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Supplement Article

Indications, Postoperative Management, and Long-term Prognosis of Crohn's Disease After Ileocecal Resection: A Multicenter Study Comparing the East and West

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Background: The Crohn's disease (CD) phenotype differs between Asian and Western countries and may affect disease management, including decisions on surgery. This study aimed to compare the indications, postoperative management, and long-term prognosis after ileocecal resection (ICR) in Hong Kong (HK) and the Netherlands (NL).

Methods: CD patients with primary ICR between 2000 and 2019 were included. The endpoints were endoscopic (Rutgeerts score ≥i2b and/or radiologic recurrence), clinical (start or switch of inflammatory bowel disease medication), and surgical recurrences. Cumulative incidences of recurrence were estimated with a Bayesian multivariable proportional hazards model.

Results: Eighty HK and 822 NL patients were included. The most common indication for ICR was penetrating disease (HK: 32.5%, NL: 22.5%) in HK vs stricturing disease (HK: 32.5%, NL: 48.8%) in the NL ($P < .001$). Postoperative prophylaxis was prescribed to 65 (81.3%) HK patients (28 [35.0%] aminosalicylates [5-aminosalicylic acid]; 30 [37.5%] immunomodulators; 0 biologicals) vs 388 (47.1%) NL patients (67 [8.2%] 5-aminosalicylic acid; 187 [22.8%] immunomodulators; 69 [8.4%] biologicals; 50 [6.1%] combination therapy) ($P < .001$). Endoscopic or radiologic evaluation within 18 months was performed in 36.3% HK vs 64.1% NL ($P < .001$) patients. No differences between both populations were observed for endoscopic (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.24-1.21), clinical (HR, 0.91; 95% CI, 0.62-1.32), or surgical (HR, 0.61; 95% CI, 0.31-1.13) recurrence risks.

Conclusion: The main indication for ICR in CD patients is penetrating disease in HK patients and stricturing disease in NL patients. Although considerable pre- and postoperative management differences were observed between the two geographical areas, the long-term prognosis after ICR is similar.

Lay Summary

This is the first study reporting similar long-term prognoses after ileocecal resection in Crohn's disease in low- and high-incidence countries despite differences in Crohn's disease phenotype at diagnosis, surgical approach, indications, and pre- and postoperative management including prophylactic medication.

Key Words: Crohn's disease, ileocecal resection, postoperative recurrence

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Introduction

The incidence of Crohn's disease (CD) is increasing globally.[1,2] Previously regarded as a disease of high-income Western countries, CD is now rising in formerly low-incidence areas such as Asia and Eastern Europe.[2] In Hong Kong (HK), the incidence of inflammatory bowel disease (IBD) has tripled from 1.0 to 3.1 per 100 000 population per year over the last 3 decades.[3,4] In comparison, the annual CD incidence in the Netherlands (NL) has slowly increased from 6.9 per 100 000 in the 1990s to 10.5 per 100 000 in 2010.[5,6] While the increased prevalence of CD in formerly low-incidence countries is not fully understood, it commonly parallels rapid urbanization, industrialization, and changes in lifestyle factors.[7]

Population-based data demonstrate more stricturing and penetrating CD disease phenotypes in Asia than in Western countries.[4] Asian CD patients also have a male predominance and lower prevalence of family history of IBD as compared with Western CD patients. Hypothetical explanations for these findings include undiagnosed milder CD phenotypes in Asian countries owing to several factors including patients' delay (eg, inferior access to specialized care) or doctors' delay (eg, lack of medical awareness).[4] Lower availability of biologicals and different treatment strategies of CD may influence prognosis, such as a limited use of immunosuppressive IBD therapies in areas with high prevalence of infections.[8]

In Western countries, the rate of ileocecal resection (ICR) and risk of re-resection are declining, which are commonly regarded as signs of improved CD prognosis and are probably attributable to several factors indicating improved CD care.[9] However, ICR remains an important treatment modality for CD despite the expanding arsenal of CD medication over the past few decades.[10,11] Comparative data on ICR in CD in Asian and Western countries are limited. Long-term data on prognosis after ICR in CD in these countries may clarify the differences in clinical course, management, and prognosis of CD. In case important differences between the two populations exist, previously reported data on CD surgery and postoperative management may not be reliably extrapolated from one geographical area to the other. In this study, we aimed to gain further insights into the potential differences in indications, postoperative management, and prognosis of CD after ICR between HK and NL.

Methods

Study Design

This multicenter, observational cohort study was performed using data collected from HK and NL. In HK, data were retrieved from a prospective, territory-wide IBD registry, covering 13 public hospitals. In NL, data were obtained from a retrospective cohort study performed in 10 hospitals, including 6 academic and 4 teaching hospitals.

Study Population

All CD patients 16 years of age and older who underwent an ICR between January 2000 and December 2019 were included. The inclusion criteria were primary ICR for an indication of ileal CD, with or without colon involvement. The exclusion criteria were prior intestinal resection, other indications for ICR (eg, malignancy), permanent ileostomy, or absence of follow-up data. Follow-up data were collected until August 2020 in HK and April 2020 in the NL.

