Rheumatoid interstitial lung disease in Canterbury New Zealand: prevalence, risk factors and long-term outcomes—protocol for a population-based retrospective study

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ABSTRACT

Introduction Rheumatoid arthritis (RA) affects approximately 0.5%–1% of the general population. Clinically significant interstitial lung diseases (ILD) develops in just under 10% of people with RA, and subclinical disease is more common. Little is known about RA-ILD in New Zealand (NZ), or the number of persons with RA in Canterbury, NZ. This study aims to determine: (1) incidence and prevalence of RA, (2) incidence and prevalence of RA-ILD, (3) clinical characteristics and risk factors for the development of RA-ILD, (4) long-term outcomes of RA-ILD, in the population resident within the Canterbury District Health Board (CDHB) catchment area. Methods and analysis Persons aged 18 years of age and older, and resident in the region covered by the CDHB with RA as well as RA-ILD will be identified by retrospective review of medical records. Prevalent as well as incident cases of RA between 1 January 2006 and 31 December 2013 will be identified, and followed until 30 June 2019. Existing as well as incident cases of RA-ILD during this time will be identified. The association between the development of ILD and clinical characteristics and environmental exposures will be examined using Cox-proportional hazard models. Kaplan-Meier methods will be used to estimate survival rates for patients with RA-ILD. Mortality for people with RA and RA-ILD will also be compared with the general population of the CDHB.

Ethics and dissemination Data will be obtained by retrospective review of medical records. Deidentified patient data will be stored in a secure online database. Data on individual patients will not be released, and all results will only be published in aggregate. Ethical approval has been obtained from the University of Otago Human Research Ethics Committee (Ref HD18/079). Results will be published in peer-reviewed medical journals and presented at conferences.

Trial registration number ACTRN12619001310156; Pre-results.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder causing joint inflammation and damage. Risk factors for developing RA include female sex, genetic determinants, such as the shared epitope, smoking, silica exposure and obesity. The frequency of RA varies between different geographic locations and over time. A 2006 systematic review found prevalence rates based on the 1987 American College of Rheumatology classification criteria for RA ranging from 1.8 to 10.7 per 1000 population, with the highest rates being reported for North American and Northern
European countries. In the same study, incidence ranged from 0.1 to 0.5 per 1000. Another systematic review published in 2015, focussing on low and middle-income countries, found overall RA prevalence rates of 0.4% for Southeast Asia, 0.37% for Eastern Mediterranean, 0.62% for European, 1.25% for American and 0.42% for Western Pacific low and middle-income countries.3

Multiple studies examining trends in the latter part of the 20th century suggested that the incidence of RA was declining.4–7 More recently, evidence suggests that the incidence is increasing in some areas and decreasing in others.8–11 Data from the Global Burden of Diseases, Injuries and Risk Factors Study 2017 reported that globally the age standardised point prevalence of RA increased by 7.4% (95% uncertainty interval (UI) 5.3 to 9.4) between 1990 and 2017, and the annual incidence increased by 8.2% (95% UI 5.9 to 10.5). The 2017 age-standardised point prevalence was 246.6 per 100000 (95% UI 222.4 to 270.8). Data in this report were derived largely from modelling, as population based data on the incidence and prevalence of RA were available from only a few countries.12 In Olmsted County, Minnesota, an increased incidence of rheumatoid factor negative and reduced incidence of rheumatoid factor positive RA have been reported for the period 2005–2014.13 Definitive causes for the changing frequency of RA over time are yet to be determined. It is possible that changes in environmental factors could be contributing, such as smoking and obesity.13

The most reliable contemporary estimates of the prevalence of RA in New Zealand come from New Zealand Health Survey data, which involve self-reported diagnoses.14 While these data provide a useful estimate of disease frequency, they may be prone to self-report and recall bias.

One of the most serious extra-articular manifestations of RA is interstitial lung diseases (ILD). The reported frequency of RA-ILD is variable due to differences in definitions, study design and the populations analysed. Subclinical disease is more common than symptomatic disease. In one study, the prevalence of clinically significant disease was 14%, compared with 44% who had abnormal findings on clinical investigations but did not have clinically significant disease.15 In a USA cohort, the lifetime incidence of clinically significant ILD among people with RA has been reported as 7.7%, leading to an approximately threefold increased risk of premature mortality.16

The most common radiological pattern of RA-ILD in the Western world is usual interstitial pneumonia (UIP), which is seen in approximately 60% of cases.17 Other patterns include non-specific interstitial pneumonia, organising pneumonia, lymphocytic interstitial pneumonia, diffuse alveolar damage and desquamating interstitial pneumonia.18

