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Original Article

Diagnosis and Clinical Features of Perianal Lesions in Newly Diagnosed Crohn's Disease: Subgroup Analysis from Inception Cohort Registry Study of Patients with Crohn's Disease (iCREST-CD)

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Abstract

Background and Aims: Perianal lesion is a refractory phenotype of Crohn's disease [CD] with significantly diminished quality of life. We evaluated the clinical characteristics of perianal lesions in newly diagnosed CD patients and the impact of perianal lesions on the quality of life in Japanese patients with CD.

Methods: Patients newly diagnosed with CD after June 2016 were included between December 2018 and June 2020 from the Inception Cohort Registry Study of Patients with CD [iCREST-CD].

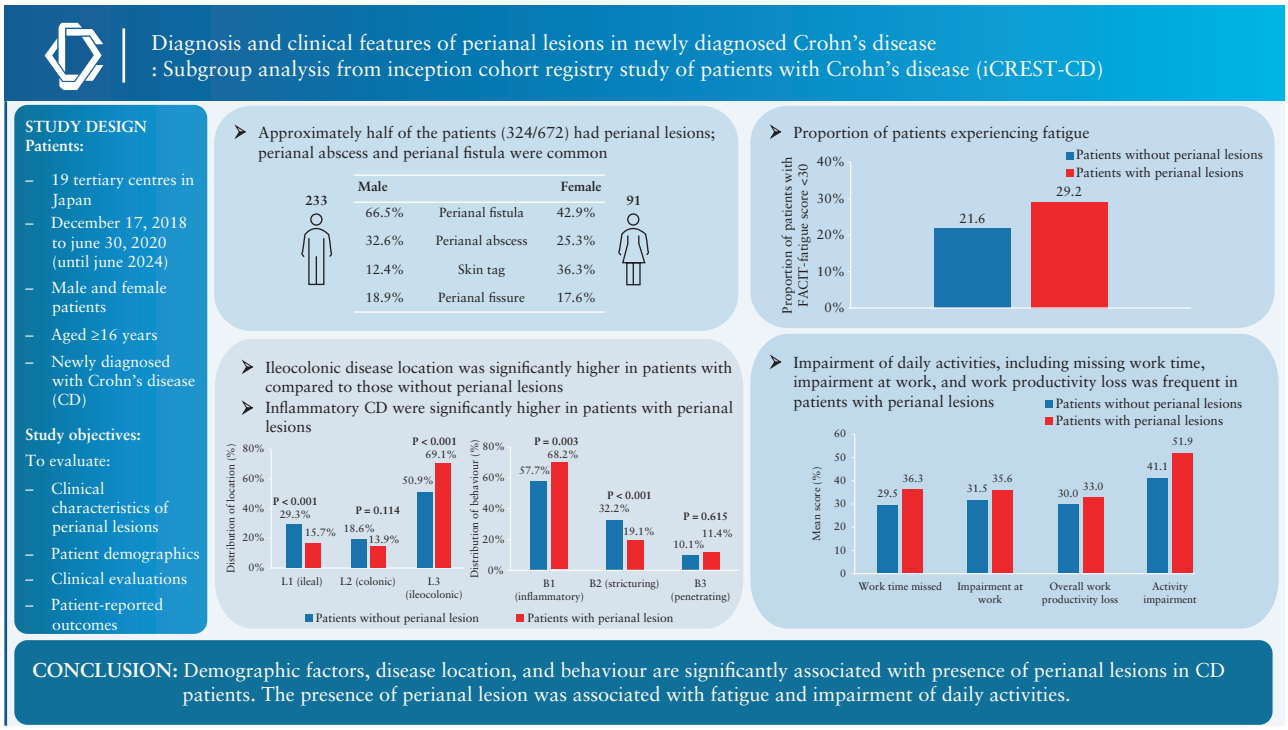
Results: Perianal lesions were present in 324 [48.2%] of 672 patients with newly diagnosed CD; 71.9% [233/324] were male. The prevalence of perianal lesions was higher in patients aged <40 years vs ≥40 years, and it decreased with age. Perianal fistula [59.9%] and abscess [30.6%] were the most common perianal lesions. In multivariate analyses, male sex, age <40 years and ileocolonic disease location were significantly associated with a high prevalence of perianal lesions, whereas stricturing behaviour and alcohol intake were associated with low prevalence. Fatigue was more frequent [33.3% vs 21.6%] while work productivity and activity impairment-work time missed [36.3% vs 29.5%] and activity impairment [51.9% vs 41.1%] were numerically higher in patients with than those without perianal lesions.

Conclusions: At the time of CD diagnosis, approximately half of the patients had perianal lesions; perianal abscesses and perianal fistulas were the most common. Young age, male sex, disease location and behaviour were significantly associated with the presence of perianal lesions. The presence of perianal lesion was associated with fatigue and impairment of daily activities.

Clinical trials registry: University Hospital Medical Information Network Clinical Trials Registry System [UMIN-CTR, UMIN000032237].

Key Words: Crohn's disease; patient-reported outcomes; perianal lesion

Graphical Abstract



1. Introduction

Crohn's disease [CD] is a chronic transmural inflammatory bowel disease [IBD].[1–3] The incidence of perianal lesions in patients with CD has been reported to be in the range 20–40% worldwide,[4,5] with a higher incidence of 30.3–58.8% in Asian countries.[6,7] An estimated 26% of patients with CD develop perianal fistula within two decades of the diagnosis.[4] The natural course of perianal CD may be affected by the location of the disease, age at diagnosis, type of intestinal fistula, and the presence of abscesses and intestinal strictures.[8,9] The retrospective Crohn's Disease Clinical Network and Cohort [CONNECT] study from Korea reported a significant association of perianal fistula with young age, male gender, diagnosis of CD at primary care centres and ileocolonic involvement.[7]

Perianal lesions, especially perianal fistula, in patients with CD are a marker of chronic, debilitating and aggressive disease, which can cause pain, swelling and discharge in the perianal region.[10] This condition has a major negative effect on the health-related quality of life [HRQoL] through increased morbidity, resulting from sphincter and perineal tissue destruction, physical disability, and a weakened sexual and psychological state.[5,11,12] Studies have demonstrated the association of perianal fistula with greater disease burden, adversely affected HRQoL and high healthcare costs.[13]

The diagnosis and treatment of perianal lesions, however, are challenging; an accurate understanding of the clinical features and the natural course of perianal CD is paramount in providing the most appropriate therapeutic strategy.[13] The Inception Cohort Registry Study of Patients with Crohn's Disease [iCREST-CD] is an ongoing large-scale, multicentre, prospective registry in Japan that is aimed at investigating the onset, diagnosis and treatment of newly diagnosed patients with CD. An interim analysis of the iCREST-CD study revealed the demographics and disease characteristics of newly diagnosed CD patients and demonstrated that the disease

phenotype varied between patients <40 and ≥40 years of age.[14]

In this current report, we present a subgroup analysis of the iCREST-CD study to understand the natural history and clinical characteristics of perianal lesions in CD, to provide an understanding of the diagnostic and clinical aspects of perianal lesions, and to assess their impact on the activities of daily living in patients newly diagnosed with CD. This study comprehensively and thoroughly evaluates the clinical features of perianal lesions associated with newly diagnosed CD using the nationwide registry database.