Data Collection: HK Population

Eligible HK patients were identified from the HK Inflammatory Bowel Disease Registry (HKIBDR). The HKIBDR is a prospective territory-wide registry developed in 2013, which aims to investigate the prevalence, disease characteristics, treatment, and prognosis of IBD patients in HK.[12] It encompasses 13 Hospital Authority hospitals across 7 clusters in HK and covers more than 95% of IBD patients in HK. In HK, all Hospital Authority hospitals use a computerized Clinical Management System to record variables including demographics, clinical events, prescription histories, endoscopy records, and laboratory results for each patient. Data after the establishment of the HKIBDR were prospectively collected, while those before 2013 were retrospectively retrieved from the Clinical Management System on a case-by-case basis. Any data not listed in the HKIBDR database needed for this study were retrospectively retrieved on a case-by-case basis from electronic medical records.

Data Collection: NL Population

Eligible Dutch patients were identified from the local pathology database using pathology coding for ICR registered by pathologists when writing the pathology report. Based on the search results, electronic patient charts in all hospitals were reviewed to select the study population based on inclusion and exclusion criteria. Data were collected retrospectively on a case-by-case basis from electronic medical records.

Outcomes

The primary endpoint was the presence of postoperative endoscopic recurrence (defined as Rutgeerts score ≥i2b) and/or radiologic recurrence (assessed by a local radiologist on ultrasonography, computed tomography, or magnetic resonance imaging), censored at 18 months after ICR. The secondary endpoints included clinical recurrence (defined as the need to start or switch corticosteroids, immunomodulators, or biologicals for symptomatic disease after ICR) and surgical recurrence (defined as re-resection of the small bowel and/or colon). Furthermore, data on patient-related (eg, age and sex), disease-related (eg, previous exposure to medication and Montreal classification), and surgery-related (eg, indication for surgery and surgical technique) factors were collected. Postoperative prophylaxis was defined as the start or continuation of IBD medication postoperatively for an indication of the prevention of postoperative recurrence within 6 months after ICR.

Statistical Analyses

Categorical variables are presented as frequencies and percentages while continuous variables are presented as medians and interquartile ranges (IQRs). The chi-square test or Fisher's exact test and Mann-Whitney *U* test were used to compare the categorical and continuous variables between HK and NL patients, respectively. A *P* value of .05 was considered statistically significant. The observed cumulative incidences of clinical, endoscopic, and surgical recurrences as well as time to prophylactic medication were calculated using the Kaplan-Meier method and compared between HK and NL using the log-rank test. Furthermore, Bayesian multivariable proportional hazards models were fitted to investigate the association of various potential risk factors with the cumulative incidence of clinical, endoscopic, and surgical recurrences.

The models included the covariates, chosen based on available literature, HK vs NL, age at diagnosis, disease localization (Montreal L), disease behavior (Montreal B), postoperative prophylactic IBD medication, IBD medication use prior to ICR, perianal fistulas, sex, surgical approach, inflammation of the surgical resection margins, length of the resected segment, calendar year of ICR, and type of anastomosis (end to end vs side to side). Owing to the low number of events for surgical recurrence, the corresponding model only included the first 7 aforementioned variables. The use of the Bayesian framework allowed the inclusion of patients in the analysis even when some covariates were missing, by simultaneously fitting the analysis models and imputing missing covariates.[13] Results from the Bayesian models are presented as posterior means and 95% confidence intervals (CIs). Additionally, to visualize differences in incidence between HK and NL, corrected for potential risk factors, the expected cumulative incidences for clinical, endoscopic, and surgical recurrences were plotted for hypothetical, representative HK and NL patients (for whom the population median or reference category was assumed for all other covariates). Analysis of endoscopic recurrence was performed in a subset of patients who had postoperative endoscopy or radiologic imaging within 18 months. In a sensitivity analysis, the model for endoscopic recurrence was repeated using Rutgeerts score ≥i2a as cutoff. All calculations were performed in R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and with the help of the package JointAI.[13]

Ethical Considerations

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was not required because this study used pseudo-anonymous data. The Institutional Research Board of the corresponding centers approved the study protocol (Ref. No. 2013.093 and METC-2017-1151).

Results

A total of 902 CD patients who underwent a primary ICR between 2000 and 2019 were included in this study, including 80 HK and 822 NL patients. The median age at ICR did not differ between the 2 groups (HK: 30.5 [IQR, 24.1-42.0] years vs (vs) NL: 32.3 [IQR, 24.1-45.1] years; P = .297). The proportion of male CD patients was significantly higher in the HK population as compared with the NL population (HK: 55 [65.0%] males vs NL: 317 [38.6%] males; P < .001) (Table 1). The median follow-up period was 8.3 (IQR, 6.0-13.6) years in HK and 5.9 (IQR, 2.5-10.7) years in NL.

