



Retrospective Cohort Study of Non-Traumatic Jejunum and Ileum Perforation: A Multi-center Study

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ABSTRACT

Aim: Non-traumatic jejunum and ileum perforation (NTJIP) is a rare clinical entity. Contrary to infective causes occurring in Eastern countries, immune-mediated pathologies are predominant in the West. The studies on NTJIP in Southeast Asia are lacking. This study is designed to describe the involved patients incidences, etiological patterns, and outcomes. This study analyzed the predictors of mortality in these patients.

Method: This retrospective cohort study involved patients with NTJIP who underwent surgery over 4 years from 2016 to 2019. Data were sourced from operative databases of five tertiary public hospitals in Sarawak, Malaysia. Small bowel perforation data were screened, and patients with adhesive obstruction from previous surgeries, trauma, and duodenal perforation were excluded. Patients' socio-demographic characteristics, surgical characteristics, and outcomes were stated in the prepared *pro forma*.

Results: From 2016 to 2019, a total of 42 patients with NTJIP were included in this study. The mean [standard deviation (SD)] age of incidence was 55.7 (19.3) years old. Twenty-nine presented within 3 days of symptoms. Their etiologies were attributed mainly to non-specific causes (29%), followed by radiation-associated perforation (17%). The mean (SD) hospital stay was 10 (3) days, with the post-operative complication rate of ileus at 21%, surgical site infection at 23%, and anastomotic leak at 23%. The mortality rate was 36%, and the Mannheim peritonitis index was a reliable predictor of mortality.

Conclusion: This study observed that radiation and vascular etiologies were the most common identifiable causes of NTJIP in the current series. Further research would prove beneficial to analyze inconclusive cases, as the dilemma surrounding etiologies for NTJIP remains.

Keywords: Ileum, jejunum, small bowel, perforated viscus, peritonitis

Introduction

Small bowel perforation is common following penetrating injuries. Blunt traumatic small bowel injury ranges from 5% to 15%, with incidences of perforation occurring in <1% of them.¹ Life-threatening spontaneous bowel perforation among premature, low-birth weight infants secondary to necrotizing enterocolitis is commonly reported, with prevalence as high as 7%.² However, small bowel perforation due to non-traumatic causes in adults is a rare clinical entity,

with a reported incidence of 1 in 350,000 people/year.³ The duodenum is the most common point of perforation due to *Helicobacter pylori* prevalence.⁴⁻⁶ Spontaneous small bowel perforation was often reported in small series or case reports. As perforation is unusual in the jejunum and ileum, this study reports a series of 42 patients. Such a series is lacking in the regional context; hence, the study intends to describe the pattern of the pathologies, management strategy, and outcome. Therefore, this study analyzes the predictors of mortality.⁷



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Materials and Methods

This retrospective cohort study involved patients with non-traumatic jejunum and ileum perforation (NTJIP) who underwent surgery over 4 years from 2016 to 2019. The data was retrieved from the operative databases of five tertiary public hospitals in Sarawak. All patients with small bowel perforation were screened. Those with previous surgery, adhesive obstruction, and traumatic and duodenal perforation were excluded. Patients' socio-demographic characteristics, surgical characteristics, and outcomes were entered in prepared *pro forma*. Presenting symptoms were stratified as acute in cases of abdominal pain within 7 days, and chronic constant symptoms were those lasting more than 3 months.⁸ Intraoperative peritoneal fluid cultures were sent off to identify potential organisms. Blood and stool cultures were sent off to exclude *Salmonella typhi*. Resected bowel segments and mesenteric lymph nodes were sent off for histopathological analysis. This study was designed to describe the involved patients' incidences, etiologies, and outcomes. The Mannheim peritonitis index was calculated based on eight parameters, including age, sex, comorbidities, clinical parameters, and peritoneal fluid analysis, to prognosticate mortality.⁹ Post-operative morbidity was graded and analyzed using the Clavien-Dindo classification.¹⁰ Perioperative mortality was defined as any death occurring during the same admission following a surgical procedure under general anesthesia. Patients were followed up six months after discharge at a surgical outpatient clinic.

This study was in compliance with the ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guideline. Ethical approval for this study was obtained from the Jawatankuasa Etika and Penyelidikan Perubatan Medical Research and Ethics Committee, Ministry of Health Malaysia (approval number: NMRR-19-3060-50836).

