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A retrospective, observational study to examine the effect of early tumor necrosis factor inhibitor use on rates of surgery for Crohn's disease in Japan

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Abstract

Background Crohn's disease (CD) is an incurable inflammatory condition that often requires multiple surgeries, negatively impacting quality of life. As such, treatment strategies that aim to prevent damage to the bowel and reduce the burden of surgeries for patients with CD are important. This retrospective, long-term, observational study investigated whether tumor necrosis factor inhibitor (TNFi) treatment was associated with decreased rates of abdominal surgery in Japanese patients with CD.

Methods Patients were divided into two groups based on prior TNFi therapy (TNFi-treated and TNFi-untreated). Outcomes assessed included surgery rate, cumulative surgery-free survival rate, and time to surgery. For surgery rate, treatment groups were compared through estimation of an odds ratio (OR) with 95% confidence intervals (CIs). Cumulative surgery-free survival rate and time to surgery was calculated using Kaplan–Meier methodology and compared using log-rank tests. The primary analysis compared outcomes between the TNFi-treated and TNFi-untreated groups. Subgroup analyses compared outcomes between two subgroups of the TNFi-treated group (infliximab-treated vs. adalimumab-treated) and the TNFi-untreated group.

Results Overall, 124 patients with CD were included in the analysis (TNFi-treated: $N=86$; TNFi-untreated: $N=38$). Of those patients who received TNFi treatment, 62 received infliximab and 24 received adalimumab. The median (range) observation period in the TNFi-treated and TNFi-untreated groups was 4.62 (0.41–13.75) years and 8.13 (0.08–30.25) years, respectively. Median time to surgery was 3 years in the TNFi-untreated group and 6.58 years in the TNFi-treated group. A significantly lower proportion of patients in the TNFi-treated group required surgery (3/86) compared with those in the TNFi-untreated group (17/38; OR [CI]: 0.0446 [0.0120–0.1667]; $P<0.0001$). Cumulative surgery-free survival rates were significantly higher in the TNFi-treated group versus the TNFi-untreated group ($P<0.0001$). Compared with the TNFi-untreated group, the proportion of patients who required surgery was significantly lower with both infliximab (1/62; OR [CI]: 0.0203 [0.0025–0.1616]; $P=0.0002$) and adalimumab (2/24; OR [CI]: 0.1123 [0.0231–0.5466]; $P=0.0068$). Cumulative surgery-free survival rates were significantly higher in the infliximab-treated group versus the TNFi-untreated group ($P<0.0001$).

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Conclusions Introduction of TNFis for the treatment of CD may lead to a reduction in surgery rates and prolong time to surgery.

Keywords Tumor necrosis factor inhibitor, Crohn's disease, Japan, Abdominal surgery, Infliximab, Adalimumab, Long-term observation

Background

Crohn's disease (CD) is an incurable inflammatory condition with unknown etiology characterized by periods of relapse and remission [1, 2]. Intestinal strictures are a common complication of CD, often requiring multiple surgeries [3], with associated detrimental effects on quality of life. As no medications exist to attenuate or reverse damage to the bowel, a specific window of opportunity exists to improve outcomes before irreversible damage to the bowel occurs [4]. Thus, recognition of CD as a progressive condition has shifted the focus of management strategies from symptom control and improvement of quality of life to slowing of disease progression with the aim of preventing damage to the bowel and associated disability [4].

The advent of biologic treatment options, such as tumor necrosis factor inhibitors (TNFis), has improved outcomes, and current data suggest that increased use of TNFis has paralleled the reduction of surgery in patients with CD [5–7]. Analysis of data from the Danish National Cohort, comprising 48,967 patients diagnosed with inflammatory bowel disease (1971–2011) and including 13,185 individuals with CD, showed a reduction in 1-year and 5-year rates of first major surgery over time, parallel to increasing use of thiopurines and TNFis [5]. A meta-analysis of the comparative efficacy of immunosuppressants and biologics in patients with CD also demonstrated that TNFis significantly reduce hospitalizations and surgery compared with placebo, while no statistically significant reduction was observed with azathioprine or vedolizumab versus placebo [7].