Disease Phenotype at CD Diagnosis

The median age at diagnosis did not differ significantly between HK and NL patients (HK: 24.6 [IQR, 18.1-39.0] years vs NL: 25.5 [IQR, 19.9-37.0] years; P = .441). A majority of the patients were diagnosed with CD between 17 and 40 years of age (Montreal classification A2, HK: 49 [61.3%] vs NL: 524 [63.7%]). Disease behavior at CD diagnosis differed between the groups: HK patients had a more stricturing (Montreal B2) and penetrating (Montreal B3) disease as compared with NL patients (B1, HK: 36 [45.0%] vs NL: 585 [71.3%]; B2, HK: 26 [32.5%] vs NL: 138 (16.8%]; B3, HK: 18 [22.5%] vs NL: 97 [11.8%]; P < .001). Disease localization at diagnosis was more often ileocolonic in the HK population (L3, HK: 61.5% vs NL: 33.3%) and ileal in the NL population (L1, HK: 19.2% vs NL: 63.0%) (Table 1). Upper gastrointestinal CD was present at diagnosis in 8 HK (10.7%) vs 42 NL (5.1%) patients (P = .045).

Drug Exposure Prior to ICR

Preoperative exposure to corticosteroids (HK: 32 [40.0%] vs NL: 676 [82.4%]; P < .001), immunomodulators (HK: 39 [48.8%] vs NL: 541 [65.8%]; P = .002) and anti-TNF drugs (HK: 14 [17.5%] vs NL: 364 [44.3%]; P < .001) were lower in the HK than in the NL group. Preoperative exposure to vedolizumab and ustekinumab was low in both populations (vedolizumab: 2 HK (2.5%) and 17 NL (2.1%) patients; ustekinumab: 0 HK and 9 NL (1.1%) patients) (Table 1).

Indication for ICR

ICR was performed at a median of 3.2 (IQR, 0.0-7.5) years (HK population) and 3.1 (IQR, 0.8-8.0) years (NL population) after CD diagnosis (P = .016). The affected location at ICR was most often ileocolonic in the HK population (HK: 66 [82.5%], NL: 299 [36.4%]) and ileal in the NL population (HK: 14 [17.5%], NL: 523 [63.6%]) (P < .001) (Table 2). Indications for ICR differed between the cohorts: the most common indication was penetrating disease in HK (HK: 26 [32.5%], NL: 185 [22.5%]) and stricturing disease in NL (HK: 26 [32.5%], NL: 398 [48.8%]) (P < .001). Other indications for ICR were recorded in 16 (20%) HK patients and 15 (1.8%) NL patients (P < .001): diagnostic laparoscopy or laparotomy (HK: 8 [10.0%], NL: 10 [1.2%]), suspected appendicitis (HK: 2 [2.5%], NL: 5 [0.6%]), and iatrogenic perforation (HK: 2 [2.4%], NL: 0). Spontaneous perforation was an indication for surgery in 4 (5.0%) HK patients and none of the NL patients. No relevant difference in presence of perianal fistula at time of surgery was observed between the groups (HK: 8 [10.5%], NL: 97 [11.8%]; P = .738).

Surgical Characteristics

While laparotomy was performed in most of the HK cases (HK: 45 [72.4%], NL: 362 [45.9%]), laparoscopy was more commonly performed in NL (HK: 16 [27.6%], NL: 426 [54.1%]) (P < .001). Length of the resected segment was 33 (IQR, 20.8-48.3) cm in the HK population and 25 (IQR, 18.0-33.5) cm in the NL population (P < .001). Type of anastomosis was most often end to end in the HK population and side to side in the NL population (P < .001) (Table 2). Temporary protective ileostomy was performed in 11 (17.5%) HK and 41 (5.6%) NL patients. Penetrating disease complications were present in the majority of these patients (HK: 7 [63.6%], NL: 25 [61.0%] patients; P = .256). Postoperative complications included anastomotic leakage (HK: 7 [8.9%], NL: 62 [7.6%]; P = .693), postoperative bleeding (HK: 1 [1.3%], NL: 25 [3.1%]; P = .722), and wound infection (HK: 2 [2.5%], NL: 46 [5.7%]; P = .305). The rate of reoperation for complications was similar in both groups (HK: 4 [5.0%], NL: 41 [5.0%]; P = 1.000). Thirty-day mortality was not observed in either group.