Risk factors for developing RA-ILD include old age, male sex, smoking and seropositivity for rheumatoid factor and anticyclic citrullinated antibodies.16–21 The risk for moderate to high disease activity versus low activity or remission has been shown to be approximately doubled (HR based on annually collected DAS-28 scores 2.22, 95% CI 1.28 to 3.82).22 A gain of function polymorphism in the promoter of MUC5B, which encodes mucin 5B, has been associated with an increased risk of RA-ILD, when comparing to persons with RA without ILD (OR 3.1, 95% CI 1.8 to 5.4). This association was significant for those with a UIP pattern, but not for those with a non-UIP pattern.23

Reported risk factors for progressive fibrosis or death include old age, male sex, UIP pattern, extent of disease on CT, impaired lung function and delay in the time from symptom onset to diagnosis of ILD.24–27 Standardised guidelines for evaluation and monitoring as well as optimal management of patients who develop RA-ILD are lacking. Many have progressive disease not responsive to currently available treatments.

Determining RA-ILD frequency and outcomes in the New Zealand context and comparing them to international data may help to better understand the relevance of disease-modifying antirheumatic drugs (DMARDs) in the aetiologyopathogenesis and management of RA-ILD. It is uncertain what effect DMARDs, particularly biologic therapies, may have on the development and progression of RA-ILD.18 Earlier literature suggested, for example, that methotrexate might promote development of RA-ILD, while more recent evidence has contributed to our current understanding that while methotrexate may rarely cause acute/subacute pneumonitis, there is no strong evidence that it has a role in the development or progression of ILD, and that control of the underlying RA disease process with agents such as methotrexate may actually reduce the risk of development of ILD.28 In addition, there is observational data that in patients with RA-ILD, those treated with methotrexate have better outcomes than those not treated with methotrexate.27 The role of biologic therapies is less certain.29 In New Zealand, access to biologic treatments occurred later and the number of biological therapies available is more restricted than in many other parts of the world.

This study is a retrospective population-based study of RA, and RA-ILD, conducted in the region covered by the Canterbury District Health Board (CDHB), New Zealand. The aims of this study are to determine: (1) incidence and prevalence of RA, (2) incidence and prevalence of RA-ILD, (3) clinical characteristics and risk factors for the development of RA-ILD, (4) long-term outcomes of RA-ILD in the population of the CDHB catchment area, compared with international cohorts.

This study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). Data collection commenced 1 October 2019.
METHODS AND ANALYSIS

Overview
To determine the prevalence and incidence of RA and RA-ILD, we will conduct a retrospective cohort study of persons aged 18 years of age and older resident in the catchment area of the CDHB, between 1 January 2006 and 31 December 2008 and between 1 January 2011 and 31 December 2013. We will identify existing as well as incident cases of RA, during these time periods. From this cohort of patients, we will identify existing as well as incident diagnoses of RA-ILD. Individuals will be followed until death, last entry in the health record or 30 June 2019. This end date for follow-up was chosen in order to maximise the time period for observation, while allowing a clear end point prior to the commencement of data collection. We will compare clinical characteristics and outcomes between patients with RA who do not have ILD and patients with RA-ILD.

Setting
The CDHB covers an area on the East Coast of the South Island of New Zealand. The total population of this region is approximately 567,870 persons. Rheumatology care is provided by rheumatologists located at Christchurch Hospital and two rheumatologists working in the private sector within the CDHB catchment area.

Data resource
The records, both inpatient and outpatient, of all persons who attended the Christchurch Hospital rheumatology service between 1 January 2006 and 31 December 2008 and between 1 January 2011 and 31 December 2013 will be reviewed. These years have been chosen because the hospital clinic letters are archived in a searchable format. Where our searches identify individuals, who met criteria for RA and were resident within the CDHB catchment area during these years, but do not attend clinic during these years, these individuals will also be included. The National Health Index (NHI), which is a unique national identification number, will be used to ensure that persons are not included in the study in duplicate and enable linkage of clinical, laboratory and radiology data, present on CDHB internal patient information system. Medical records for persons treated by private sector rheumatologists working within the CDHB catchment area will also be obtained to identify any cases managed in the private sector. In order to ensure we capture all possible cases of RA-ILD, the Canterbury radiology database will also be searched for individuals who had a chest radiograph, or chest or abdominal CT with ILD or like descriptions in the radiology report. The clinical medical records of these individuals be reviewed to ascertain if they had ever visited respiratory or rheumatology clinics.