2. Materials and Methods

2.1. Study design

iCREST-CD is a prospective cohort study being conducted at 19 tertiary centres in Japan, with an observation period until June 2024. Details of the study design have been described in the primary publication of the iCREST-CD study.[14] The present study is a subgroup analysis using a prospectively maintained database [iCREST-CD] to investigate the impacts of perianal lesions on the clinical features of patients with newly diagnosed CD.

2.2. Study population

Male and female patients, newly diagnosed with CD as per the Japanese diagnostic criteria [including suspected diagnosis][15–17] after June 1, 2016, aged ≥16 years at the time of informed consent, were enrolled from December 17, 2018 to June 30, 2020. Patients with an unknown date of diagnosis of CD and/or those who had used a biologic agent indicated for autoimmune disease prior to the diagnosis of CD were excluded.

2.3. Data collection

Patients were identified from the medical records, and data prospectively collected from the day of informed consent were obtained. Data on activities of daily living and QoL were self-reported by patients. Patient-completed questionnaires were recorded into the study database through an internet-based application by patients' smartphone or tablet terminals and were considered as source data. Patients will be prospectively followed up for 4 years during the observation period; additionally, retrospective data will be collected. Data such as patient demographics, clinical characteristics and imaging tests from the initial diagnosis until enrolment were retrospectively collected. An interim analysis of the iCREST-CD study was conducted on Japanese patients registered in this study. The current interim analysis of the iCREST-CD study describes the clinical characteristics of patients with perianal involvement at the time of diagnosis of CD. Longitudinal perianal data after the diagnosis of CD will be analysed in future studies.

2.4. Study investigations

The study investigations included patient demographics, clinical characteristics, clinical evaluation and patient-reported outcomes [PROs]. Demographic and clinical characteristic data included age, gender, age at disease onset, CD characteristics, body mass index [BMI], extra-intestinal complications, history of hospitalization and occupation. Other clinical observations included the types of perianal lesions observed at the definitive diagnosis of CD, the implementation rate of imaging tests (colonoscopy, small bowel follow-through, balloon-assisted endoscopy, small bowel capsule endoscopy, bowel ultrasonography, computed tomography [CT] enterography, and magnetic resonance [MR] enterography), and the sites of intestinal involvement associated with perianal lesions at diagnosis of CD.

The characteristics of intestinal lesions by perianal lesion type at CD diagnosis were determined by [i] the location and type of intestinal lesions, [ii] the location and behaviour of intestinal lesions through the modified Montreal system of classification,[18] and [iii] the types of fistula and abscesses in the intestinal lesions.

Clinical evaluation was performed using the imaging findings and the Harvey–Bradshaw Index [HBI]. Disease activity in patients with perianal lesions at CD diagnosis was determined using HBI, patient general well-being, abdominal pain and the number of liquid/soft stools at diagnosis.

For PROs of the lifestyle survey, health status and QoL, data were collected using an internet-based application for patients who provided written informed consent at the time of study enrolment [December 17, 2018 to June 30, 2020]. Baseline PROs could not be collected from patients who were already diagnosed with CD prior to this period. The health status of patients was determined by their general condition and abdominal pain.

QoL was measured through the impairment of daily living activities using the Functional Assessment of Chronic Illness Therapy-Fatigue scale version 4 [FACIT-Fatigue],[19,20] Work Productivity and Activity Impairment Questionnaire-General Health version 2.2 [WPAI-GH],[21,22] and Short-form Inflammatory Bowel Disease QoL [SIBDQ].[23] The lifestyle survey evaluated the frequency of meals, smoking and drinking history, amount of exercise, sleep and work status.

2.5. Statistical analysis

This subgroup analysis from the interim data of the iCREST-CD study was performed after the last patient was enrolled. Data at the time of CD diagnosis were taken from the data closest to the date of diagnosis within 3 months before and after CD diagnosis. The statistical analysis was performed on SAS System version 9.4 [SAS]. Summary statistics, frequency and proportion were calculated for the patient characteristics at the time of CD diagnosis. The age-wise and gender-wise distribution of the prevalence of perianal lesions was reported. The distribution of location and behaviour of intestinal CD in patients with and without perianal lesions was compared using Fisher's exact test. The difference in the types of perianal lesions was also evaluated in the male and female patient subgroups using Fisher's exact test. Differences in patient characteristics at CD diagnosis were assessed using the chi-square test [age at diagnosis—modified Montreal classification, smoking history, alcohol history and social background], Fisher's exact test [gender, age at diagnosis—Vienna classification, diagnosis of CD] and Student's *t*-test [mean age at diagnosis, BMI]. The chi-square test was conducted to compare differences in the disease activity classification, well-being status, abdominal pain and episodes of liquid stools according to the Bristol Scale. The Student *t*-test was used to evaluate the differences in the mean HBI scores between patients with/without perianal lesions. To determine the presence of significant associations between risk factors and perianal lesions in patients with CD, logistic regression analysis was performed. Univariate analysis included sex, age, BMI, family history, disease location, disease

behaviour, extra-intestinal manifestation [EIM], smoking history and alcohol intake as covariates; all patients observed for each item were included. Subsequently, multivariate analysis was performed to determine the dependent variables; only patients with data available for all covariates [sex, age, BMI, family history, disease location, disease behaviour, EIM, smoking history and alcohol intake] were included. Fischer's exact test was carried out to compare significant differences in the FACIT-Fatigue score categories [<30 vs ≥30]. To detect significant differences in the WPAI-GH and SIBDQ scores between subgroups, a Student *t*-test and/or a Wilcoxon rank sum test was performed. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Eligibility for the study and summary of the eligible patients

A total of 673 newly diagnosed patients with CD were enrolled, of whom 672 [male: 458, female: 214; mean age at diagnosis of CD: 29.4 years] were eligible for the interim analysis. One patient did not meet the diagnosis [probable] criteria; the subsequent re-diagnosis was ulcerative colitis. This patient was excluded from the analysis. Detailed information for the patient baseline characteristics of the 672 patients is presented in Table 1.