Prophylactic IBD Medication

Median time to prophylactic medication, defined as postoperative start or continuation of IBD medication for the indication of prevention of recurrence, was 1.1 weeks in

TABLE 1. Baseline characteristics of the study population in Hong Kong and the Netherlands

	Hong Kong (n = 80)	The Netherlands (n = 822)	*P* Value
Age at surgery, y	30.5 (24.1-42.1)	32.3 (24.1-45.1)	.297[a]
Male	52 (65.0)	317 (38.6)	<.001[b]
Smoking status at time of ICR			
Active smoker	1 (1.3)	285 (34.7)	<.001[b]
Previous smoker	2 (2.6)	115 (14.0)	
Never	62 (79.5)	369 (44.9)	
Missing	13 (16.7)	53 (6.4)	
Age at diagnosis (Montreal)			.857[b]
≤16 y(A1)	13 (16.3)	116 (14.1)	
17-40 y (A2)	49 (61.3)	525 (63.8)	
> 40 y (A3)	18 (22.5)	182 (22.1)	
Location at diagnosis (Montreal)			<.001[b]
Ileum (L1)	15 (19.2)	517 (63.0)	
Colon (L2)	15 (19.2)	31 (3.8)	
Ileocolon (L3)	48 (61.5)	273 (33.3)	
Concomitant upper gastrointestinal (L4)	8 (10.7)	42 (5.1)	<.045[b]
Behavior at diagnosis (Montreal)			<.001[b]
Luminal (B1)	68 (45.0)	585 (71.3)	
Stricturing (B2)	26 (32.5)	138 (16.8)	
Penetrating (B3)	18 (22.5)	97 (11.8)	
Perianal fistula at baseline	15 (19.5)	84 (10.2)	.013[b]
Exposure to immunomodulator prior to ICR (methotrexate and/or thiopurine)	39 (48.8)	541 (65.8)	.002[b]
Exposure to anti-TNF prior to ICR (adalimumab and/or infliximab)	14 (17.5)	364 (44.3)	<.001[b]
Exposure to vedolizumab prior to ICR	2 (2.5)	17 (2.1)	.683[c]
Exposure to ustekinumab prior to ICR	0	9 (1.1)	1.000[c]

Values are median (interquartile range) or n (%). In case of missing data, valid percentages are presented.
Abbreviations: ICR, ileocecal resection; TNF, tumor necrosis factor.
[a]Mann-Whitney *U* test.
[b]Chi-square test.
[c]Fisher's exact test.

HK and 0 weeks in NL ($P < .001$). Postoperative prophylactic medication was prescribed in 65 (81.3%) HK vs 386 (47.1%) NL patients ($P < .001$). Prophylactic treatment included aminosalicylates (5-aminosalicylic acid) in 28 (35.0%) HK vs 67 (8.2%) NL patients and corticosteroids in 7 (8.8%) HK vs 13 (1.6%) NL patients. Immunomodulators were prescribed in 30 (37.5%) HK vs 187 (22.8%) NL patients. Biologics (69 [8.4%] patients) and combination therapy (50 [6.1%] patients) were prescribed for a small group of NL patients, but none was prescribed for the HK patients. Instead, postoperative metronidazole was prescribed in 18 (22.5%) HK patients.

Postoperative Prognosis: Endoscopic Recurrence During Follow-Up

A total of 29 (36.3%) HK vs 527 (64.1%) NL patients underwent endoscopy or radiologic imaging within 18 months after ICR ($P < .001$). Time to first postoperative endoscopy was similar in both groups (HK: 7.9 [IQR, 5.6-12.4] months vs NL: 6.8 [IQR, 5.2-9.4] months; $P = .085$). Endoscopic and/or radiologic recurrence (defined as Rutgeerts ≥i2b) was diagnosed in 10 (31.3%) HK and 219 (41.6%) NL patients with endoscopy or radiologic assessment within 18 months ($P = .250$). The observed cumulative incidence of endoscopic and/or radiologic recurrence after 6, 12, and 18 months was 0.16, 0.28, and 0.32 in HK patients and 0.18, 0.35, and 0.43 in NL patients, respectively ($P = .254$). The expected cumulative incidence of endoscopic and/or radiologic recurrence, corrected for potential risk factors, also showed no significant difference between the 2 groups (Figure 1B and C). The most severe Rutgeerts score at endoscopy within 18 months after ICR is listed in Table 3. A sensitivity analysis was performed using Rutgeerts score ≥i2a as a cutoff for endoscopic and/or radiologic recurrence, which showed comparable results (HR endoscopic recurrence Rutgeerts ≥i2a: 0.54 [IQR, 0.26-1.05] vs HR Rutgeerts≥i2b: 0.54 (IQR, 0.24-1.21).

Clinical and Surgical Recurrence During Follow-Up

Overall, 51 (63.8%) HK and 495 (60.2%) NL patients developed clinical recurrence ($P = .537$), and 12 (15.0%) HK vs 136 (16.5%) NL patients underwent re-resection during total follow-up (HK: 10 [83.3%] re-resection of the ileum, 2 [16.7%] ileocolonic; NL: 25 [18.4%] ileum, 12 [8.8%] colon, 99 [72.8%] ileocolonic; $P < .001$). The observed incidence of clinical recurrence at 12, 24, and 60 months after ICR was 0.34, 0.38, and 0.52 in HK patients vs 0.25, 0.40, and 0.59 in NL patients, respectively ($P = .341$) (Figure 1A). Observed incidence of surgical recurrence at 12, 24, and 60 months after ICR was 0.03, 0.03, and 0.07 in HK patients vs 0.03, 0.05, and 0.1 in NL patients, respectively ($P = .139$).