Statistical Analysis

All data was compiled using SPSS analytical software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). All quantitative and qualitative data were analyzed using the t-test or chi-squared test to identify predictors for mortality, respectively. For normality testing, the Mann-Whitney test was used if variables were not normally distributed, and t-tests were used if data were normally distributed.

Results

From 2016 to 2019, this study retrieved 17,145 emergency surgical cases from the operative databases of five tertiary public hospitals in Sarawak, Malaysia. Data from 99 patients

with non-traumatic small bowel perforation were retrieved. Forty-two patients with NTJIP were included for analysis after exclusion (Figure 1).

The mean [standard deviation (SD)] age of affected NTJIP patients was 55.7 (19.3) years old. Most participants (69%) were in the bottom 40% of the Malaysian income classification system. They had similar gender and racial distributions (Table 1). Twenty-nine out of 42 patients presented within 3 days of symptoms, and six presented after 14 days. There were 13 deaths, giving rise to a 31% mortality rate within the same admission. The surgical complication rates ranged between 21% to 26%. (Table 2).

Despite the standard algorithm for small bowel perforation in all tertiary hospitals being used to diagnose etiologies, 29% of the cases were inconclusively labeled with non-specific etiologies following laboratory and histopathological examination (HPE) correlation. Radiation-induced and vascular pathologies were leading etiologies for NTJIP, followed by infective and immune-related causes (Table 3). Six patients physiologically unsuitable for anastomosis had segmental bowel resection with stoma creation, and the rest had resection anastomosis. The current series included two patients with more than one perforation area due to vasculopathy or gastrointestinal lymphoma.

The analysis observed that a higher Mannheim peritonitis index (SD) of 32.9 (7.0) vs 20.6 (8.2) was predictive of mortality ($p < 0.001$). Cardiorespiratory complications were predictive of mortality ($p < 0.001$) (Table 4).

Discussion

NTJIP is a rare clinical entity and almost always presents a diagnosis dilemma among clinicians. The clinical presentation of the non-traumatic small bowel perforation

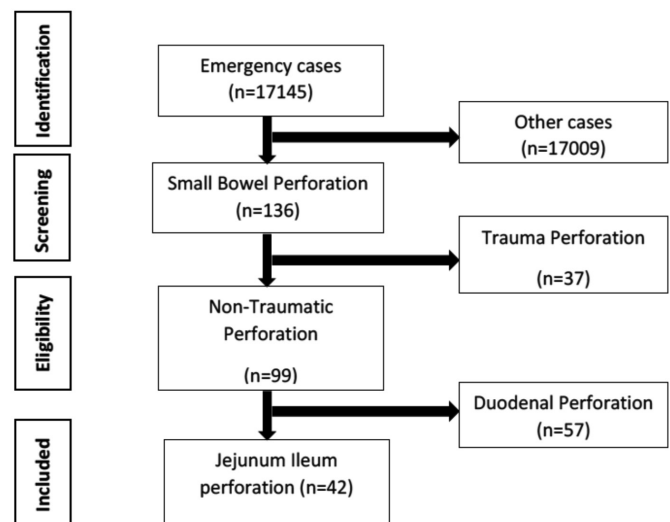


Figure 1. Study flow diagram

evolves from chronic abdominal pain to sudden abdominal distension, pain, and vomiting. NTJIP in developing countries is primarily associated with infective causes, whereas autoimmune etiologies are common in industrial countries.^{3,6} Establishing a causative pathology based on clinical features and investigations is a challenge. Surgical management is urgently warranted; hence, a definitive preoperative diagnosis is nearly impossible. Delayed presentation and management may result in highly negative outcomes. The difficulty in classifying NTJIP based on clinical presentation, examination, serology, culture, and histopathology examinations is often regarded as a non-specific etiology.

The Dal et al.¹¹ single-center Turkish case study had comparable cases over 10 years with a similar mortality rate.

