1	(18.3)	0.02
Occupation					
Officer	16,360	46%	16,721	47%	0.02
Worker	8198	23%	7964	22%	0.02
Farmer	685	2%	602	2%	0.02
Fisher	6215	17%	6275	18%	0.004
Others	4393	12%	4289	12%	0.01
Comorbidities					
Hypertension	10,584	30%	10,266	29%	0.02
Diabetes	5733	16%	5529	15%	0.02
Hyperlipidemia	2900	8%	2401	7%	0.05
Coronary artery disease	4129	12%	3830	11%	0.03
Cerebrovascular accident	3798	11%	3255	9%	0.05
Chronic kidney disease	1211	3%	1207	3%	0.001
COPD	2455	7%	2226	6%	0.03
Chronic liver disease	1836	5%	1631	5%	0.03
Autoimmune disease	451	1%	406	1%	0.01
Psoriasis	87	0.24%	74	0.21%	0.01
Vasculitis	27	0.08%	14	0.04%	0.02
IBD	673	2%	772	2%	0.02

Table 1. Demographic Characteristics of Patients with and without Bowel Resection. *SD* standard deviation, *SMD* standardized mean difference, *COPD* chronic obstructive pulmonary disease, *IBD* Inflammatory bowel disease.

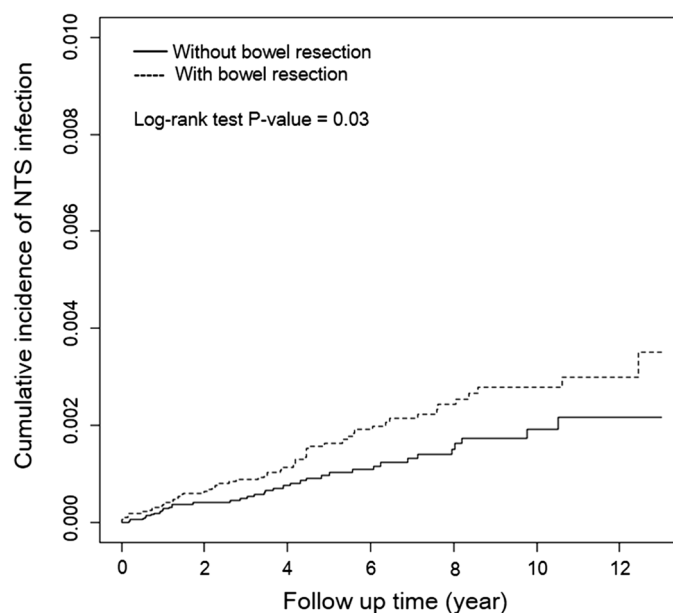


Figure 2. Cumulative incidence curves of nontyphoidal salmonella (NTS) infection among the propensity score-matched Cohort using The Kaplan–Meier method.