Despite improved outcomes with biologic treatments, up to 40% of patients with CD undergo surgery for CD during their lifetime [8, 9]. Consequently, surgery is an important contributor to the direct costs of CD [10], accounting for approximately one-third of total CD-related healthcare expenditure in a recent European study [11]. In Japan, the TNFi infliximab became available for the management of CD in 2002, followed by adalimumab in 2010 [12], and biosimilar products (e.g., CT-P13) have more recently become available. In the pre-TNFi era (i.e., before 2002), long-term hospitalization and the need for repeated surgery had a substantial negative impact on employment and education in patients with CD, with 10-year re-surgery rates reported to be up to ≥ 70% [13–15]. In contrast, a 2017 study (i.e., following the availability of TNFis) reported an average time from surgery to recurrence in patients with CD of 29.2 ± 23.4 months, a 5-year postoperative recurrence rate of 54.9%, and 5-year cumulative repeat surgery rates of 18.7% [16]. While it appears that these more recent reductions in reported rates of postoperative recurrence may be attributable to the introduction of TNFis, there are a lack of long-term data to support the hypothesis that TNFis lead to a reduction in surgery rates. As such, we conducted a retrospective, observational study to examine whether anti-tumor necrosis factor (TNF) treatment was associated with reduced rates of abdominal surgery at two tertiary treatment centers in Japan.

Methods

Study design

This was a retrospective, long-term, observational study in patients with CD who underwent treatment at the Ishida Clinic of IBD and Gastroenterology and Oita Red Cross Hospital (Oita, Japan), from initial diagnosis to January 2019. The earliest initial diagnosis was January 1978.

This study was conducted in accordance with the Declaration of Helsinki; however, given it is a retrospective observational study, formal ethical approval from an ethics committee was not required. Written approval to use the data included in the current study was obtained from Oita Red Cross hospital. Patient consents were obtained in accordance with the corresponding institutional ethic guidelines at the time of patients' visits.

Patients

Eligible patients had a diagnosis of CD (i.e., based on clinical, endoscopic, radiological, and histopathological criteria according to diagnostic guidelines for Japan) and were treated according to a step-up or top-down approach, per Japanese clinical guidelines [2, 17–19].

Patients with the following information available were included in the study: gender, age of disease onset, disease type (small, small and large, large intestine), pathological conditions (inflammation, perforation, stenosis), and history of abdominal surgery. Patients missing any component/element of the required demographic/disease history information were excluded from the study.

Patients were divided into two groups (TNFi-treated and TNFi-untreated) based on prior anti-tumor necrosis therapy for the management of CD. The TNFi-treated group included patients who received infliximab (IFX; reference product or biosimilar) or adalimumab (ADA; reference product) either before and/or after abdominal surgery, within 1 year after the diagnosis of CD. For

patients in the TNFi-treated group, patients with CD who had received only one TNFi treatment (IFX or ADA) were included; patients who had received two or more TNFis or switched from IFX to ADA (or vice versa) were excluded from the study.

IFX (5 mg/kg) was administered intravenously (IV) on Weeks 0, 2 and 6, and every 8 weeks thereafter; if the treatment effect diminished, the dose could be modified to either 10 mg/kg IV every 8 weeks or 5 mg/kg IV every 4 weeks. ADA (160 mg) was administered via a subcutaneous (SC) injection on Day 1, 80 mg SC 2 weeks later, then 40 mg SC every 2 weeks; if the treatment effect diminished, the dose could be modified to 80 mg SC every 2 weeks. All patients were switched from reference IFX to biosimilar IFX (CT-P13) from September 2018 onwards (following receipt of patient consent). Patients in the TNFi-untreated group did not receive a TNFi for the management of their CD.

Patients in both groups could additionally receive azathioprine, corticosteroid, and parenteral nutrition as conventional treatments, or abdominal surgery (bowel resection).

Outcomes and analyses

Primary analysis

The primary analysis compared patient baseline characteristics, surgery rate, cumulative surgery-free survival rates (time from initial diagnosis to surgery), and time to surgery between the TNFi-treated and TNFi-untreated patient groups.