TABLE 2. Surgical data comparing ileocolonic resection in Hong Kong and the Netherlands

	Hong Kong (n = 80)	The Netherlands (n = 822)	*P* Value
Indication for surgery			<.001[a]
Refractory noncomplicated disease or instead of step-up therapy	12 (15.0)	224 (27.3)	
Stricture	26 (32.5)	398 (48.8)	
Penetrating disease (fistula or abscess)	26 (32.5)	185 (22.5)	
Spontaneous perforation	4 (5.0)	0	
Other	16 (20.0)	15 (1.8)	
Time between CD diagnosis and ICR, y	3.2 (0.0-7.5)	3.1 (0.8-8.0)	.016[b]
Montreal L at time of surgery[c]			<.001[a]
Ileum (L1)	14 (17.5)	523 (63.6)	
Colon (L2)	0	0	
Ileocolon (L3)	66 (82.5)	299 (36.4)	
Montreal B at time of surgery[d]			.175[a]
Luminal (B1)	24 (30.0)	177 (21.5)	
Stricturing (B2)	32 (40.0)	400 (48.7)	
Penetrating (B3)	24 (30.0)	245 (29.8)	
Perianal fistula at time of surgery	8 (10.5)	97 (11.8)	.738[a]
Surgical approach			
Laparoscopy	16 (27.6)	426 (54.1)	<.001[a]
Laparotomy	42 (72.4)	362 (45.9)	
Type of anastomosis			<.001[a]
End to end	40 (63.5)	71 (9.8)	
End to side	1 (1.6)	44 (6.1)	
Side to side	11 (17.5)	571 (78.5)	
Two-stage procedure with secondary anastomosis	11 (17.5)	41 (5.6)	
Length of resected segment, cm	34 (20.5-48.5)	25 (18-33.5)	<.001[b]
Resection margin			.146[a]
No inflammation at both margins	38 (70.4)	386 (64.4)	
Inflammation at ileal resection margin	7 (13.0)	135 (22.5)	
Inflammation at colonic resection margin	2 (3.7)	37 (6.2)	
Inflammation at both ileal and colonic resection margin	7 (13.0)	41 (6.8)	
Postoperative complications			
Wound infection	2 (2.5)	46 (5.7)	.305[b]
Anastomotic leakage	7 (8.9)	62 (7.6)	.693[b]
Hemorrhage	1 (1.3)	25 (3.1)	.722[b]
Reintervention (not related to CD recurrence)	4 (5.0)	41 (5.0)	1.000[b]
30-d mortality	0	0	NA

Values are n (%) or median (interquartile range). In case of missing data, valid percentages are presented.
Abbreviations: CD, Crohn's disease; ICR, ileocecal resection; NA, not applicable.
[a]Chi-square test.
[b]Mann-Whitney *U* test.
[c]Disease localization according to Montreal classification.
[d]Disease behavior according to Montreal classification.

Multivariable Analysis

Results of the multivariable proportional hazards models, with hazard ratios (HR) and 95% CIs, for clinical, endoscopic and/or radiologic, and surgical recurrence are displayed in Table 4. The expected cumulative incidence of endoscopic recurrence, corrected for potential risk factors, showed no difference in the risk of endoscopic recurrence for HK and NL patients (HR, 0.54; 95% CI, 0.24-1.21). No significant differences were observed between HK and NL patients for clinical (HR, 0.91; 95% CI, 0.62-1.32) (Figure 1A) and surgical (HR, 0.61; 95% CI, 0.31-1.13) (Figure 1D) recurrence.

Discussion

To the best of our knowledge, this is the first study comparing differences in phenotype and surgical management with long-term prognosis after ICR in CD between low- and high-incidence countries. The risk of CD recurrence after primary ICR was found to be similar for high-incidence and newly industrialized, low-incidence countries despite differences in CD phenotype at diagnosis, surgical approach, indications, and pre- and postoperative management including prophylactic medication. The observed differences between both populations need to be carefully considered when extrapolating data