3.2. Prevalence of perianal lesions

Perianal lesions were present in 48.2% of patients [324/672] and absent in 50.3% of patients [338/672]; data were not available for the remaining ten patients. In patients with perianal lesions, 94.4% [306/324] had a definitive diagnosis of CD, whereas 5.6% [18 patients] had a suspected diagnosis. Only two of the 324 patients [0.6%] showed Crohn's perianal lesions without involvement of the intestine [perianal fistula for both patients]. The majority [71.9%; 233/324] of patients with perianal lesions were male, and the mean ± standard deviation [SD] age at diagnosis was 25.6 ± 9.3 years [Table 1]. Perianal lesions were more common in younger patients [<40 years], and the prevalence of perianal lesions decreased with age [Table 1; Figure 1A]. The proportion of patients younger than 40 years was significantly higher in patients with perianal lesions as compared with those without perianal lesions (92% [298/324] vs 70.1% [237/338]; $p < 0.001$; Table 1). Patients younger than 16 years of age had the highest prevalence of perianal lesions [63%], while elderly patients over 75 years of age did not have perianal lesions [Figure 1A]. With respect to the subgroups of age [<40 vs ≥40 years] and sex [male vs female], the prevalence of perianal lesions was highest in young males [aged <40 years] as compared with those older than 40 years, or female patients [Figure 1]. Mean BMI was not significantly different between patients with and without perianal lesions [Table 1]. The proportion of patients with and without perianal lesions having a history [current/past] of smoking [31.9 vs 31.8%] and current alcohol intake [59.7 vs 56.1%] was comparable. Regarding social background, there was a significant difference between patients with and without perianal lesions across the different categories [$p = 0.004$, Table 1].

3.3. Types of perianal lesions

In a total of 672 patients, the most common type of perianal lesion observed at the time of CD diagnosis was perianal fistula [59.9%], followed by perianal abscess [30.6%], skin tag [19.1%], perianal fissure [18.5%], ulcer [11.1%], stenosis [4.6%] and others [3.7%] [Table 2]. In total, 58 [58.6%] of 99 patients with perianal abscess had an underlining fistula. In both males and females, perianal fistulas were the most common type of perianal lesions [66.5 and 42.9%, respectively]. The second most common type of lesion observed was perianal abscess [32.6%] in males and skin tag [36.3%] in females [Table 2]. The prevalence of both perianal fistulas and abscesses was numerically higher in males. Skin tags were more commonly observed in females [36.3 vs 12.4% in males, $p < 0.001$], and the prevalence of ulcers was numerically higher in females [15.4% vs 9.4% in males, $p = 0.167$]. The prevalence of fissure and stenosis was similar between males and females.

3.4. Disease activity

At CD diagnosis, the mean HBI score was similar in patients with and without perianal lesions [Table 3], although disease activity was affected not only by perianal lesions but also by coexisting intestinal lesions and EIMs. There was no difference between patients with and without perianal lesions based on the severity of disease activity, the status of general well-being and abdominal pain. Overall, there were few patients with EIMs [24/672; 3.6%, Table 4]. The prevalence of EIMs was similar between patients with vs without perianal lesions [4.0 vs 3.0%], with erythema nodosum being the most frequent complication in patients with [3.4%] or without [2.1%] perianal lesions. The levels of laboratory markers including white blood cells [WBCs], platelets and erythrocyte sedimentation rate [ESR] were significantly higher in patients with perianal lesions at CD diagnosis [Supplementary Table 1].

3.5. Location and behaviour of coexisting intestinal CD

The distribution of intestinal location and disease behaviour in patients with and without perianal lesions is shown in Figure 2. The most common location was L3 [ileocolonic], followed by L1 [ileal] and L2 [colonic] in both patients with and without perianal lesions [Figure 2A]. Ileocolonic disease location was significantly higher and ileal location was significantly lower in patients with perianal lesions compared to those without [both $p < 0.001$]. The most common behaviour was B1 [inflammatory], followed by B2 [stricturing] and B3 [penetrating], in patients with and without perianal lesions [Figure 2B]. The proportion of inflammatory CD was significantly higher in patients with perianal lesions [68.2 vs 57.7%, respectively; $p = 0.006$], while stricturing CD was significantly lower in patients with perianal lesions compared to those without [19.1 vs 32.2%, respectively; $p < 0.001$]. Details of behaviour and location of intestinal CD in patients with each type of perianal lesion are presented in Supplementary Table 2.

3.6. Clinical factors associated with presence of perianal lesions at CD diagnosis

In univariate analyses, sex, age, ileocolonic location [L3 vs L1], stricturing behaviour [B2 vs B1], history of smoking, and alcohol intake were significantly [$p < 0.05$] associated with the presence of perianal lesions, while no association was found with colonic location [L2 vs L1], positive EIMs, BMI, family history or penetrating disease behaviour [B3 vs B1]. Multivariate multiple regression analyses (odds ratio, OR

Table 1. Characteristics of patients with/without perianal lesions at the diagnosis of Crohn's disease