Table 1 Patient demographics and disease characteristics at baseline

Characteristic	TNFi-treated (*n* = 86)	TNFi-untreated (*n* = 38)	*P*-value
Male, n (%)	67 (77.9)	20 (52.6)	0.0060[a]
Age of disease onset, median (IQR), years	21.0 (17.0–30.0)	24.5 (20.0–34.0)	0.04821[b]
Disease type, n (%)			
Small intestine	19 (22.1)	13 (34.2)	0.3715[c]
Small and large intestine	39 (45.3)	14 (36.8)	
Large intestine	28 (32.6)	11 (28.9)	
Pathological conditions, n (%)			
Inflammation	28 (32.6)	13 (34.2)	0.6642[c]
Perforation	36 (41.9)	13 (34.2)	
Stenosis	22 (25.6)	12 (31.6)	
History of abdominal surgery, n (%)	12 (14.0)	2 (5.26)	0.2231[a]
Anal fistula, n (%)	33 (38.4)	10 (26.3)	0.2239[a]

[a]Fisher's exact test for independence test 2×2 contingency table; [b]Mann–Whitney U test; [c]Fisher's exact test for independence test 2×3 contingency table

IQR, interquartile range; TNFi, tumor necrosis factor inhibitor

Subgroup analyses

Subgroup analyses compared baseline characteristics between the two subgroups of patients in the TNFi-treated group (who received either IFX or ADA), and surgery and cumulative surgery-free survival rates between the IFX- and ADA-treated subgroups versus the TNFi-untreated group.

Statistics

Data collection in the TNFi-treated group was suspended if a patient experienced a decrease in effectiveness or a change of treatment due to side effects, or was relocated to another treatment center. Categorical variables were expressed as numbers and percentages and compared using a Fisher's exact test for independence. Continuous variables were expressed as medians and interquartile ranges and compared using a Mann–Whitney U test. For surgery rate, treatment groups were compared through estimation of an odds ratio (OR) with 95% confidence intervals (CI). Cumulative surgery-free survival rates and time to surgery were calculated using Kaplan–Meier methodology and compared using log-rank tests. A significance level of 0.05 was used for all statistical analyses. RStudio software was used for the Shapiro-wilk, Fisher's exact, and Mann–Whitney U tests. Kaplan–Meier analysis and log-rank tests were performed using survival [20, 21] and survminer packages in the RStudio software [22].

Results

Patients

A total of 124 patients were enrolled in the study (TNFi-treated group: 86 patients; TNFi-untreated group: 38 patients). Of patients who were TNFi-treated, 62 had received IFX and 24 had received ADA. The median (range) observation period in the TNFi-treated and TNFi-untreated groups was 4.62 (0.41–13.75) years and 8.13 (0.08–30.25) years, respectively; corresponding total patient-years of follow-up were 458.7 and 345.4, respectively.

Primary analysis

At the time of disease onset, patients in the TNFi-treated group were slightly younger than patients in the TNFi-untreated group (21 vs. 24.5 years; $P = 0.04821$; Table 1). The distribution of disease type was similar between the TNFi-treated and TNFi-untreated groups, respectively (small intestine, 22.1% vs. 34.2%; small and large intestines, 45.3% vs. 36.8%; large intestine, 32.6% vs. 28.9%), as were the proportions of patients with pathological conditions (inflammation, 32.6% vs. 34.2%; perforation, 41.9% vs. 34.2%; stenosis, 25.6% vs. 31.6%; Table 1). Similar proportions of patients in the TNFi-treated and TNFi-untreated groups had anal fistula (38.4% vs. 26.3% respectively; Table 1).

Overall, 96.5% (n/*N* = 83/86) of patients in the TNFi-treated group did not undergo surgery compared with 55.3% (n/*N* = 21/38) of patients in the TNFi-untreated group (OR [95% CI] 0.0446 [0.0120–0.1667]; *P* < 0.0001; Table 2). Median time to surgery was 3 years in the TNFi-untreated group and 6.58 years in the TNFi-treated group. The cumulative surgery-free survival rate was significantly higher in the TNFi-treated group compared with the TNFi-untreated group (log-rank *P* < 0.0001; Fig. 1).