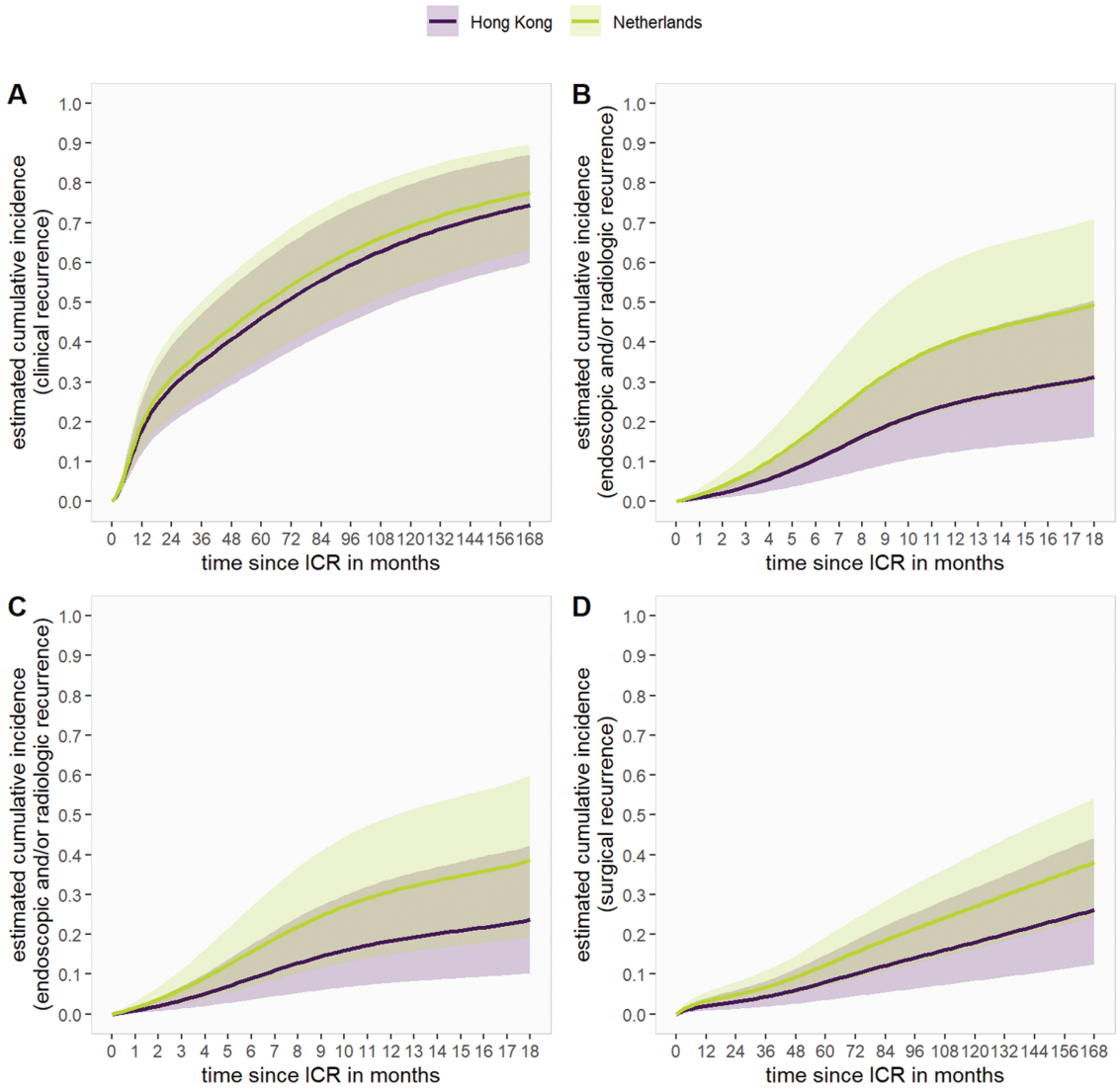

FIGURE 1. The estimated cumulative incidence of recurrence comparing patients in Hong Kong and the Netherlands (which have the same reference values [median or reference category] for all other covariates). A and D, Expected cumulative incidence of recurrence over the first 168 months after surgery for clinical and surgical recurrence are shown for the total population (n = 902). B and C, Expected incidence of recurrence over the first 18 months after surgery for endoscopic and/or radiological recurrence (Rutgeerts ≥i2a and Rutgeerts ≥i2b) are shown in a subset of patients with endoscopic or radiologic examination within 18 months after surgery (n = 559). ICR, ileocecal resection.

TABLE 3. Most severe Rutgeerts score at endoscopy within 18 months after ileocecal resection

Rutgeerts Score	Hong Kong (n = 25)	The Netherlands (n = 465)	Total (n = 490)
No lesions in distal ileum (i0)	11 (44.0)	144 (31.0)	155 (31.6)
≤5 aphthous ulcers (i1)	2 (8.0)	85 (18.3)	87 (17.8)
Lesions confined to the anastomosis (i2a)	5 (20.0)	70 (15.1)	75 (15.3)
>5 aphthous lesions with normal mucosa between lesions; areas scattered with larger erosions (i2b)	3 (12.0)	93 (20.0)	96 (19.6)
Diffuse aphthous ileitis (i3)	2 (8.0)	46 (9.9)	48 (9.8)
Diffuse inflammation with larger ulcers, nodules, and/or strictures (i4)	2 (8.0)	26 (5.6)	28 (5.7)

Values are n (%).

regarding postoperative management and prognosis after ICR from one geographical area to the other.

