

Prevalence and patient awareness of inflammatory bowel disease in Kazakhstan: a cross-sectional study

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Background/Aims: There has been a paucity of published data on the epidemiology of inflammatory bowel disease (IBD) in Central Asia and Kazakhstan. Therefore, we aimed to study IBD prevalence and patient awareness among adults in Kazakhstan. **Methods:** The cross-sectional study was carried out among subjects of both sexes aged 18 years and older using IBD Alert Questionnaire (CalproQuest), single fecal calprotectin test, and endoscopy with biopsy to verify IBD from January to December 2017, across regions of Kazakhstan. All participants were included in the study after providing informed consent. **Results:** Out of 115,556 subjects, there were 128 confirmed IBD cases, in which 36 Crohn's disease (CD) and 92 ulcerative colitis (UC) cases identified. The age and sex-adjusted IBD prevalence were 113.9 (95% confidence interval [CI], 69.0–158.9) per 100,000 population. The age- and sex-adjusted prevalence for UC were 84.4 (95% CI, 44.8–123.9) and for CD were 29.5 (95% CI, 8.2–50.9) per 100,000 population. **Conclusions:** This is the first report on the prevalence of IBD with a verified diagnosis in the Central Asia and could be used to better plan and allocate healthcare resources for IBD management program. (**Intest Res, Published online**)

Key Words: Inflammatory bowel diseases; Prevalence; Kazakhstan

INTRODUCTION

Having an early onset and chronic course, inflammatory bowel disease (IBD) significantly reduces quality of life and increases permanent disability resulting in a heavy burden to patients, their families and healthcare systems.¹⁻⁴ Historically, IBD was mainly considered as a disease of the Westernized countries; it has become a global disease spreading in many Asian, African and South American countries.⁵ The Ministry of Health of Kazakhstan (MoH) reported that the prevalence of Crohn's disease (CD) and ulcerative colitis (UC) was 6.3 and 31.5 per 100,000 populations, respectively.⁶ However, due to the lack of

relevant databases and registries on IBD in Kazakhstan, this prevalence was reported based on the number of hospital admissions, which underestimates the true prevalence of the disease. Despite this fact, there has been a paucity of published data on the epidemiology of IBD in Central Asia and Kazakhstan. Therefore, we aimed to study IBD prevalence and patient awareness among adults in Kazakhstan.

METHODS

1. Study Design and Subjects

This cross-sectional study was carried out among subjects of both sexes aged 18 years and older using IBD Alert Questionnaire (CalproQuest)⁷ from January 1 to December 31, 2017, across regions of Kazakhstan. IBD Alert Questionnaire has been tested and found practicable in primary care.⁸ The questionnaires were distributed both electronically and in hard

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copy (details below). At the first stage, we sent the questionnaire contained introductory information about the study, and a consent to participate in the first stage of the study. Next, participants who advanced to the second stage (fecal calprotectin [FCAL] testing) signed informed consent for the remainder of the study. The Ethics Committee of the Kazakh Research Institute of Cardiology and Internal Medicine approved the study protocol (approval No. #4, 21.09.2016).

2. Case Identification

IBD case identification was done by the following steps. The first step consisted of an active IBD case identification among the adult population through the questionnaire proposed by Hasler et al.^{7,8} The second step was the examination of the suspected cases with positive symptoms by a qualified gastroenterologist who also performed a FCAL test⁹ by a semi-quantitative method (PreventID[®] CalDetect[®] 50/200; Preventis GmbH, Bensheim, Germany). Next, we verified diagnosis among positive calprotectin cases (calprotectin concentration ≥ 50 $\mu\text{g/g}$). The IBD diagnosis was finally established based on clinical, endoscopic and histological criteria under the Kazakhstani protocol of diagnosis and treatment and the European consensus on the diagnosis and management of UC and CD.^{10,11}

3. Data Collection

Before data collection, the official information letter, which describes study goals, methods, and participant confidentiality protection as well as request permission for the survey, had been sent to the administration of each institution such as companies, universities, polyclinics located across the regions of Kazakhstan. After receiving permission, the interviewers surveyed subjects using a complete coverage method. We calculated the minimum required sample size of 99,174 respondents assuming low prevalence of the disease⁶ based on the number of adult population from the Kazakhstan census and sample size calculation method¹² to estimate the prevalence with good precision.