Parameters		Patients with perianal lesions [*N* = 324], *n* [%]	Patients without perianal lesions [*N* = 338], *n* [%]	*p*-Value
Gender	Male	233 [71.9]	219 [64.8]	$p = 0.055$
	Female	91 [28.1]	119 [35.2]	
Age at diagnosis of CD	Mean [SD]	25.6 [9.3]	32.9 [15.1]	$p < 0.001$*
	Median [min–max]	23.0 [13–73]	28.0 [14–86]	
	≤16 years	30 [9.3]	28 [8.3]	$p < 0.001$*
	≥17 to <40 years	268 [82.7]	209 [61.8]	
	≥40 to <65 years	25 [7.7]	86 [25.4]	
	≥65 years	1 [0.3]	15 [4.4]	
	<40 years	298 [92.0]	237 [70.1]	$p < 0.001$*
	≥40 years	26 [8.0]	101 [29.9]	
Diagnosis of CD	Definite	306 [94.4]	312 [92.3]	$p = 0.348$
	Suspected	18 [5.6]	25 [7.4]	
BMI [kg/m^2]	Number of patients	259	258	
	Mean ± SD	20.41 ± 3.63	20.67 ± 3.36	$p = 0.396$
Smoking history[#]	Number of patients	72	66	
	No history of smoking	49 [68.1]	45 [68.2]	$p = 0.947$
	Current smoker	11 [15.3]	9 [13.6]	
	Has smoked in the past	12 [16.7]	12 [18.2]	
Alcohol history[#]	Number of patients	72	66	
	Did not drink/stopped drinking	29 [40.3]	29 [43.9]	$p = 0.609$
	Hardly drinks	28 [38.9]	19 [28.8]	
	Occasional	11 [15.3]	14 [21.2]	
	Drinks frequently	4 [5.6]	4 [6.1]	
Social background	Student	124 [38.3]	76 [22.5]	$p = 0.004$*
	Company employee	142 [43.8]	165 [48.8]	
	Corporate Officer	4 [1.2]	6 [1.8]	
	Officers and employees of private organizations	2 [0.6]	2 [0.6]	
	Civil servants	6 [1.9]	11 [3.3]	
	Faculty member	3 [0.9]	3 [0.9]	
	Self-employed	8 [2.5]	10 [3.0]	
	Housewife	14 [4.3]	25 [7.4]	
	Others	10 [3.1]	23 [6.8]	
	Unemployed	11 [3.4]	15 [4.4]	
	Unknown/not specified	0 [0.0]	2 [0.6]	

Abbreviations: BMI, body mass index; CD, Crohn's disease; SD, standard deviation.
Details on perianal lesion were unknown for ten patients, which are not included here.
All data are presented as *n* [%] unless otherwise stated. The denominator for the proportion of patients with or without perianal lesion includes all patients.
The *p*-values are calculated using the chi-square test [age at diagnosis—Modified Montreal classification, smoking history, alcohol history, social background], Fisher's exact test [gender, age at diagnosis—Vienna classification, diagnosis of CD] and *t*-test [mean age at diagnosis, BMI].
[#]At informed consent—however, data were collected within 3 months from the diagnosis of CD.
*$p < 0.05$.

[95% confidence interval]) further confirmed that male sex (1.566 [1.029–2.384], $p = 0.037$), age <40 years (4.181 [2.288–7.639], $p < 0.001$) and ileocolonic location L3 (2.259 [1.379–3.700]; $p = 0.001$ vs L1) were significantly and independently associated with a high prevalence of perianal lesions [Table 5]. In contrast, stricturing behaviour B2 (0.544 [0.345–0.856]; $p = 0.009$ vs B1) and a history of alcohol intake (0.589 [0.376–0.922]; $p = 0.020$) were significantly and independently associated with a low prevalence of perianal lesions [Table 5].

3.7. Impacts on activities of daily living

Participation in daily activity questionnaires was encouraged but not mandatory. Data on activities of daily living were available for 138 patients [72 for patients with perianal lesions and 66 for those without perianal lesions]. The proportion of patients experiencing fatigue [FACIT-Fatigue < 30] was higher in patients with vs without perianal lesions [29.2 vs 21.6%; $p = 0.465$]; however, the difference was not significant [Figure 3A]. Patients with perianal lesions had numerically higher WPAI scores on missing work time 'absenteeism'