Table 1. Clinical characteristics of the subjects (n=42)

Factors	n (%) or mean (SD)
Socio-demographic	
Age (years), mean (SD)	55.67 (19.25)
Gender	
Male	20 (48%)
Female	22 (52%)
Ethnicity	
Malay	16 (38%)
Chinese	8 (19%)
Iban	10 (24%)
Bidayuh	8 (19%)
Education level	
Preschool	3 (7%)
Primary	27 (64%)
Secondary	12 (29%)
Family Income Based on Malaysia Income Classification System*	
Bottom 40%	29 (69%)
Middle 40%	13 (31%)
Co-morbid condition	
Hypertension	14 (33%)
Smoking	11 (26%)
Underlying malignancy	10 (24%)
Diabetes mellitus	2 (5%)
Dyslipidemia	2 (5%)
Cardiovascular	1 (2%)

*Household Income Estimates and Incidence of Poverty Report, Malaysia 2020. SD: Standard deviation

A single-center study from a Singaporean group reported 47 patients with spontaneous small bowel perforation. The prevalent causes were foreign body ingestion (17.0%), adhesions (14.9%), idiopathic (14.9%), and malignancy (12.8%).⁷ Contrary to the current series, no etiology pattern was revealed due to set exclusion criteria. Interestingly, the rate of idiopathic causes was 29%, much higher than

Table 2. Surgical outcome characteristics

Factor	n (%) or mean (SD)
Duration of symptoms	
Acute	29 (69%)
Subacute	7 (16.9%)
Chronic	6 (14.3%)
Duration of Op (min.) mean (SD)	148 (52)
ASA score*, n (%)	
1	10 (24%)
2	15 (36%)
3	14 (33%)
4	3 (7%)
Mannheim Peritonitis Index Score mean (SD)	24 (10)
Perforation site	
Jejunum	8 (29%)
Ileum	20 (71%)
Number of perforations	
Single	35 (92%)
Multiple	3 (8%)
Duration of hospitalization (days) mean (SD)	10 (3)
Post-operative complication	
Surgical site infection	10 (24%)
Anastomotic leak	9 (21%)
Ileus	10 (24%)
Respiratory	15 (36%)
Cardiovascular	18 (43%)
Surgical site infection	10 (24%)
Mortality**	
Same admission	13 (31%)
1 month	2 (5%)
3 months	0
6 months	0

*ASA: American Society of Anesthesiology, **Two cases of mortality after discharge, Min.: Minimum, SD: Standard deviation

in studies from the West with comparable morbidity and mortality.

In studies from low-income countries, such as Pakistan, infective causes such as tuberculosis are prevalent.¹² Despite Sarawak State Public Hospital catering to a lower-income population, this study did not observe a similar pattern, as there were only two cases of gastrointestinal tuberculosis in the study.¹³ Additionally, the study did not identify any typhoid-related bowel perforations. Despite being in Southeast Asia, where pulmonary tuberculosis and typhoid are high, the current data from Sarawak revealed an opposite epidemiology.^{14,15} Diversified pathologies of small bowel perforation are evident in each country despite being in the same region and having similar socio-economic statuses.

The current study observed 29% of HPE, and workups did not reveal an actual cause (Table 3). The rate was slightly higher than in the literature from the West.⁷ As per the example mentioned above, there was no incidence of typhoid-related perforation, as the Widal test and HPE results were negative. The Widal test reported a mean sensitivity, specificity, and a positive and negative predictive value of below 80%. HPE tend to reveal a non-specific pattern with various immune cells and exhibit diffuse mononuclear cell infiltration with macrophage-rich hyperplasia and T-lymphocytes with lymphoplasmacytic infiltrate.¹² The reliabilities of individual diagnostic tests are inadequate, requiring multiple diagnostic tools and clinical features to increase their diagnostic value.¹⁶ Therefore, taken together, these factors may falsely increase the rate of idiopathic causes.

The second common etiology was radiation-induced perforation. A considerable number of patients in this study presented with radiation-associated perforation

from a previously radiated pelvis, whereby five cervical adenocarcinoma and two rectal adenocarcinoma patients underwent pelvic radiation therapy for a mean duration of 10.2 months and 8 months, respectively. Radiation colitis is insidious and progressive in nature. It frequently develops following 6 months to 5 years following radiation and is rarely curable. The presence of radiation poses an additional risk for intestinal surgery, and its management remains a constant challenge due to the nature of progressive radiation evolution. Surgical intervention in perforated cases will require resection of the affected segment and anastomosis, which involves using a bowel segment that has not been exposed to radiation to reduce the risk of an anastomotic leak.¹⁷

The Mannheim peritonitis index in regards to cardiovascular and respiratory complications was considered to be significant predictors for post-operative mortality. The sub-analysis did not identify underlying malignancies as mortality predictors, as only two deaths were associated with them.