Researchers have distributed 135,000 questionnaires considering potential loss during the distribution and collection process. The total number of correctly completed questionnaires was 115,556 (85.6%).

Specifically, the questionnaires distributed in the universities involved all 2nd- and 3rd-year undergraduate students and master's students. Each region was represented by one university. Likewise, the questionnaires were carried out among office, factory and plant workers. We also recruited general physicians who assisted in completing questionnaires

in their communities. During the survey, the interviewers recorded response and explained the questions if respondents needed. To prevent subjects from being sampled twice, we conducted a survey in each organization once as well as included questions on contact information to communicate with a suspected duplicate subject if needed.

We used Mayo score¹³ and Crohn's Disease Activity Index¹⁴ to assess the UC and CD severity levels and the Montreal classification to describe the disease phenotype.¹⁵

Cases were also defined based on IBD awareness status, stool frequency (times/day), need for steroids treatment, having a history of gastrointestinal surgery (colectomy, small bowel resection, and appendectomy) due to IBD, blood in the stool, abdominal pain, perianal disease, abdominal infiltrate based on ultrasound or palpation findings, aphthae in the oral cavity, skin manifestations (erythema nodosum, gangrenous pyoderma) and comorbidities such as musculoskeletal system (arthralgia, arthritis; ankylosing spondylitis, sacroiliitis; granulomatous myositis), and hepatobiliary system (liver steatosis, gallstone disease, biliary cirrhosis, primary sclerosing cholangitis, hepatitis and cirrhosis); having subfebrile fever was defined when body temperature was higher than 37°C.

4. Statistical Analysis

We reported a mean and standard deviation for continuous variables and frequencies, and percentages for categorical variables. Prevalence and 95% confidence intervals (CIs) were calculated based on the Wald method modified by the Agresti-Coull method.¹⁶ The prevalence of IBD by region is represented by crude and adjusted methods of direct standardization by age and sex indicators.¹⁷ Associations between IBD and age, sex, place of residence, and clinical characteristics were assessed by using two-tailed Fisher exact test and Pearson chi-square test. Since the variables "age" and "body mass index" were categorized, the two-tailed Fisher exact test and Pearson chi-square test were used to study the associations of these indicators with IBD. A *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed by using IBM SPSS Statistics software version 19.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Prevalence of IBD

Out of 115,556 subjects, there were 128 confirmed IBD cases, in which 36 CD cases and 92 UC cases identified. The age and

sex-adjusted IBD prevalence were 113.9 (95% CI, 69.0–158.9) per 100,000 population. The age- and sex-adjusted prevalence for UC were 84.4 (95% CI, 44.8–123.9) and for CD were 29.5 (95% CI, 8.2–50.9) per 100,000 population (Fig. 1). The overall mean ± standard deviation age was 44.2 ± 15.1 years, 36.1% were males and 63.9% were females. Demographic characteristics are described in Table 1. The overall response rate was 86.5%, in which polyclinic participants accounted for 57.5%, 11.0% of students, and 31.5% of workers from various institutions. Specifically, the response rates in polyclinics, universities and works were 83.6%, 92.4%, and 90.2% respectively.

The highest IBD prevalence was in the age group of 30 to 39 years, which was similar to the UC age pattern. In contrast, the CD cases were more prevalent at younger age adults. Overall, IBD was more prevalent in males than females, but the CD was present more in females. The urban population has a higher IBD prevalence than the rural population. The difference in prevalence of IBD and its types across age, sex and geographical location are shown in Table 2.

The eastern region had the highest age- and sex-adjusted prevalence of IBD in Kazakhstan; whereas; the south region had the lowest rate (126.5 [95% CI, 15.4–237.6] and 87.7 [95% CI, 0–176.2] per 100,000, respectively). The age- and sex-adjusted prevalence of UC was the highest in the eastern region and the lowest was in Almaty and western region (108.2 [95% CI, 3.6–212.9], 72.4 [95% CI, 9.4–135.5], and 72.5 [95% CI, 0–190.7] per 100,000, respectively). In contrast, the highest age- and sex-adjusted prevalence of CD was seen in Almaty and the

lowest rate was in the southern region (48.7 [95% CI, 0–98.2] and 6.6 [95% CI, 0–35.5] per 100,000, respectively). The difference in the prevalence of IBD and its types across regions is shown in Table 3.