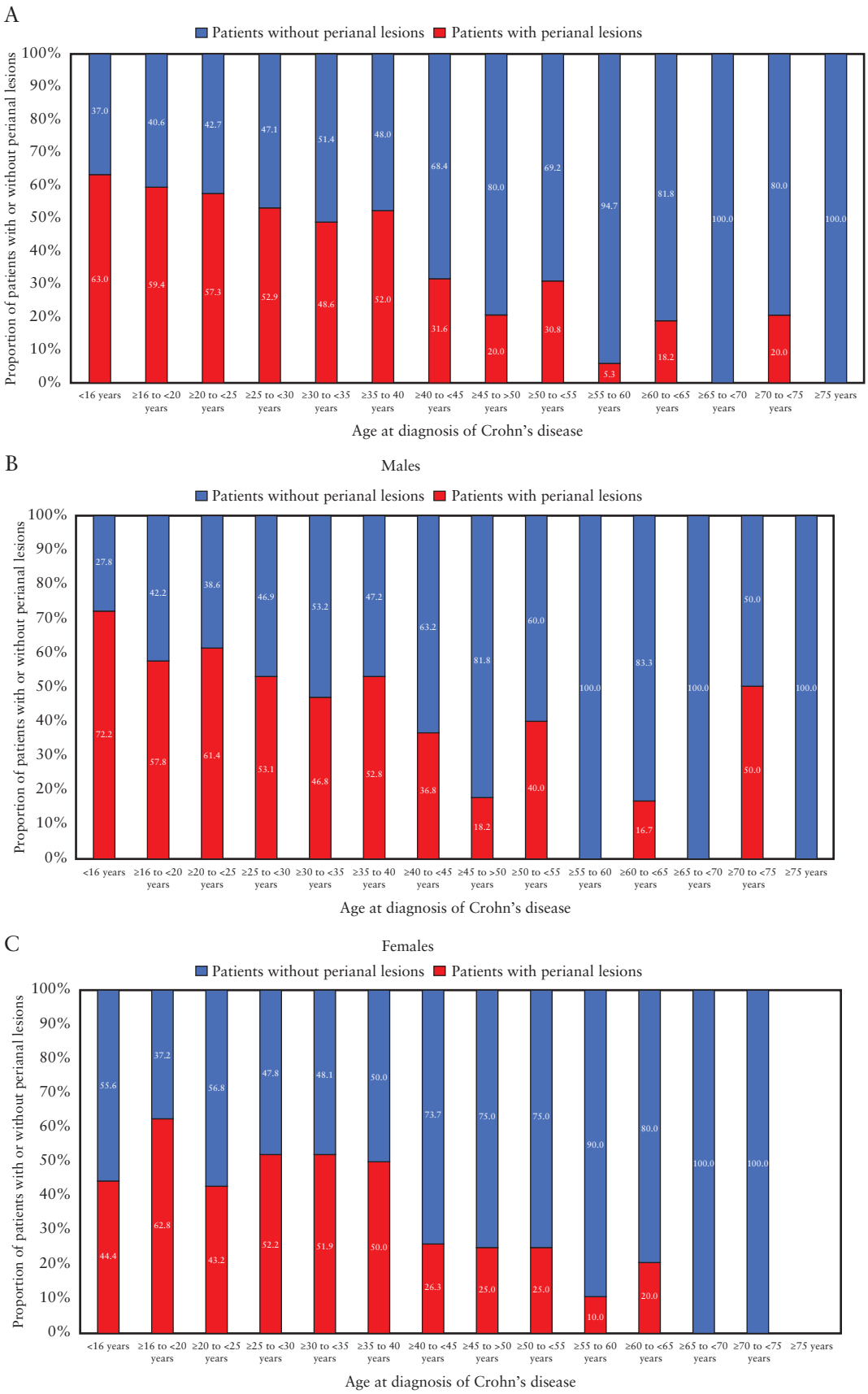


Figure 1. Prevalence of perianal lesions by [A] age group, and by age group in [B] male and [C] female patients.

Table 2. Percentage of males and females with types of perianal lesions observed at the diagnosis of Crohn's disease

Parameter	Patients with perianal lesions [*N* = 372], *n* [%]	Males [*N* = 233], *n* [%]	Females [*N* = 91], *n* [%]	*p*-value
Perianal fistula	194 [59.9]	155 [66.5]	39 [42.9]	$p < 0.001$*
Perianal abscess	99 [30.6]	76 [32.6]	23 [25.3]	$p = 0.228$
Skin tag	62 [19.1]	29 [12.4]	33 [36.3]	$p < 0.001$*
Perianal fissure	60 [18.5]	44 [18.9]	16 [17.6]	$p = 0.874$
Ulcer	36 [11.1]	22 [9.4]	14 [15.4]	$p = 0.167$
Stenosis	15 [4.6]	10 [4.3]	5 [5.5]	$p = 0.769$
Others	12 [3.7]	6 [2.6]	6 [6.6]	$p = 0.103$

The *p*-values were calculated using Fisher's exact test. *$p < 0.05$.

[36.3 vs 29.5%; $p = 0.645$], impairment at work 'presenteeism' [35.6 vs 31.5%; $p = 0.610$], overall work productivity loss [33.0 vs 30.0%; $p = 0.683$] and activity impairment [51.9 vs 41.1%; $p = 0.102$] when compared with patients without perianal lesions [Figure 3B]. The mean total SIBDQ score did not differ significantly in patients with perianal lesions vs without perianal lesions [48.2 vs 49.8; $p = 0.581$]. Similarly, the SIBDQ systemic, social, bowel and emotional subscores were not significantly different between the two groups [Figure 3C].

4. Discussion

Perianal lesion, particularly perianal fistula, is an aggressive disease phenotype that can have a substantial detrimental impact on QoL of patients with CD. Crohn's perianal fistulas exert a heavy negative physical and emotional impact on patients. The natural history of perianal CD remains poorly described and is based mostly on retrospective studies from referral centres. Our prospective cohort study comprehensively and thoroughly investigated patients with various types of perianal lesions at the diagnosis of CD. The impacts of demographic and habitual parameters along with disease presentation of coexisting intestinal CD and EIMs on the prevalence of perianal lesions were evaluated based on univariate and multivariate statistical analyses. To our knowledge, no previous research has assessed harmful effects of perianal lesions on the health status and QoL of patients at the diagnosis of CD. To resolve this issue, we prospectively collected PRO data using three types of questionnaire surveys, FACIT-Fatigue, WPAI-GH and SIBDQ.

In a Western cohort study from Olmsted county in Minnesota, USA, the cumulative incidence of perianal fistula was 21% at 10 years and 26% at 20 years after the diagnosis of CD.[4] A cohort study from Stockholm county, Sweden, reported that anorectal fistulas occurred in 13.7% of 1293 patients before or after the diagnosis of CD.[24] In a recent French cohort study, at the time of diagnosis of CD, 116 [4%] of 2906 patients had fistulizing perianal CD.[25] The prevalence of perianal lesions in Asian patients with CD appears to be much higher than that of Western countries. Consistent with the high prevalence reported among the Asian population [30.3–58.8%], perianal lesions were present in 48.2% of the patients included in the iCREST study.[6,7] The multicentre, retrospective CONNECT study showed a prevalence of perianal fistulas of 39% [*n* = 465] of patients with CD.[7] The results from the Hong Kong territory-wide IBD Registry [HKIBDR] showed perianal involvement at diagnosis in 42.4% of patients.[26] Male sex was more prevalent in the population of patients with perianal lesions [71.9%] and in the overall study population [68%]; this is also in line with the results reported by Zhu *et al.* [76.9%] in their single-centre study in Chinese patients,[27] and the CONNECT [73.8%][7] and the HKIBDR studies [78.8%].[26] Furthermore, the HKIBDR study showed that male gender was significantly associated with the development of perianal CD.[26]

In our study, perianal lesions were more prevalent in patients with disease onset at 17–40 years of age. The CONNECT study also showed a significant association between perianal lesions with a younger age at diagnosis.[7] Similar to our study, most of the patients aged 17–40 years in the CONNECT study[7] had perianal lesions [82.7% and 81.1%, respectively]. In the HKIBDR study, younger age at diagnosis of CD was associated with the development of perianal lesions.[26] A decrease in the proportion of both male and female patients with perianal lesions with increasing age was noted in our study. The higher prevalence of perianal fistulas in male and young CD patients was also confirmed in Western cohort studies.[4,24,25] The reason for the high prevalence of perianal lesions in young and male patients with CD remains unknown, although the role of genetic, microbiological and immunological factors has been investigated in the pathogenesis of perianal CD.[28]

Our results showed that perianal fistulas and perianal abscesses were the most common types of perianal lesions [59.9 and 30.6%, respectively]. These are corroborated by the results of Zhu *et al.* and HKIBDR studies, wherein the majority of patients with perianal lesions had anal fistula followed by perianal abscess.[26,27] In our study, the prevalence of both perianal fistulas and abscesses were numerically higher in males than in females. In contrast, skin tag was more commonly observed in females [36.3 vs 12.4% in males] and the prevalence of the ulcer was only numerically higher in females [15.4 vs 9.4% in males].