Identification of study subjects
Identification of cases of RA: clinical records will be reviewed to identify individuals who meet the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatology (previously known as European League Against Rheumatism) Rheumatoid Arthritis Classification Criteria. Identification of cases of RA-ILD: no widely accepted classification criteria for RA-ILD exist at present. Current practice at CDHB is that cases of RA-ILD are principally diagnosed by consensus at dedicated ILD multidisciplinary meetings. These meetings began in 2017, subsequent to the beginning of the study period. For the purposes of this study, a pragmatic set of criteria will be used to define cases of clinically evident RA-ILD, which can be readily applied to our data resource, in a reproducible manner, as shown in table 1. Our criteria have been informed by a previous study from the USA, which applied clinical data, pulmonary function tests (PFTS), radiologic studies and lung biopsies to identify cases of ‘probable ILD’, and ‘definite ILD’. We have removed the criterion for abnormal PFTS, to reflect that a confident diagnosis of RA-ILD can often be made based on clinical features and radiological findings alone, without requirement for abnormal PFTS or histology.

Identification of outcomes
The information recorded for each case of RA and RA-ILD is listed in table 2. All retrospective clinical data will be collected and entered by HF, with assistance from an experienced rheumatology research nurse. In addition to the basic data listed in the table, we will also

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Case definitions of clinically evident ILD in people with RA according to ACR/EULAR classification criteria</th>
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<tbody>
<tr>
<td>Probable ILD</td>
<td><img src="image" alt="Chest radiograph/chest CT evidence of ILD" /> AND <img src="image" alt="Treating physician diagnosis of ILD" /></td>
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<tr>
<td>Definite ILD</td>
<td><img src="image" alt="Chest radiograph/ chest CT consistent with ILD" /> AND 1 of: <img src="image" alt="Diagnosis of ILD by a respiratory physician" /> OR <img src="image" alt="Presence of 2 longitudinal chest CT studies documenting the persistence of a diffuse interstitial pulmonary process consistent with reported interstitial pneumonia patterns in RA" /> OR <img src="image" alt="Lung biopsy consistent with ILD" /></td>
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ACR, American College of Rheumatology; EULAR, European Alliance of Associations for Rheumatology (previously known as European League Against Rheumatism); ILD, interstitial lung disease; RA, rheumatoid arthritis.
document the date that a person moved into the CDHB catchment area if they were diagnosed with RA outside of the area and moved into the area after 1 January 2006. If they moved away from the CDHB catchment area, we will document the date that this occurred. Cause of death will be recorded if it is documented in the CDHB internal patient information system. Usually death certificates are not available in this system. Date of RA and RA-ILD diagnosis will be taken as the date that classification criteria were met.