Table 1. Demographic Characteristics of the Study Participants

Characteristics	Value (n = 115,556)
Age (yr)	44.2 ± 15.1
Age group (yr)	
18–29	24,707 (21.4)
30–39	21,224 (18.4)
40–49	21,364 (18.5)
50–59	27,973 (24.2)
≥ 60	20,288 (17.6)
Sex	
Male	41,708 (36.1)
Female	73,848 (63.9)
Area	
Urban	92,908 (80.4)
Rural	22,648 (19.6)
Region	
Almaty	37,444 (32.4)
East	25,332 (21.9)
West	11,108 (9.6)
North	29,107 (25.2)
South	12,565 (10.9)

Values are presented as mean ± standard deviation or number (%).

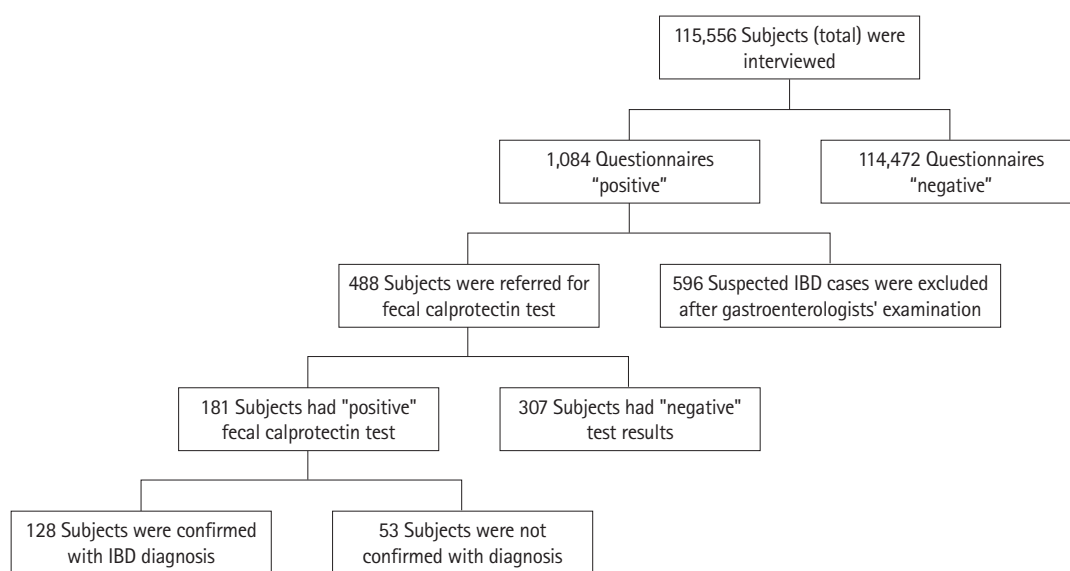


Fig. 1. Steps for inflammatory bowel disease (IBD) case identification.

Table 2. Prevalence of IBD and Its Types across Age, Sex and Geographical Location in Kazakhstan

Characteristics	IBD		UC		CD	
	Per 100,000	95% CI	Per 100,000	95% CI	Per 100,000	95% CI
Age group (yr)						
18–29	129.5	83.3–175.7	89.0	50.2–127.9	40.5	13.0–67.9
30–39	155.5	100.9–210.1	117.8	69.8–165.7	37.7	8.5–66.9
40–49	117.0	69.4–164.7	74.9	36.0–113.8	42.1	11.7–72.5
50–59	75.1	41.5–108.7	53.6	24.7–82.5	21.4	1.6–41.3
≥ 60	83.8	41.7–125.9	69.0	30.4–107.6	14.8	0–36.4
Total	110.8	91.5–130.1	79.6	63.2–96.1	31.2	20.7–41.6
Sex						
Male	129.5	94.3–164.6	107.9	75.7–140.1	21.6	6.0–37.2
Female	100.2	77.1–123.3	63.6	45.1–82.2	36.6	22.3–50.9
Area						
Urban	114.1	92.2–136.0	81.8	63.2–100.4	32.3	20.4–44.2
Rural	97.1	54.8–139.5	70.6	33.9–107.3	26.5	2.0–51.0

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CI, confidence interval.