Variables	NTS infection			cHR	(95% CI)	aHR†	(95% CI)
	n	PY	IR				
Bowel resection							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	56	188,270	2.97	1.56	(1.03, 2.37)*	1.64	(1.08, 2.48)*
Small bowel resection							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	29	79,213	3.66	1.93	(1.18, 3.14)**	1.96	(1.20, 3.19)**
Large bowel resection							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	28	98,288	2.85	1.52	(0.93, 2.48)	1.59	(0.97, 2.60)
Right hemicolectomy							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	12	36,091	3.32	1.77	(0.92, 3.39)	1.96	(1.02, 3.77)*
Transverse colon resection							
No	37	192,902	1.92	1.00	–		
Yes	0	2847	0.00	0.00			
Left hemicolectomy							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	6	12,670	4.74	2.51	(1.06, 5.95)*	2.12	(0.89, 5.04)
Sigmoidectomy							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	6	16,997	3.53	1.84	(0.78, 4.37)	1.66	(0.70, 3.96)
Total colectomy							
No	37	192,902	1.92	1.00	–		
Yes	0	3392	0.00	0.00			
Bowel anastomosis							
No	37	192,902	1.92	1.00	–	1.00	–
Yes	11	57,857	1.90	1.01	(0.52, 1.99)	1.18	(0.60, 2.33)
Gender							
Female	34	174,426	1.95	1.00	–		
Male	59	206,746	2.85	1.48	(0.97, 2.26)		
Age, year							
18–30	2	43,760	0.46	1.00	–	1.00	–
31–40	12	53,443	2.25	4.86	(1.09, 21.7)*	4.71	(1.05, 21.1)*
41–50	6	70,720	0.85	1.83	(0.37, 9.07)	1.67	(0.34, 8.31)
> 50	73	213,249	3.42	7.36	(1.81, 30.0)**	5.25	(1.27, 21.8)*
Occupation							
Officer	38	174,857	2.17	1.00	–		
Worker	16	88,397	1.81	0.83	(0.47, 1.50)		
Farmer	1	7159	1.40	0.65	(0.09, 4.70)		
Fisher	21	65,542	3.20	1.48	(0.87, 2.51)		
Others	17	45,218	3.76	1.73	(0.98, 3.06)		
Comorbidities							
Hypertension							
No	53	292,983	1.81	1.00	–	1.00	–
Yes	40	88,190	4.54	2.48	(1.64, 3.75)***	1.61	(1.00, 2.58)*
Diabetes							
No	72	332,861	2.16	1.00	–	1.00	–
Yes	21	48,312	4.35	1.98	(1.22, 3.23)**	1.28	(0.76, 2.14)
Hyperlipidemia							
No	84	358,349	2.34	1.00	–		
Yes	9	22,823	3.94	1.66	(0.84, 3.31)		
Coronary artery disease							
No	79	347,841	2.27	1.00	–	1.00	–
Yes	14	33,332	4.20	1.82	(1.03, 3.21)*	0.92	(0.50, 1.70)
Cerebrovascular accident							
Continued							

Variables	NTS infection			cHR	(95% CI)	aHR†	(95% CI)
	n	PY	IR				
No	85	353,319	2.41	1.00	–		
Yes	8	27,854	2.87	1.16	(0.56, 2.41)		
Chronic kidney disease							
No	86	373,043	2.31	1.00	–	1.00	–
Yes	7	8130	8.61	3.62	(1.67, 7.85)**	2.35	(1.06, 5.21)*
COPD							
No	80	362,642	2.21	1.00	–	1.00	–
Yes	13	18,530	7.02	3.12	(1.73, 5.61)***	2.18	(1.18, 4.02)*
Chronic liver disease							
No	88	366,101	2.40	1.00	–		
Yes	5	15,071	3.32	1.35	(0.55, 3.34)		
Autoimmune disease							
No	89	377,224	2.36	1.00	–	1.00	–
Yes	4	3948	10.13	4.26	(1.56, 11.59)**	3.83	(1.4, 10.47)**
Psoriasis							
No	93	380,403	2.44	1.00	–		
Yes	0	770	0.00	0.00			
Vasculitis							
No	93	380,965	2.44	1.00	–		
Yes	0	207	0.00	0.00			
IBD							
No	91	372,731	2.44	1.00	–		
Yes	2	8442	2.37	0.98	(0.24, 3.97)		

Table 2. Incidence Rate and Hazard Ratio of NTS Infection. NTS nontyphoidal salmonella, COPD chronic obstructive pulmonary disease, IBD Inflammatory bowel disease, PY person-year, IR incidence rate per 10,000 person-year, cHR crude hazard ratio, aHR adjusted hazard ratio. †Adjusted by age, hypertension, diabetes, coronary artery disease, chronic kidney disease, COPD and rheumatoid autoimmune disease. * p value < 0.05; ** p value < 0.01; *** p value < 0.001.

Results of sensitivity analysis. Results of our sensitivity analysis were almost consistent with those of our primary analyses (Table 4). The differences are that our sensitivity analysis even indicated that patients would have an increased risk of NTS infection receiving large bowel resection (aHR of 1.69, 95% CI = 1.02–2.80) or left hemicolectomy (aHR of 2.41, 95% CI = 1.01–5.77). The patient baseline characteristics in our sensitivity analysis are shown in Table 5.

Discussion

Our study first demonstrated that bowel resection was associated with a significantly increased risk of NTS infection. Of note, the HR of NTS infection for patients with small bowel resection or right hemicolectomy was nearly two times greater than for those without small bowel resection or right hemicolectomy.