Despite the current study's limitation of only including a single state in Malaysia, the study subjects were representative of the whole country's racial profiles and included a multi-center database. Some intraoperative data was missing regarding anatomical site documentation and perforation number. Another potential confounding factor would be the lack of higher-income group patients, as they mostly visited the private hospital, which could not be included in this study. Nevertheless, the higher-income group has a comparatively lower incidence of small bowel perforation.^{13,15}

Conclusion

The Mannheim peritonitis index and associated cardiovascular and respiratory complications were key predictors for mortality following intestinal surgery for NJTIP. This study's etiological pattern of NTJIP is distinct from the studies of regional centers. This highlights the need for a national level of collaboration to attain better insight into this subject. This study observed that radiation and vascular etiologies were common identifiable causes of NTJIP. Further research would prove beneficial to analyze inconclusive cases, as the dilemma surrounding etiologies for NTJIP remains.

Table 3. Etiologies of non-traumatic jejunum ileum perforation

Etiology*	n (%)
Non-specific/idiopathic	12 (29%)
Radiation association perforation	7 (17%)
Vascular	5 (12%)
Crohn's disease	3 (7%)
Meckel's diverticulitis	3 (7%)
Adenocarcinoma	3 (7%)
Lymphoma	3 (7%)
Tuberculosis	2 (5%)
GIST	2 (5%)
Fungal infection	1 (2%)
Kikuchi-Fujimoto disease	1 (2%)

*Following laboratory and histopathological correlation, GIST: Gastrointestinal stromal tumor

Table 4. Predictors of mortality in small bowel perforation

Predictors	Mean (SD) Death, (n=11)	Mean (SD) Survived, (n=31)	p-value ^a
Age	56.91 (18.00)	55.23 (20.00)	0.807
Duration of symptoms	1.55 (0.82)	1.42 (0.72)	0.633
Duration of surgery	143.36 (57.93)	150.39 (50.45)	0.705
Manheim Peritonitis Index	32.91 (6.978)	20.61 (8.151)	<0.001
Number of perforation	1.36 (1.206)	1.07 (0.267)	0.238

^aAnalyses were done with a t-test

Predictors	Death, n (%)	Survived, n (%)	p-value ^a
Male	4 (20.0%)	16 (80.0%)	0.491
Female	7 (31.8%)	15 (68.2%)	
Smoker	3 (27.3%)	8 (72.7%)	1.000
Non-smoker	8 (25.8%)	23 (74.2%)	
Diabetic	1 (50.0%)	1 (50.0%)	0.460
Non-diabetic	10 (25.0%)	30 (75.0%)	
Hypertensive	4 (28.6%)	10 (71.4%)	1.000
Non-hypertensive	7 (25.0%)	21 (75.0%)	
Underlying malignancy	2 (20.0%)	8 (80.0%)	1.000
No underlying malignancy	9 (28.1%)	23 (71.9%)	
ASA1	1 (10.0%)	9 (90.0%)	0.070 ^b
ASA2	4 (26.7%)	12 (75.0%)	
ASA3	4 (28.6%)	10 (71.4%)	
ASA4	2 (100.0%)	0 (0.0%)	
Surgical site infection	1 (10.0%)	9 (90.0%)	0.245
No surgical site infection	10 (31.2%)	22 (68.8%)	
Respiratory complication	9 (60.0%)	6 (40.0%)	<0.001
No respiratory complication	2 (7.4%)	25 (92.6%)	
Ileus	2 (20.0%)	8 (80.0%)	1.000
No ileus	6 (23.1%)	20 (76.9%)	
Cardiovascular complication	11 (61.1%)	7 (38.9%)	<0.001
No cardiovascular complication	0 (0.0%)	24 (100.0%)	
Anastomotic leak	2 (22.2%)	7 (77.8%)	1.000
No anastomotic leak	6 (22.2%)	21 (77.8%)	

^aAll analyses were performed using Fisher's exact test except, ^bchi-squared analysis. SD: Standard deviation, ASA: American Society of Anesthesiology

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Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Jawatankuasa Etika and Penyelidikan Perubatan Medical Research and Ethics Committee, Ministry of Health Malaysia (approval number: NMRR-19-3060-50836).

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Authorship Contributions

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