Table 3. Prevalence of IBD and Its Types by Regions

Region	IBD		UC		CD	
	Per 100,000	95% CI	Per 100,000	95% CI	Per 100,000	95% CI
Crude rates						
Almaty	120.2	84.3–156.1	72.1	43.9–100.3	48.1	24.7–71.5
East	114.5	71.5–157.5	94.7	55.3–134.2	19.7	0–40.2
West	108.0	42.0–174.0	72.0	16.3–127.8	36.0	0–79.2
North	106.5	67.8–145.2	79.0	45.4–112.7	27.5	6.2–48.8
South	87.5	31.3–143.7	79.6	25.6–133.6	8.0	0–35.0
Total	110.8	91.5–130.1	79.6	63.2–96.1	31.2	20.7–41.6
Age/sex-adjusted rates						
Almaty	121.1	41.0–201.3	72.4	9.4–135.5	48.7	0–98.2
East	126.5	15.4–237.6	108.2	3.6–212.9	18.3	0–55.5
West	102.4	0–235.3	72.5	0–190.7	29.9	0–90.5
North	109.4	20.7–198.1	84.9	4.6–165.3	24.5	0–62.0
South	87.7	0–176.2	81.1	0–164.8	6.6	0–35.5
Total	113.9	69.0–158.9	84.4	44.8–123.9	29.5	8.2–50.9

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CI, confidence interval.

2. Impact of Demographic and Clinical Characteristics on IBD Awareness

Out of 128 identified IBD cases, 25 cases (19.5%) were unaware of their diagnosis. Among these unaware subjects, 16 cases (64%) had UC and 9 (36%) had CD.

Most patients with UC had left side colitis (44.6%), while patient with CD had cases of ileal location (41.7%) and ileoco-

lonic disease (38.9%) (Table 4).

Table 5 indicates that demographic characteristics such as age, sex and geographical location were not statistically associated with IBD awareness status.

Stool frequency and hepatobiliary system disorders were significantly associated with previous IBD awareness status (Table 6).

Table 4. Clinical Characteristics of IBD-Based on the Montreal Classification

Localization	No. (%)
UC (n = 92)	
Extent	
E1 (proctitis)	30 (32.6)
E2 (left side colitis)	41 (44.6)
E3 (pancolitis)	21 (22.8)
Severity	
S1 (mild UC)	21 (22.8)
S2 (moderate UC)	47 (51.1)
S3 (severe UC)	24 (26.1)
CD (n = 36)	
Location	
L1 (ileal)	15 (41.7)
L2 (colonic)	7 (19.4)
L3 (ileocolonic)	14 (38.9)
Behavior	
B1 (non-stricturing, non-penetrating)	20 (55.6)
B2 (stricturing)	14 (38.9)
B3 (penetrating)	2 (5.6)
p (perianal disease modifier)	1 (2.8)

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease.

Table 5. An Association between Inflammatory Bowel Disease Awareness Status and Demographic Characteristics

Characteristics	Unaware (n = 25)	Aware (n = 103)	P-value ^a
Sex			0.121
Male	7 (28)	47 (45.6)	
Female	18 (72)	56 (54.4)	
Age (yr)			0.187
18–40 (A2)	16 (64)	50 (48.5)	
> 40 (A3)	9 (36)	53 (51.5)	
Area			0.943
Urban	19 (76)	75 (72.8)	
Rural	6 (24)	28 (27.2)	

Values are presented as number (%).

^aFisher exact test.