Our multivariate analyses found that in addition to male sex and age <40 years, an increased prevalence of perianal lesions was significantly associated with ileocolonic disease location, whereas stricturing CD and alcohol intake were associated with a decreased prevalence of perianal lesions. The presence of perianal lesions was reported to be associated with coexisting intestinal CD.[29,30] Ileocolonic involvement was present in 69.1% of patients in our study, while the same

Table 3. Disease activity in patients with/without perianal lesions at the diagnosis of Crohn's disease

Parameter		Patients with perianal lesions [*N* = 324]	Patients without perianal lesions [*N* = 338]	*p*-Value
HBI	Number of patients	108	114	
	Mean ± SD	5.8 ± 4.8	5.1 ± 5.0	$p = 0.256$
Disease activity	Number of patients	108	114	
	Remission	47 [43.5]	63 [55.3]	$p = 0.059$
	Mild activity	36 [33.3]	20 [17.5]	
	Moderate activity	23 [21.3]	29 [25.4]	
	Severe activity	2 [1.9]	2 [1.8]	
General well-being	Number of patients	117	121	
	0: Good	39 [33.3]	51 [42.1]	$p = 0.673$
	1: Slightly poor	36 [30.8]	35 [28.9]	
	2: Poor	22 [18.8]	17 [14.0]	
	3: Very poor	14 [12.0]	12 [9.9]	
	4: Very poor	6 [5.1]	6 [5.0]	
Abdominal pain	Number of patients	120	126	
	0: None	42 [35.0]	57 [45.2]	$p = 0.352$
	1: Mild	55 [45.8]	48 [38.1]	
	2: Moderate	19 [15.8]	19 [15.1]	
	3: Severe	4 [3.3]	2 [1.6]	
Number of watery or muddy stools per day according to the Bristol Scale	Number of patients	114	121	
	0 to <3 episodes	61 [53.5]	71 [58.7]	$p = 0.030$*
	≥3 to <6 episodes	39 [34.2]	24 [19.8]	
	≥6 to <10 episodes	9 [7.9]	21 [17.4]	
	≥10 episodes	5 [4.4]	5 [4.1]	

Abbreviations: HBI, Harvey–Bradshaw Index; SD, standard deviation.
Remission: HBI < 5, mild activity: 5 ≤ HBI ≤ 7, moderate activity: 8 ≤ HBI ≤ 16, and severe activity: 16 < HBI.
All data are presented as *n* [%] unless otherwise stated. The *p*-values are calculated using: a chi-square test [disease activity, general well-being, abdominal pain, number of episodes of muddy stools], or *t*-test [HBI]. *$p < 0.05$.

was reported in 51.9% of patients by Zhu *et al.*,[27] 44.9% of patients in the HKIBDR study[26] and 69.7% of patients in the CONNECT study.[7] In another study, the rectum and sigmoid colon were the most frequently involved regions; the more distal the intestinal site of CD, the higher the risk of perianal CD.[30] The impact of the location of intestinal CD on perianal lesions needs to be further investigated. The inflammatory disease behaviour in 68.2% of patients in our study is also in line with findings of the HKIBDR study [56.5%][26] and Zhu *et al.* [75.0%].[27] Non-perianal fistulas and intra-abdominal abscesses were significantly more common in CD patients with perianal lesions compared to those without in the CONNECT study.[7] In our study, the prevalence of penetrating-type lesions in intestinal CD was 11.4% in patients with perianal lesions. This prevalence of penetrating type lesions, though lower than expected, may be appropriate since we studied the patients at the diagnosis of CD, and it will increase with time. Additionally, it is interesting that the prevalence of stricturing CD was significantly lower in patients with vs without perianal lesions. The present study investigated patients at the diagnosis of CD and therefore the majority of the patients had inflammatory behaviour of intestinal CD. The prevalence of stricturing behaviour will increase with time along with penetrating disease behaviour. The change in disease behaviour of intestinal CD after the diagnosis of perianal lesions should be further investigated with a longer

Table 4. Prevalence and proportion of patients with extra-intestinal manifestations

Complications	Number of patients [%]	
	Patients with perianal lesions [*N* = 324]	Patients without perianal lesions [*N* = 338]
Overall	13 [4.0]	10 [3.0]
Iritis	2 [0.6]	1 [0.3]
Uveitis	1 [0.3]	0
Ankylosing spondylitis	0	1 [0.3]
Sacroiliitis	1 [0.3]	2 [0.6]
Erythema nodosum	11 [3.4]	7 [2.1]
Pyoderma gangrenosum	2 [0.6]	1 [0.3]
Venous thrombosis	0	0
Primary sclerosing cholangitis	0	0

Statistical comparisons were not conducted because of the low prevalence of extra-intestinal manifestations.

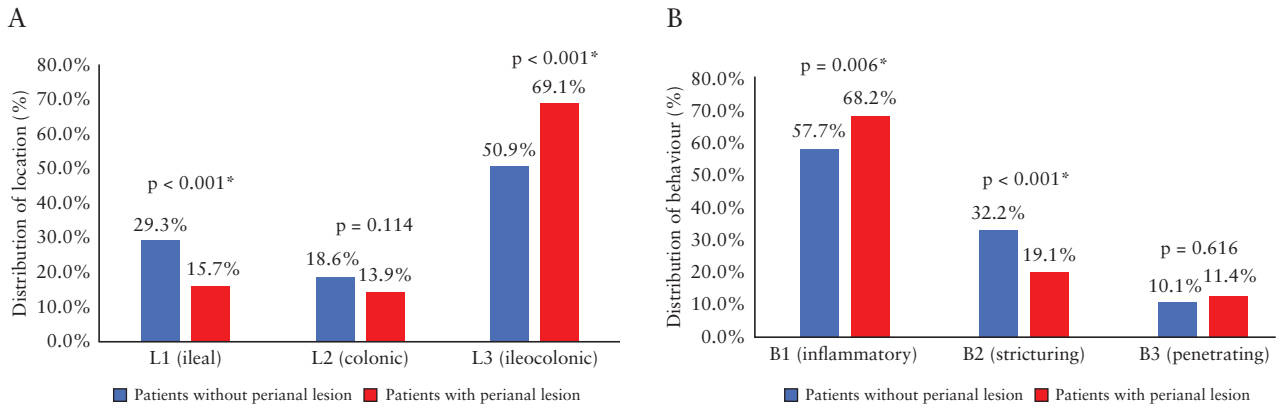


Figure 2. The distribution of [A] location and [B] behaviour of intestinal Crohn's disease in patients with and without perianal lesions.Fischer's exact test was carried out to compare significant differences in the proportion of disease location and behaviour [L1, L2, L3, B1, B2 and B3] in patients with and without perianal lesions. *$p < 0.05$.