This study showed a marked difference in CD phenotype between the HK and NL patients, both at CD diagnosis and at ICR. At diagnosis, CD phenotype is luminal in the majority of NL patients vs stricturing or penetrating in HK patients. At ICR, penetrating disease is the main ICR indication in the East while stricturing disease is the most common indication in the West. The explanation for these differences could simply be a matter of diagnostic delay or management differences between the 2 geographical areas after diagnosis.[3] In addition, differences in the pathogenesis between the populations should not be disregarded. Although the data used in this study could not unravel the complex interplay between CD characteristics and management, they provide new insights into geographical differences. We hypothesize that the observed differences in ICR indications could be explained by a more severe phenotype at diagnosis combined with less aggressive CD treatment in HK. More information on explanations for a possible delay at diagnosis might provide clues on

TABLE 4. Results from the multivariable proportional hazards models for clinical and surgical recurrence in total population and endoscopic or radiologic recurrence in subset of patients who had an endoscopy or radiology exam within 18 months after ICR

	Clinical Recurrence		Endoscopic Recurrence		Surgical Recurrence	
	HR	95% CI	HR	95% CI	HR	95% CI
Male	0.84	0.70-1.01	1.19	0.89-1.57	1.24	0.88-1.73
Hong Kong vs the Netherlands	0.91	0.69-1.32	0.54	0.24-1.21	0.61	0.312-1.13
Age at diagnosis	1.10	0.99-1.01	1.00	0.99-1.01	0.99[a]	0.97-0.998[a]
Montreal L[b]						
Ileum	Ref		Ref		Ref	
Ileocolonic	1.17	0.97-1.41	1.35[a]	1.01-1.78[a]	1.38	0.98-1.95
Montreal B[c]						
Nonstricturing, nonpenetrating	Ref	Ref	Ref	Ref	Ref	Ref
Stricturing	0.97	0.78-1.12	0.57	0.64-1.22	1.17	0.77-1.80
Penetrating	0.87	0.67-1.12	0.78	0.54-1.14	0.72	0.43-1.19
Postoperative prophylactic medication						
Non/5-ASA/CS	Ref		Ref		Ref	
Immunomodulator	0.54[a]	0.42-0.67[a]	0.62[a]	0.43-0.89[a]	0.42[a]	0.26-0.65[a]
Biological	0.65[a]	0.45-0.92[a]	0.70	0.42-1.14	1.38	0.73-2.43
Immunomodulator and biological	0.27[a]	0.15-0.46[a]	0.16[a]	0.08-0.43[a]	0.07[a]	0.00-0.51[a]
Biological use prior to surgery	1.35[a]	1.07-1.70[a]	1.07	0.78-1.47	1.50	0.98-2.23
Immunomodulator use prior to surgery	1.10	0.89-1.37	1.22	0.88-1.71		
Perianal fistula	1.31	0.99-1.70	1.21	0.89-1.57		
Surgical approach, laparotomy	1.28[a]	1.04-1.56[a]	0.92	0.67-1.27		
Microscopic activity at resection margin						
No inflammation	Ref		Ref			
Proximal inflammation	1.10	0.85-1.41	1.530[a]	1.03-2.22[a]		
Distal inflammation	1.13	0.73-1.69	1.405	0.69-2.62		
Both sides inflammation	1.41[a]	0.97-2.00[a]	2.689[a]	1.58-4.44[a]		
Length of resected segment in cm	1.00	0.99-1.01	1.001	0.99-1.01		
Year of ICR	1.04[a]	1.02-1.07[a]	1.021	0.99-1.06		
Anastomosis (end to end vs side to side)	1.06	0.79-1.45	1.18	0.67-2.27		

Abbreviations: 5-ASA, 5-aminosalicylic acid; CI, confidence interval; CS, corticosteroids; HR, hazard ratio; ICR, ileocecal resection.
[a]Statistically significant.
[b]Disease localization according to Montreal classification.
[c]Disease behavior according to Montreal classification.

whether a truly different phenotype exists. Another important issue for further study is whether early medical treatment can influence disease progression, especially because previous studies have reported that an early introduction of biological treatment resulted in lower surgical rates.[8,14]

Several clues on a different pathogenesis of CD in both geographical areas have been reported. First, important genetic differences have been observed. In a meta-analysis with data from 93 studies, most of the genetic variants commonly identified in Caucasian IBD patients, such as NOD-2 (nucleotide oligomerization domain 2) variants, were not detected in the Asian population.[15] In contrast, other rare amino acid polymorphisms were reported to be disease associated in Asians.[15] Because only 13% of CD heritability can be explained by genetic variation, it appears that the increase in CD incidence in Asia is not merely due to genetic factors, but also due to environmental factors.[16] As the emergence of CD in low-incidence countries has followed industrialization and environmental changes, it has been suggested that the increase in CD incidence might be partially explained by a shift toward a Westernized environment and diet.[1] These differences warrant further investigation, as they may indicate whether intrinsic differences in CD truly exist, and the observed differences may have health care implications in terms of a need for IBD medication, hospitalization, and surgery.