DISCUSSION

To our knowledge, this is the first report on IBD prevalence among adults in Kazakhstan with verified diagnoses. We found

Table 6. An Association between IBD Awareness Status and Clinical Manifestations

Characteristics	Unaware (n = 25)	Aware (n = 103)	P-value
IBD type			0.332 ^a
UC	16 (64)	76 (73.8)	
CD	9 (36)	27 (26.2)	
Stool frequency, time/day			<0.001
< 5	23 (92)	49 (47.6)	
6–10	2 (8)	37 (35.9)	
> 10	0 (0)	17 (16.5)	
Requires steroids treatment (yes)	9 (37.5)	42 (48.3)	0.367 ^a
History of GIT surgery due to IBD (yes)	2 (8)	12 (11.7)	0.867 ^b
Blood in stool (yes)	7 (28)	26 (25.2)	0.801 ^a
Abdominal pain (yes)	8 (32)	19 (18.4)	0.171 ^a
Subfebrile fever (yes)	10 (40)	33 (32.0)	0.487 ^a
Perianal disease (yes)	2 (8)	22 (21.4)	0.159 ^b
Aphthae (yes)	5 (20)	23 (22.3)	1.000 ^a
Abdominal infiltrate (yes)	3 (12)	8 (7.8)	0.448 ^b
Skin disorders (yes)	4 (16)	8 (7.8)	0.248 ^b
Musculoskeletal disorders (yes)	11 (44)	58 (56.3)	0.371 ^a
Hepatobiliary system disorders (yes)	2 (8)	33 (32.0)	0.022 ^b
BMI (kg/m ²)			0.243 ^a
< 18.5	2 (8)	11 (10.7)	
18.5–24.99	16 (64)	68 (66.0)	
25–30	7 (28)	18 (17.5)	
> 30	0	6 (5.8)	

^aChi-square test.

^bFisher exact test.

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; GIT, gastrointestinal tract; BMI, body mass index.

that the age- and sex-adjusted IBD prevalence was 110.8 (95% CI, 91.5–130.1) per 100,000 population, with UC more prevalent than CD (79.6 [95% CI, 63.2–96.1] per 100,000 population vs. 31.2 [95% CI, 20.7–41.6] per 100,000 population, respectively). Our estimated prevalence rates are much higher than those reported by the MoH, which are 31.5 per 100,000 population for UC and 6.3 per 100,000 population for CD.⁶ This inconsistency with the MoH could be explained by the different database system where MoH uses the hospital-based data that counts only the number of hospitalized IBD patients and misses many undetected cases. Another explanation could be in limited access to gastroenterological care, especially in rural areas, resulting in under detection of cases. The primary care settings that have a low index of suspicion for IBD, especially

for CD, distinguished by the variety of symptoms might also be a reason for under detection of IBD cases. Our findings were closed to what we expected, being in the prevalence range between Western and Eastern Asian countries.⁵ A recently published systematic review on the global epidemiology of IBD also supports rising IBD incidence in the newly industrialized countries.⁵ In general, the situation concerning the IBD prevalence in Asian countries is very similar to a West-East gradient of 2:1 in IBD incidence in Europe,¹⁸ but with lower rates. An epidemiological study in Russia, for example, found that its European part had 20.4 per 100,000 population for UC and 3.7 per 100,000 population for CD.¹⁹ In one hand, the observed prevalence could partially be explained by the differences in healthcare access, database system, lifestyle and various risk factors as reported previously.^{20,21} Another possible explanation might be that Central Asian, including Kazakhstan, has a traditional nomadic diet, which may lie somewhere between West and East Asian cuisines, resulting in intermediate prevalence rates.

In our study, the highest prevalence for UC was observed at the age group 30 to 39 years; and CD was more prevalent among younger adults. This observed age pattern was not consistent with the literature.² Usually, most chronic diseases with low mortality as in the case of IBD tend to be more prevalent in older age groups, having the highest prevalence over 50 years old.²² Higher IBD prevalence rates at young age groups in this study partially could be associated with an increase in the IBD incidence in Kazakhstan in the last 20 to 30 years due to the changes in diet,²³ urbanization²⁴ and improved gastroenterological care as well as an increased health awareness among population.