Table 5. Clinical factors associated with the presence of perianal lesions at the diagnosis of CD

Parameter		Univariate analysis				Multivariate analysis			
		N	Patients with perianal lesion, *n* [%]	OR [95% CI]	*p*-Value	*N*	Patients with perianal lesion, *n* [%]	OR [95% CI]	*p*-Value
Sex	Female	210	91 [43.3]			167	73 [43.7]		
	Male	452	233 [51.5]	1.391 [1.001; 1.934]	$p = 0.049$*	343	182 [53.1]	1.566 [1.029; 2.384]	$p = 0.037$*
Age, years	≥40	127	26 [20.5]			96	18 [18.8]		
	<40	535	298 [55.7]	4.884 [3.072; 7.765]	$p < 0.001$*	414	237 [57.2]	4.181 [2.288; 7.639]	$p < 0.001$*
BMI, kg/m^2	<20.53	300	157 [52.3]			296	154 [52.0]		
	≥20.53	217	102 [47.0]	0.808 [0.569; 1.146]	$p = 0.232$	214	101 [47.2]	0.960 [0.652; 1.414]	$p = 0.837$
Family history	No	626	306 [48.9]			485	242 [49.9]		
	Yes	34	18 [52.9]	1.176 [0.589; 2.349]	$p = 0.645$	25	13 [52.0]	0.859 [0.356; 2.075]	$p = 0.736$
Disease location	L1	150	51 [34.0]			117	38 [32.5]		
	L2	108	45 [41.7]	1.386 [0.832; 2.310]	$p = 0.210$	77	33 [42.9]	1.450 [0.746; 2.818]	$p = 0.273$
	L3	396	224 [56.6]	2.528 [1.708; 3.741]	$p < 0.001$*	316	184 [58.2]	2.259 [1.379; 3.700]	$p = 0.001$*
Disease behaviour	B1	416	221 [53.1]			310	171 [55.2]		
	B2	171	62 [36.3]	0.502 [0.348; 0.724]	$p < 0.001$*	140	53 [37.5]	0.544 [0.345; 0.856]	$p = 0.009$*
	B3	71	37 [52.1]	0.960 [0.580; 1.589]	$p = 0.874$	60	31 [51.7]	1.258 [0.675; 2.344]	$p = 0.470$
EIM	No	639	311 [48.7]			490	244 [49.8]		
	Yes	23	13 [56.5]	1.371 [0.593; 3.172]	$p = 0.461$	20	11 [55.0]	1.282 [0.480; 3.422]	$p = 0.620$
Smoking history[#1]	No	447	237 [53.0]			345	188 [54.5]		
	Yes	213	87 [40.8]	0.612 [0.440; 0.851]	$p = 0.004$*	165	67 [40.6]	0.951 [0.600; 1.507]	$p = 0.832$
Alcohol intake[#2]	No	479	250 [52.2]			372	199 [53.5]		
	Yes	180	74 [41.1]	0.639 [0.452; 0.905]	$p = 0.012$*	138	56 [40.6]	0.589 [0.376; 0.922]	$p = 0.020$*

Abbreviations: BMI, body mass index; CI, confidence interval; EIM, extra-intestinal manifestation; OR, odds ratio.
[#1]Smoking history: 'Yes' is the total of 'I am smoking now' and 'I have smoked in the past'.
[#2]Alcohol intake: 'Yes' is the total of 'sometimes drink' and 'drink often', and 'no' is the total of 'do not drink/stop' and 'almost never drink'.
Logistic regression analysis with sex, age, BMI, family history, disease location, disease behaviour, extra-intestinal manifestation [EIM], smoking history and alcohol intake as covariates.
*$p < 0.05$.

observation time. In our study, alcohol intake was associated with a low prevalence of perianal lesions. However, patients with perianal symptoms might have ceased consumption of alcohol before the diagnosis of CD. The impacts of smoking and alcohol consumption on the occurrence and progression of perianal lesions should be re-investigated over a longer observational period.

Previous studies have reported that compared to healthy individuals, patients with CD usually feel fatigued.[31–34] The FACIT-Fatigue scale is a generic PRO instrument to assess and compare the degree of fatigue regardless of any disease, with higher scores indicating lower fatigue. Complications or conditions other than perianal lesions or CD may affect the findings of fatigue. In the present study, the proportion of