In this study, HK patients were less exposed to IBD medication prior to surgery as compared with NL patients. The interpretation of this finding requires an acknowledgment that the use of standard validated international treatment guidelines and recommendations from the West may not be suitable for Asian countries. Besides, the current therapeutic approach and clinical management of IBD differ even among Asian countries.[17] A high prevalence of infectious diseases, including tuberculosis and hepatitis B virus, has resulted in a limited use of immunosuppressive IBD therapies within the Asia-Pacific region.[18] Corticosteroids and 5-aminosalicylic acid remain important agents for the induction of remission in IBD throughout Asia.[19,20] Furthermore, the utilization of biologic therapy is low in HK owing to a high cost and lack of insurance coverage.[21,22]

Postoperative drug therapy based on risk stratification, combined with early postoperative colonoscopy and treatment

for recurrence, is considered superior to conventional drug therapy alone for the prevention of postoperative CD recurrence.[23] Remarkably, our study showed that the adherence to international guidelines concerning postoperative endoscopy strategies was low, as no colonoscopy was performed in a considerable proportion of the HK patients in this study; this could be partly explained by ICR prior to the implementation of these guidelines. An additional difference found was that the vast majority of the HK patients, in comparison with less than half of the NL patients, received postoperative prophylaxis. Because their prognosis did not differ from that of the NL patients, according to the used definitions in this study, further investigation of the additional value of early postoperative endoscopy in the Asian CD population may be considered before an adaptation of the strategy. In addition, more data on the indication of prophylactic medication are required in both geographical areas.

Interestingly, despite the high rate of penetrating disease in HK, postoperative complication and reintervention rates were similar between the East and West. Risk factors for postoperative complications in CD surgery include preoperative steroid use, presence of abscess or fistula at time of resection, low levels of preoperative serum albumin, and malnutrition.[24,25] Insufficient data were available in this study to further explore the risk factors for postoperative complications. Laparoscopic ICR in CD appears to reduce the risk of postoperative complications compared with open surgery, and offers advantages including less adhesion formation which reduces the risk of bowel injury during future operative interventions.[26,27] Laparotomy was more common in the HK population as compared with NL population. The most important reason for laparotomy is the surgeon's preference, as especially in the first years of the study period, surgeons in HK were not familiar with laparoscopic surgery in CD patients. This was in line with the data in our study: 26 (83.9%) of 31 were ICRs by laparotomy in the period from 2000 to 2010, vs 16 (59.3%) of 58 from 2010 to 2019. In addition, we hypothesize that the higher total rate of penetrating disease complications, massive bleeding, and iatrogenic or spontaneous perforations (62% HK vs 22.5% NL cases) is a second plausible reason for the higher rate of laparotomy in HK. Because CD patients are at a high risk of recurrence and reoperation, the implementation of laparoscopy as the standard surgical technique is recommended in HK.

A few limitations were noted in this study. First, the relatively low number of patients included in HK during a longer study period was a drawback of this study. The findings on prognosis after ICR need to be interpreted with caution, especially because the management of CD has changed during the study period. This drawback is difficult to overcome when studying a (formerly) low-incidence region, and should be weighed against the important advantage of the regional coverage of the registration (HKIBD registry coverage ± 95%). Second, identification of patients was performed differently for both countries (pathology database in NL vs HKIBD registry). Nevertheless, both methods are valid to identify nearly all patients. Third, owing to the retrospective study design, data on clinical disease activity scores were not available, nor were correlation data between symptoms and endoscopic data. As data on postoperative indication for endoscopy were not recorded in our study, confounding by indication cannot be ruled out. Additionally, the definition of endoscopic recurrence within 18 months may potentially overestimate (early) recurrence rates. We chose to present (continuous) data on endoscopic recurrence on the time frames of 6, 12, and 18 months. Presently, endoscopy at 6 to 12 months is a widely accepted time frame to evaluate endoscopic recurrence. During the study period, a time frame of 18 months was common, also in trials.[17,23] Last, information on several factors possibly associated with the postoperative course of CD was lacking, such as body composition, nutritional status, ethnicity, socioeconomic status, extraintestinal manifestations, and family history of IBD, as well as data on the drug survival of postoperative prophylaxis.

Conclusions

In conclusion, the main indication for ICR in CD patients is penetrating disease in the East and stricturing disease in the West. Although considerable differences between both geographical areas were observed in terms of pre- and postoperative management, the long-term prognosis after ICR is similar.

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CONFLICTS OF INTEREST

J.M. has received research grants from Janssen and Gilead Sciences. F.H. has served on advisory boards or as a speaker for AbbVie, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk; received research funding from Dr. Falk, Janssen-Cilag, AbbVie, and Takeda; and received consulting fees from Celgene and Janssen-Cilag, outside of the submitted work. A.B. has served on the advisory board for Takeda, AbbVie, and Janssen, outside of the submitted work. G.D. has received grant support from DSM Nutritional Products LTD and speaker fees from Janssen Pharmaceuticals, AbbVie, and Takeda, outside of the submitted work. K.H.N.d.B. has served as a speaker for AbbVie and MSD; served as a consultant and principal investigator for TEVA Pharma BV and Takeda;

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