We also determined that males had more UC prevalence; whereas, females had more CD cases. Our findings match those observed in earlier studies.²⁵⁻²⁷ CD is more prevalent among females, while in population-based studies of UC no significant differences were observed.²⁵

In our study, a slight predominance of IBD prevalence was observed in the urban population. This further supports the idea of an association between IBD and the growth of urbanization.^{20,28} We also think that these results are likely to be related to the poorer quality and limited access to healthcare services, especially gastroenterology care, and health literacy, being better in cities than in rural areas.

Although IBD was prevalent across Kazakhstan, it has been disproportionately distributed in it. The eastern region had the highest prevalence and the southern region had the least prev-

alence. This regional heterogeneity might be due to the environmental factors. For example, the eastern region is the most industrially developed region, so it is possible that people are more likely to be exposed to potential health hazards resulting in an increased IBD incidence. Evidence from literature review demonstrates the relationship between environmental risk factors and IBD development,²⁹ supporting our speculations.

Interestingly, almost one-fifth of IBD cases were unaware of their disease status. Stool frequency and hepatobiliary system disorders were signaling reasons to seek for medical care. It is possible that these unaware cases did not know about their disease due to the low IBD activity and poor health literacy that were supported by the findings.

This could suggest that there may be more undetected IBD cases that are at a higher risk for developing negative outcomes.³⁰

Several limitations of this study must be noted. The main limitation is that this study had a non-random sample, having a potential for the selection bias and underestimating the true IBD prevalence. In fact, we may have surveyed a relatively healthy population who can socialize by attending school, work and visiting general physicians. Since IBD could hugely impact on patients' quality of life making them not to perform daily activities as mentioned above,^{3,4} the moderate to relatively severe IBD cases might not be captured in this study. However, to overcome these challenges and identify as many IBD cases as possible from the general population, we used an active case identification strategy, including colonoscopy with biopsy, the gold standard for IBD diagnosis as reported previously.^{7,8,31} Moreover, we involved general physicians who can also have a piece of good knowledge about diagnosed and suspected IBD cases in their communities. Another limitation is since the large geographical spread of rural areas in Kazakhstan, unavailability of appropriate gastroenterological care in it and the limited financial resources, rural residents were partially underrepresented, specifically remote rural residents. Yet we surveyed those rural residents who were living close to the cities and tried to cover as far as we could access them.

In our study, the single FCAL demonstrated a sensitivity of 100% (97.2–100), specificity of 85.3% (81.2–88.8), positive predicted value of 70.7% (65.3–75.6), and negative predicted value of 100%. However, we should be cautious about a high diagnostic accuracy of the used test in our study and admit its limitation in determining who should be referring for invasive procedures to verify the IBD diagnosis. The FCAL test is concentration-sensitive, so the sensitivity and specificity of the test could vary based on the used threshold, which has its ad-

vantages and disadvantages.^{9,32-34} Furthermore, since we used a single FCAL test and did not investigate further negative FCAL cases for IBD present to rule out the diagnosis, we could miss a few IBD cases. Therefore, the single FCAL test diagnostic accuracy could be overestimated in our study. Likewise, the usage of the single FCAL test might miss a few true cases but it could prevent many people from unnecessary costly invasive procedures and patient discomfort.³⁴

This is the first report on the prevalence of IBD with a verified diagnosis in Central Asia. The age- and sex-adjusted prevalence of UC was 84.4 (95% CI, 44.8–123.9) per 100,000 population and CD was 29.5 (95% CI, 8.2–50.9) per 100,000 population. The results could be used for politicians, clinicians and public health practitioners to better plan and allocate health resources on IBD prevention and treatment programs. Furthermore, Kazakhstan holds an intermediate position between East and West Asia, with diet and lifestyle traditions similar to other Central Asian countries. Therefore, the epidemiology of IBD in Kazakhstan could be used as a proxy for its prevalence throughout Central Asia to fulfill gaps in knowledge of the burden of IBD in the region.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

Study design: Kaibullayeva J, Ualiyeva A, Oshibayeva A. Data collection: Kaibullayeva J, Ualiyeva A, Oshibayeva A, Dushpanova A. Data analysis: Kaibullayeva J, Ualiyeva A, Oshibayeva A. Discussion of results: Kaibullayeva J, Ualiyeva A, Oshibayeva A, Marshall JK. Writing the manuscript: all authors. Approval of final manuscript: all authors.

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