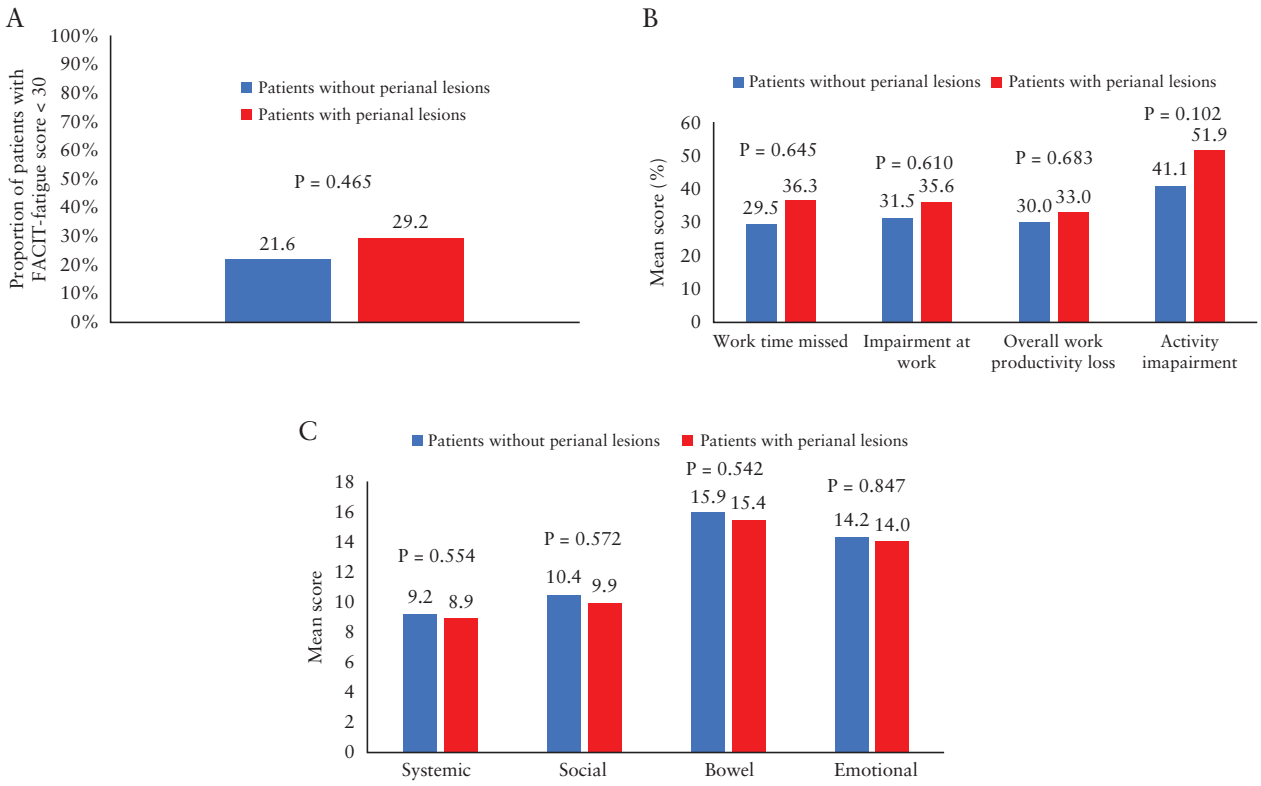


Figure 3. Impairment of activities of daily living: [A] FACIT-Fatigue, [B] WPAI-GH and [C] SIBDQ subscore.The *p* values were calculated using: Fisher's exact test for FACIT-Fatigue, and Student's *t*-test for WPAI-GH and SIBDQ subscore. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue scale; SIBDQ, Short-form Inflammatory Bowel Disease Questionnaire; WPAI-GH, Work Productivity and Activity Impairment Questionnaire-General Health.

patients experiencing fatigue [FACIT-Fatigue < 30] was numerically higher in patients with vs without perianal lesions [29.2 vs 21.6%]. Fatigue has been associated with work productivity loss and reduced HRQoL.[35] The presence of active perianal disease was a predictor of work productivity loss in the WORK-IBD study.[35] The WPAI questionnaire is a validated PRO tool to evaluate work productivity impairment due to perianal CD, as impaired work time resulted from both absenteeism [work time missed] and presenteeism [impairment while working][22,36]; higher scores indicate severe impairment. In the present study, patients with perianal lesions had numerically higher WPAI scores on missing work time [absenteeism: 36.3 vs 29.5%], impairment at work [presenteeism: 35.6 vs 31.5%], overall work productivity loss [33.0 vs 30.0%] and activity impairment [51.9 vs 41.1%] as compared with those without perianal lesions. In particular, activity impairment was more frequently observed in the presence of perianal lesions. In our study, patients with perianal lesions frequently presented with fatigue and impairment of work productivity and daily activities; however, the differences between patients with and without perianal lesions were not statistically significant, probably because data on daily living activities were available in a limited number of patients.

Disease severity is correlated with poor QoL in CD patients.[37,38] SIBDQ is a simplified version of the IBDQ, with higher scores indicating better QoL. In our study, there was no significant difference in the SIBDQ total score and subscores [systemic, social, bowel and emotional subscores] between patients with and without perianal lesions. A cross-sectional prospective study showed similar mean SIBDQ scores in patients with vs without perianal lesions [49.53 vs 48.71].[39] The overall higher SIBDQ score reported in our study suggests improved QoL and reflects disease severity, which was 'mild' or 'in remission' in the majority of patients. The lowest score was obtained for the systemic symptoms domain [subscore] and the highest score was observed for the bowel symptoms domain, similar to the findings reported by Parra *et al.* in their observational study.[36] The SIBDQ is an index evaluated mainly to determine the deterioration of QoL caused by intestinal symptoms.[23] Hence, deterioration of QoL caused by perianal lesions cannot be properly reflected by this index. Data from future studies using the newly developed and validated PRO measure, the Crohn's Anal Fistula Quality of Life [CAF-QoL] scale,[40] may provide valuable insights into the impact on QoL due to perianal CD.

There are no established and validated methods to timely and accurately diagnose perianal CD in clinical practice. The morphology, anatomy and activity of perianal CD are varied and changeable. Therefore, it is challenging to obtain a precise diagnosis of perianal CD and accurately determine its prevalence. In addition, the clinical evaluation of patients with CD with perianal lesions is affected by the presence of coexisting intestinal lesions; only a few patients with CD with perianal lesions did not display the presence of intestinal lesions. Furthermore, the data on daily living activities were available in only a limited number of patients since the survey was not mandatory; this may have led to statistically non-significant results. As this study presents data on perianal lesions at the early stage of CD diagnosis, further studies are warranted to ascertain these findings in the later stages of the disease.

At the time of CD diagnosis, nearly half of the patients had perianal lesions with a higher prevalence observed in males and younger patients. Additionally, perianal abscess/fistula tended to be more common than other types of lesions. Patients with perianal lesions frequently experienced fatigue and impairment of daily activities, including missing work time, impairment at work and work productivity loss. The 4-year follow-up data from this registry study will provide robust evidence on the characteristics of perianal disease in newly diagnosed patients with CD in a real-world clinical setting.

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Conflicts of Interest

Yoko Murata, Shinichi Yoshigoe, Shinya Nagasaka and Tsutomu Yajima are employees of Janssen Pharmaceutical K.K. and may hold stock or stock options of Johnson & Johnson.

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Author Contributions

All authors participated in the interpretation of study results, drafting, critical revision, and approval of the final version of the manuscript.

Ethics Approval

The iCREST-CD study was approved by the ethics committee of Kyorin University, the principal medical institution. The study protocol and informed consent form were approved by the ethics committee or institutional review board of each study site, and the study was conducted in accordance with 'Ethical Guidelines for Medical and Health Research Involving Human patients [December 22, 2014, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare, partially revised on February 28, 2017]' and 'World Medical Association Declaration of Helsinki [WMA Fontaleza general meeting revised in October 2013]'. All patients who participated in this study provided written informed consent. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry System [UMIN-CTR, UMIN000032237] in April 2018.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to the confidentiality clauses signed with the participating medical institutions.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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