We hypothesized that based on the bowel resection site, the microbiota composition change would result in NTS infection. As mentioned above, the reported bacterial species in the intestine included Bacilli (Firmicutes), Streptococcaceae (Firmicutes), Actinobacteria, Clostridium, Staphylococcus, Bacteroides, Lactobacillus, Enterococcus, Bifidobacterium, Enterobacteriaceae, and Ruminococcus. Oh et al. demonstrated the potential protective effects of using *Bacillus subtilis* CSL2, against *Salmonella gallinarum* infection on laying hens¹⁵. Actinomyces might have antimicrobial potency toward NTS¹⁶. Jacobson et al. discovered that in mice, *Bacteroides* spp. limit intestinal *Salmonella typhimurium* expansion and fecal shedding¹⁷. Lactobacillus has remarkable anti-salmonella activities in vivo and in vitro^{18,19}. Strains of *Bifidobacterium* were antagonistic to *Salmonella*²⁰. *Bifidobacterium thermophilum* RBL67 influences the transcriptome of *Salmonella* and causes an imbalanced virulence gene expression, but can protect hosts from infection²¹. *Clostridia*, including the genera *Roseburia* and *Blautia* from the family *Lachnospiraceae* and the genera *Ruminococcus* and *Anaerovibrio*, were more abundant in *Salmonella*-negative pigs⁸. A metabolite from bacteria—indole, is probably associated with NTS infection in our gut. Indole can prevent NTS infection because of its effects on decreasing *Salmonella* invasion in vivo, *Salmonella* motility, virulence gene expression, and increasing epithelial cells' resistance to *Salmonella* invasion²².

Gordon et al. indicated that host risk factors included extremes of age and immunocompromised status such as rheumatologic disease, which corresponded with our results³. We discovered that patients aged 31–40 years had an increased risk of NTS infection, which was first reported by us. Our study demonstrated other risk factors for NTS infection like hypertension, chronic kidney disease, and COPD. Atherosclerosis was demonstrated a risk factor for endovascular *Salmonella* bacteremia²³. Traditional risk factors for atherosclerosis included

Variables	Without bowel resection			With bowel resection			cHR	(95% CI)	aHR†	(95% CI)
	n	PY	IR	n	PY	IR				
Gender										
Female	14	88,765	1.58	20	85,661	2.33	1.51	(0.76, 3.00)	1.61	(0.81, 3.19)
Male	23	104,137	2.21	36	102,609	3.51	1.59	(0.94, 2.68)	1.63	(0.96, 2.75)
Age, year										
18–30	1	22,053	0.45	1	21,707	0.46	1.07	(0.07, 17.1)	1.71	(0.10, 30.2)
31–40	3	27,077	1.11	9	26,366	3.41	3.19	(0.86, 11.8)	3.66	(0.94, 14.2)
41–50	3	35,047	0.86	3	35,674	0.84	0.97	(0.19, 4.80)	1.07	(0.21, 5.34)
> 50	30	108,726	2.76	43	104,523	4.11	1.49	(0.93, 2.38)	1.54	(0.96, 2.45)
Occupation										
Officer	14	86,403	1.62	24	88,454	2.71	1.70	(0.88, 3.28)	1.77	(0.92, 3.43)
Worker	8	45,223	1.77	8	43,174	1.85	1.03	(0.38, 2.75)	1.07	(0.40, 2.88)
Farmer	0	3893	0.00	1	3266	3.06				
Fisher	9	33,987	2.65	12	31,554	3.80	1.44	(0.60, 3.41)	1.44	(0.61, 3.43)
Others	6	23,397	2.56	11	21,821	5.04	2.01	(0.74, 5.44)	2.02	(0.75, 5.47)
Comorbidities										
Hypertension										
No	16	145,886	1.10	37	147,097	2.52	2.31	(1.28, 4.15)**	2.34	(1.3, 4.22)**
Yes	21	47,017	4.47	19	41,173	4.61	1.04	(0.56, 1.93)	1.07	(0.58, 2.00)
Diabetes										
No	24	167,344	1.43	48	165,517	2.90	2.04	(1.25, 3.33)**	2.11	(1.29, 3.46)**
Yes	13	25,559	5.09	8	22,753	3.52	0.70	(0.29, 1.68)	0.74	(0.30, 1.78)
Hyperlipidemia										
No	30	179,471	1.67	54	178,879	3.02	1.82	(1.16, 2.84)**	1.91	(1.22, 2.98)**
Yes	7	13,432	5.21	2	9392	2.13	0.41	(0.09, 2.00)	0.37	(0.08, 1.78)
Coronary artery disease										
No	29	174,143	1.67	50	173,698	2.88	1.74	(1.10, 2.75)*	1.82	(1.15, 2.88)*
Yes	8	18,759	4.26	6	14,572	4.12	0.96	(0.33, 2.76)	0.90	(0.31, 2.58)
Cerebrovascular accident										
No	34	176,656	1.92	51	176,663	2.89	1.51	(0.98, 2.33)	1.59	(1.03, 2.46)*
Yes	3	16,247	1.85	5	11,607	4.31	2.34	(0.56, 9.79)	2.21	(0.53, 9.27)
Chronic kidney disease										
No	35	188,352	1.86	51	184,691	2.76	1.50	(0.97, 2.30)	1.56	(1.01, 2.39)*
Yes	2	4551	4.39	5	3579	13.97	3.19	(0.62, 16.5)	2.63	(0.50, 13.8)
COPD										
No	29	182,097	1.59	51	180,545	2.82	1.78	(1.13, 2.82)*	1.85	(1.17, 2.93)**
Yes	8	10,806	7.40	5	7725	6.47	0.86	(0.28, 2.62)	0.87	(0.28, 2.70)
Chronic liver disease										
No	35	184,434	1.90	53	181,667	2.92	1.55	(1.01, 2.37)*	1.62	(1.05, 2.48)*
Yes	2	8468	2.36	3	6603	4.54	1.95	(0.33, 11.7)	1.88	(0.31, 11.3)
Autoimmune disease										
No	37	190,628	1.94	52	186,596	2.79	1.45	(0.95, 2.21)	1.51	(0.99, 2.31)
Yes	0	2274	0.00	4	1674	23.89				
Psoriasis										
No	37	192,392	1.92	56	188,011	2.98	1.56	(1.03, 2.37)*	1.51	(0.99, 2.31)
Yes	0	510	0.00	0	259	0.00				
Vasculitis										
No	37	192,762	1.92	56	188,204	2.98	1.56	(1.03, 2.37)*	1.64	(1.08, 2.48)*
Yes	0	141	0.00	0	67	0.00				
IBD										
No	37	188,948	1.96	54	183,783	2.94	1.52	(1.00, 2.3)	1.59	(1.04, 2.42)*
Yes	0	3955	0.00	2	4487	4.46				