Table 2 Odds ratios for surgery in TNFi (IFX or ADA)-treated or TNFi-untreated patients

Comparator	Odds ratio (95% CI)[a]	Z statistics	*P*-value[b]
TNFi vs. non-TNFi	0.0446 (0.0120–0.1667)	4.625	< 0.0001
IFX vs. non-TNFi	0.0203 (0.0025–0.1616)	3.680	0.0002
ADA vs. non-TNFi	0.1123 (0.0231–0.5466)	2.708	0.0068
IFX vs. ADA	0.1803 (0.0156–2.0886)	1.371	0.1705

[a]Odds ratios were calculated from 2 × 2 contingency tables by TNFi use and surgery; [b]*P*-values calculated according to Sheskin 2004 [31]. A standard normal deviate (Z-value) is calculated as ln(OR)/SE[ln(OR)], and the *P*-value is the area of the normal distribution that falls outside ± Z

ADA, adalimumab; CI, confidence interval; IFX, infliximab; TNFi, tumor necrosis factor inhibitor

Subgroup analyses

Compared with patients in the ADA subgroup, patients in the IFX subgroup had less inflammation at baseline and were more likely to have perforation as a feature of their CD (*P* = 0.0007; Additional file 1; Table 1). There was no significant difference between the IFX-treated and ADA-treated subgroups in the proportions of patients who had anal fistula at baseline (43.5% vs. 25.0%; *P* = 0.1415; Additional file 1; Table 1).

In the subgroups of TNFi-treated patients receiving IFX or ADA, respectively, 98.4% (n/*N* = 61/62) and 91.7% (n/*N* = 22/24) did not undergo surgery, while 1.6% (n/*N* = 1/62) and 8.3% (n/*N* = 2/24) underwent a single surgery. The proportion of patients who required surgery was significantly lower in the IFX- and ADA-treated subgroups compared with the TNFi-untreated group (*P* = 0.0002 and *P* = 0.0068, respectively; Table 2).

Cumulative surgery-free survival rates (Fig. 2) were significantly higher in IFX-treated patients compared with TNFi-untreated patients (*P* < 0.0001), but were not significantly different between ADA-treated patients and TNFi-untreated patients (*P* = 0.2).

Discussion

In this long-term, retrospective, observational study of patients with CD treated in routine clinical practice in Japan, surgery rate was significantly lower in the TNFi-treated group compared with the TNFi-untreated group. In addition, cumulative surgery-free survival rate was significantly higher in the TNFi-treated group compared with the TNFi-untreated group. In subgroup analyses comparing TNFi-treated patients who received IFX or ADA with TNFi-untreated patients, both TNFi agents significantly reduced the proportion of patients requiring surgery. Furthermore, cumulative surgery-free survival rates were statistically significantly higher in IFX-treated patients compared with TNFi-untreated patients, but were not significantly different between ADA-treated