Table 3. The Stratification Analysis of NTS Infection. *NTS* nontyphoidal salmonella, *COPD* chronic obstructive pulmonary disease, *IBD* inflammatory bowel disease, *PY* person-year, *IR* incidence rate per 10,000 person-year, *cHR* crude hazard ratio, *aHR* adjusted hazard ratio. †Adjusted by age, hypertension, diabetes, coronary artery disease, chronic kidney disease, COPD and rheumatoid autoimmune disease. **p* value < 0.05, ***p* value < 0.01, ****p* value < 0.001.

Type of bowel resection	NTS infection		cHR	(95% CI)	aHR†	(95% CI)
	n					
Bowel resection	52		1.58	(1.02, 2.43)*	1.66	(1.07, 2.56)*
Small bowel resection	27		1.93	(1.17, 3.21)*	1.92	(1.04, 3.19)*
Large bowel resection	27		1.58	(0.95, 2.62)	1.69	(1.02, 2.80)*
Right hemicolectomy	12		1.90	(0.98, 3.68)	2.27	(1.17, 4.43)*
Transverse colon resection	0					
Left hemicolectomy	6		2.71	(1.14, 6.46)*	2.41	(1.01, 5.77)*
Sigmoidectomy	6		2.01	(0.84, 4.78)	1.91	(0.79, 4.57)
Total colectomy	0					
Bowel anastomosis	9		0.90	(0.43, 1.88)	1.06	(0.51, 2.23)

Table 4. Sensitivity Analysis (Excluding Peptic Ulcer Disease Patients). *NTS* nontyphoidal salmonella, *n* number of event, *cHR* crude hazard ratio, *aHR* adjusted hazard ratio. †Adjusted by age, hypertension, diabetes, coronary artery disease, chronic kidney disease, COPD and rheumatoid autoimmune disease. **p* value < 0.05, ***p* value < 0.01, ****p* value < 0.001.

Variables	Bowel resection				SMD
	No (n = 35,004)		Yes (n = 35,004)		
	n	%	n	%	
Gender					0.01
Female	17,098	49%	16,886	48%	
Male	17,906	51%	18,118	52%	
Age, year					
18–30	3396	10%	3195	9%	0.02
31–40	4621	13%	4592	13%	0.002
41–50	6345	18%	6217	18%	0.01
> 50	20,642	59%	21,000	60%	0.02
Mean, (SD)	55.4	(18.4)	56.0	(18.3)	0.03
Occupation					
Officer	16,298	47%	16,332	47%	0.002
Worker	7586	22%	7762	22%	0.01
Farmer	738	2%	582	2%	0.03
Fisher	6076	17%	6119	17%	0.00
Others	4306	12%	4209	12%	0.01
Comorbidities					
Hypertension	10,099	29%	9965	28%	0.01
Diabetes	6247	18%	5371	15%	0.07
Hyperlipidemia	2683	8%	2329	7%	0.04
Coronary artery disease	4192	12%	3714	11%	0.04
Cerebrovascular accident	3674	10%	3159	9%	0.05
Chronic kidney disease	1111	3%	1176	3%	0.01
COPD	2449	7%	2153	6%	0.03
Chronic liver disease	1977	6%	1585	5%	0.05
Autoimmune disease	400	1%	390	1%	0.003
Psoriasis	72	0.2%	74	0.2%	0.001
Vasculitis	166	0.5%	14	0.04%	0.09
IBD	665	2%	752	2%	0.02

Table 5. Demographic Characteristics of Patients with and without Bowel Resection (Excluding Peptic Ulcer Disease Patients). *SD* standard deviation, *SMD* standardized mean difference, *COPD* chronic obstructive pulmonary disease, *IBD* inflammatory bowel disease.

hypertension, so the hypertension might be associated with NTS infection²⁴. Chronic kidney disease was not identified as a risk factor for NTS infection before. The possible explanation is that chronic kidney disease could result in immunocompromised status so that patients easily got NTS infection. Lisowska's study showed

peripheral CD4+ and CD8+ T cells and B cells in the blood decrease²⁵, and Fernández-Fresnedo et al. indicated an increased incidence of apoptosis in B cells in chronic kidney disease patients²⁶. In end-stage renal disease patients, increased apoptosis and diminished populations of naïve and central memory T cells were found, and their antigen-specific memory CD4+ T cells were impaired²⁷. In smokers with COPD, Knobloch's research revealed that interferon- γ release from ex vivo generated CD4⁺ effector cells of the Th1 subtype upon challenge with lipopolysaccharide (LPS) purified from *Salmonella minnesota* would decrease²⁸.

Our stratification analysis showed patients without hypertension, diabetes, hyperlipidemia, coronary artery disease, cerebrovascular accident, chronic kidney disease, COPD, chronic liver diseases, vasculitis, or IBD would be at higher risk of NTS infection after bowel resection. We might explain this phenomenon by the fact that affected patients usually have underlying diseases, so that NTS poses significant health threats⁴. If underlying covariates did not exist, bowel resection would play a significant predisposing factor of NTS infection. Our results reaffirm that in patients without underlying diseases, bowel resection should be considered carefully to avoid possible NTS infection in the future.

Our study has the advantage that it is a large-scale nationwide analysis with longitudinal follow-up. However, we admit several limitations to our study. First, we lacked information regarding body mass index, alcohol consumption, betel nut use, smoking, and other immunomodulator prescription. However, we used adjusted covariates, such as autoimmune diseases, psoriasis, and IBD, which could represent immune-related medication use. Second, the potential misclassification in establishing study cohorts might exist. We used bowel resection procedure codes to identify the case group. The policy of patient anonymity within the NHIRD prevented us from confirming patients' diagnoses. Third, we demonstrated that right hemicolectomy in our primary analyses and left hemicolectomy in our sensitivity analysis increased the risk of NTS infection, but we did not discover any reference which could explain the mechanism.

Conclusions

Bowel resection causes an increased risk of NTS infection. Patients aged 31–40 and > 50 years or those with comorbidities such as hypertension, chronic kidney disease, COPD, and autoimmune disease have an elevated risk of NTS infection. Furthermore, in patients without comorbidities, bowel resection should be considered carefully.

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Competing interests

The authors declare no competing interests.

Additional information

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