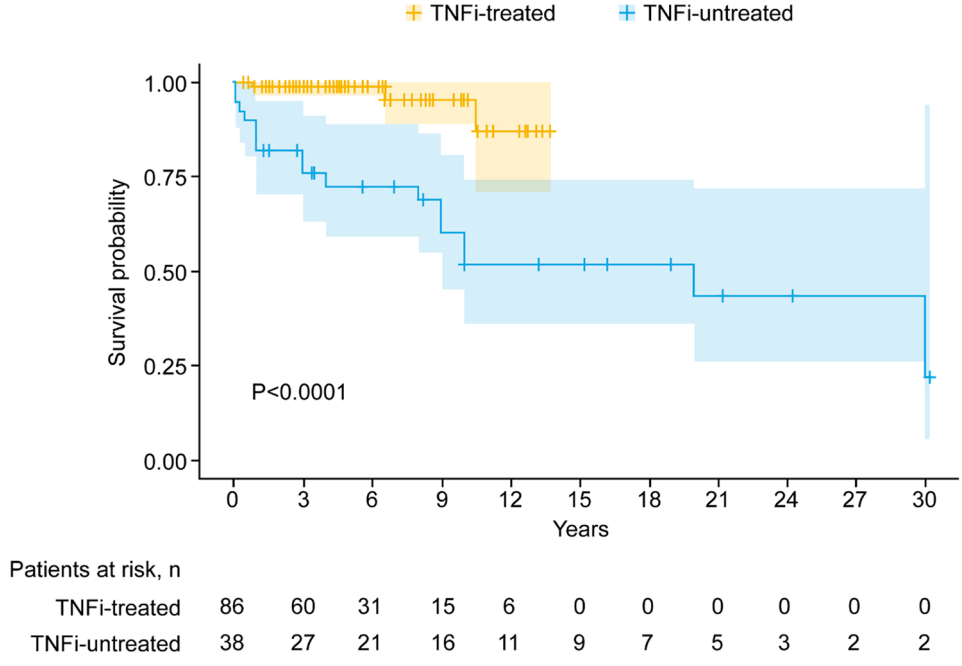

Fig. 1 Cumulative surgery-free survival rates in TNFi-treated and TNFi-untreated patients. TNFi, tumor necrosis factor inhibitor

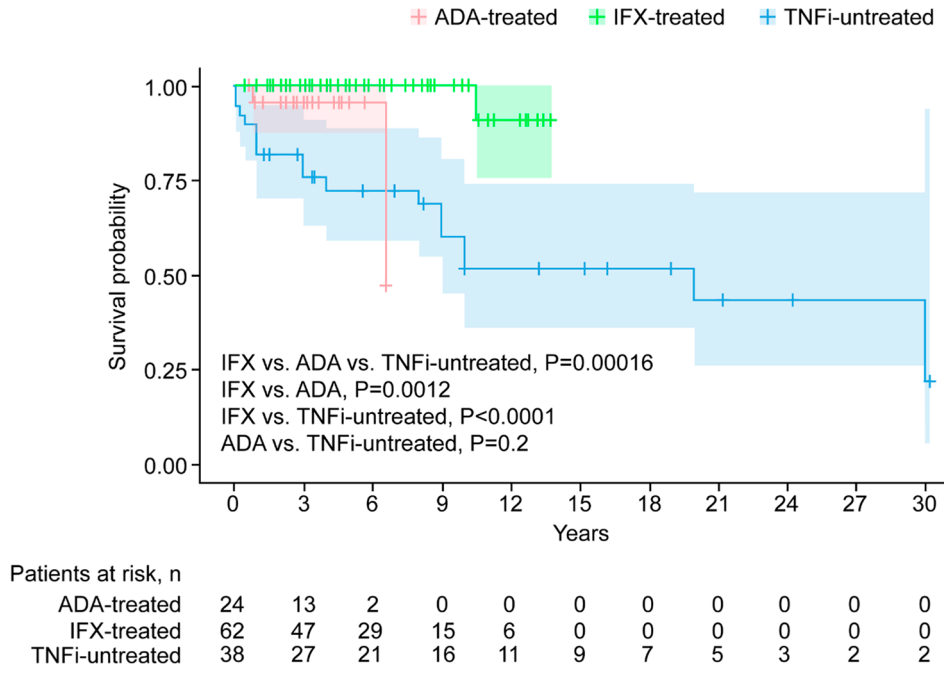

Fig. 2 Cumulative surgery-free survival rates in ADA-treated, IFX-treated, and TNFi-untreated patients. ADA, adalimumab; IFX, infliximab; TNFi, tumor necrosis factor inhibitor

patients and TNFi-untreated patients, despite patients in the IFX group having more severe pathological features at baseline (i.e., perforation) than the ADA group. This latter finding is particularly notable given that perforating complications (e.g., abscess, fistula, or free perforation) leading to surgery are associated with high morbidity from sepsis-related complications and are the principal cause of deaths directly attributable to CD [23]. Free perforation – the most severe complication affecting patients with CD – frequently requires emergency surgery [23, 24].

Findings from this study support the limited data that have been published. To date, the largest real-world study to evaluate the association between TNFi use and surgery rates in patients with CD included 5,003 TNFi-treated patients with CD from the Swedish National Patient Register [25]. Most patients (62%) continued TNFi treatment for 12 months or more, and this was associated with a lower risk of abdominal surgery compared with TNFi treatment for less than 12 months [25]. Data from smaller studies also support the association between TNFi treatment and a lower risk for surgery [26, 27]. In an observational, referral center-based cohort study of 296 patients with newly diagnosed CD in France, long-term TNFi treatment was associated with a lower risk for surgery [26]. In another study, conducted in an Italian tertiary center and involving 51 patients with CD and a small bowel or colonic stenosis, 61% of those treated with TNFis avoided abdominal surgery [27]. The results prompted the authors to suggest that for patients with CD who have strictures without associated non-perianal fistulae, anti-TNF treatment may be administered prior to consideration of surgery [27].

While the incidence of CD has plateaued in Western countries, CD rates have continued to increase in Japan [28], highlighting the need to continually review and update national clinical guidelines to improve patient outcomes. Clinical practice guidelines for the management of CD in Japan are primarily based on a global evidence base, with consensus input from Japanese experts [29]. Given that most studies to evaluate the optimal timing of TNFi initiation after diagnosis have been performed in Western countries, the effectiveness of early TNFi initiation in Asian patients with CD is less well established [30]. To address this gap, a recent study based on data from the Korean National Health Insurance Claims Database examined the effect of early TNFi initiation in 1,207 patients with CD [30]. Initiation of TNFi treatment within 1 year of diagnosis was associated with lower rates of surgery and emergency room visits compared with late TNFi initiation [30]. Reflecting this evidence, the present study included patients who initiated TNFi treatment within 1 year of diagnosis.

The findings from the current study are reflective of routine clinical practice in a tertiary healthcare setting in Japan. Furthermore, the range of patient characteristics can be considered illustrative of the typical spectrum of patients with CD, with some having received treatment for up to 30 years and others having initiated treatment more recently. In this latter group of patients, the shorter

follow-up time may have limited the evaluation of surgical outcomes to the acute setting. However, median follow-up times indicate that most patients were followed for a sufficient length of time in which complications leading to surgery would be likely to arise. Indeed, a key strength of the current study was the duration of the observation period, which comprised 458.7 patient-years in the TNFi-treated group and 345.4 patient-years in the TNFi-untreated group.

Findings from this study should be considered based on the following potential limitations. First, the study had a relatively small sample size and therefore the potential for extrapolation of the findings to other populations is limited. Second, the study was based in two centers in a single prefecture; however, treatment patterns were consistent with guideline recommendations and are thus representative of routine clinical practice across Japan. Another limitation to consider when interpreting the results is the difference in median observation period for the TNFi-treated and TNFi-untreated groups (4.62 and 8.13 years, respectively) which may have contributed to between-group differences, including in the proportion of patients requiring surgery. In common with all retrospective studies, the results cannot be used to establish causality. Finally, there was a lack of available information regarding the use of other drugs, and the availability of newer targeted therapies, including but not limited to TNFis, which may have resulted in an overall secular trend favoring non-surgical interventions.

In terms of implications for clinical practice, the findings show that the use of TNFis for the treatment of CD may reduce the need for abdominal surgery compared with conventional treatments; 96.5% of patients in the current study were able to avoid surgery with the use of TNFis. If TNFis are not used, surgery may be required approximately once every 10 years. As such, it may be beneficial to transition patients with CD to treatment with biologics (i.e., TNFis) before and after surgery, where clinically indicated.

Conclusions

In summary, results from this retrospective, observational study suggest that the introduction of TNFis, such as infliximab and adalimumab, may lead to reduced surgery rates and prolong time to surgery for patients with CD.

Abbreviations

ADA Adalimumab
CD Crohn's disease
CI Confidence interval
IFX Infliximab
IV Intravenously
OR Odds ratio
SC Subcutaneous
TNF Tumor necrosis factor
TNFi Tumor necrosis factor inhibitor

Supplementary Information

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Supplementary Material 1

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Author contributions

Tetsuya Ishida designed the study, collected and analyzed the data, reviewed and critically revised the manuscript, and approved the submitted version. Dr Ishida is accountable for the accuracy and integrity of the information presented in this article.

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Data availability

The datasets supporting the conclusions of this article are included within the article (and its additional file).

Declarations

Ethical approval

All patients provided written, informed consent. This study was conducted in accordance with the Declaration of Helsinki; however, given it is a retrospective observational study, formal ethical approval from the Oita Red Cross hospital ethics committee was not required. Written approval to use the data included in the current study was obtained from Dr Fukuwaza, Director of the Oita Red Cross hospital.

Patient consent to participate

Consent obtained.

Consent for publication

Not applicable.

Competing interests

The author declares no competing interests.

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