### Table 2: Information collected for cases of RA and RA-ILD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
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<tr>
<td><strong>Basic data/demographics</strong></td>
<td>NHI, capture source (public sector or private sector rheumatology clinic letter, radiology report, hospital discharge coding), date of birth, sex/gender, ethnicity, occupation at RA and RA-ILD diagnosis. Date meets ACR/EULAR 2010 RA criteria, post-code at RA diagnosis, date meets RA-ILD criteria, post-code at RA-ILD diagnosis, whether classified as probable or definite RA-ILD, date of last follow-up, status at last follow-up (alive/dead), date of death (if deceased). Cause of death (if deceased).</td>
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<td><strong>Exposures</strong></td>
<td>Smoking status, asbestos, metals, mould/damp, chemical/gases, birds, mineral dusts/silica, compost/potting mix, farm, TB, other(specify).</td>
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<tr>
<td><strong>RA characteristics</strong></td>
<td>Status (positive/negative/not available or not done) for the following immunological tests: RF, anti-CCP, ANA, ANCA. CRP closest to RA diagnosis date. Date of CRP. Presence of erosive joint disease. Presence of other extra-articular manifestations of RA including cervical myelopathy, Felty’s syndrome, pericarditis, glomerulonephritis, keratoconjunctivitis sicca, xerostomia, secondary Sjögren’s, pleuritis, scleritis/episcleritis/retinal vasculitis, vasculitis involving skin or other organ, neuropathy, subcutaneous rheumatoid nodules.</td>
</tr>
<tr>
<td><strong>Other morbidities</strong></td>
<td>Drug related acute pneumonitis (if yes, date, and drug causing pneumonitis). Comorbidities included in the Charlson Comorbidity Index at time of RA diagnosis, and at time of RA-ILD diagnosis, and at any point during follow-up will be recorded, and the index calculated at time of RA diagnosis, and at time of RA-ILD diagnosis. Other forms of drug induced pneumonitis will be classified according to previously published criteria. Other forms of drug induced pneumonitis will be classified according to previous immunological tests: RF, anti-CCP, ANA, ANCA, CRP closest to RA diagnosis date. Date of CRP. Presence of erosive joint disease. Presence of other extra-articular manifestations of RA including cervical myelopathy, Felty’s syndrome, pericarditis, glomerulonephritis, keratoconjunctivitis sicca, xerostomia, secondary Sjögren’s, pleuritis, scleritis/episcleritis/retinal vasculitis, vasculitis involving skin or other organ, neuropathy, subcutaneous rheumatoid nodules.</td>
</tr>
<tr>
<td><strong>Treatments</strong></td>
<td>Treatments for RA at the following time-points, at any time, at or 6 months prior to diagnosis of RA-ILD, following diagnosis of RA-ILD: oral glucocorticoids, azathioprine, cyclophosphamide, cyclosporine, gold, hydroxychloroquine, leflunomide, methotrexate, mycophenolate, d-penicillamine, sulfasalazine, minocycline, abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab. Drugs used for treatment of RA-ILD: glucocorticoids, azathioprine, cyclophosphamide, mycophenolate, rituximab, other(specify).</td>
</tr>
<tr>
<td><strong>Lung physiology</strong></td>
<td>Need for long-term oxygen therapy, PFT data at diagnosis of RA-ILD, the first set of PFTS that shows a clinically significant decline, and the most recent set of PFTS: FEV1, FVC, TLC, DLCO, weight, height, BMI, and 6 min walk time and distance. If RA but not RA-ILD lung physiology data collected at earliest available date, the first set of PFTS that shows a clinically significant decline, and the most recent set of PFTS.</td>
</tr>
<tr>
<td><strong>CT chest findings</strong></td>
<td>For persons who meet criteria for RA-ILD in table 1; CT chest closest to date that meets criteria for RA-ILD, and most recent CT will be reviewed for the presence of the following: honeycombing, traction bronchiectasis, ground glass opacification, reticulation, mosaic attenuation, non-emphysematous cysts, architectural distortion, consolidation, and emphysema. Distribution of these features in the cranio-caudal and transverse planes. Extent of CT ILD features will be estimated as &lt;20%, &gt;20%, or indeterminate based on criteria previously used in scleroderma, that have also been applied in RA-ILD. An impression of whether the extent of ILD progresses, remains unchanged, or reduces over time will also be made. The pattern of ILD will be classified based on the Fleischner diagnostic criteria for IPF. These guidelines will be adapted for an RA-ILD population, based on previous work, by removal of mosaic attenuation from the list of features that preclude a UIP diagnosis, and considering distribution of changes not classically seen in IPF. For persons with RA only, who do not meet criteria for RA-ILD in table 1, who have had CT chest imaging, the radiology reports for the CT chest closest to RA diagnosis date, and their most recent CT chest will be reviewed. If reported, the presence of alveolar opacities, bronchiectasis, bronchiolitis, bronchioloectasis, diffuse alveolar damage pattern, diffuse parenchymal interstitial lung disease, emphysema, ground glass opacity, reticular abnormalities, traction bronchiectasis, honeycomb, non-emphysematous cysts, mosaic attenuation, pleural fluid, nodule(s), architectural distortion, NSIP pattern, UIP pattern, hypersensitivity pneumonitis pattern, other(specify) will be recorded.</td>
</tr>
<tr>
<td><strong>Lung biopsy findings</strong></td>
<td>For persons with RA-ILD, who have had a lung biopsy: AIP, DIP, LIP, OP, NSIP cellular, NSIP fibrosing, UIP, UIP with atypical features, other(specify).</td>
</tr>
<tr>
<td><strong>Cardiac parameters</strong></td>
<td>Closest to time of RA-ILD diagnosis, and most recently: NYHA functional class, echocardiographic findings, right heart catheterisation study findings.</td>
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</table>
pneumonitis will be classified according to physician diagnosis.

We will determine if individuals had a clinically significant decline in PFTs, defined as ≥10% relative decline in forced vital capacity predicted. This forms part of the definition of progressive disease used in a recent randomised controlled trial of nintedanib in patients with fibrosing ILD that included people with RA, and is supported by clinical guidelines for connective tissue disease-associated ILD. We will calculate the time to progression based on the number of months from the baseline PFTs, to the first set of PFTs that had a clinically significant decline.

Three members of the CDHB radiology department will assist with reviewing CT chest images of persons who meet our retrospectively applied criteria for RA-ILD for specific ILD features as outlined in table 2. For other individuals who have RA but do not meet the criteria in table 1 for RA-ILD, CT chest images will not be reviewed, but if they have had a CT chest, we will review the radiology reports and document features compatible with ILD. These include ground glass or reticular abnormalities, traction bronchiectasis, lung distortion, honeycombing and non-emphysematous cysts. These are based on the abnormalities described in a recently proposed definition for interstitial lung abnormality, which refers to the presence of CT abnormalities compatible with ILD in persons without previous clinical suspicion of ILD. We will not specify that these abnormalities are non-dependent or involve at least 5% of a lung zone, as this will likely not have been reported in a standardised manner in our CT reports. Other findings documented in CT chest reports that we will record are outlined in table 2.

**Statistical analyses**

For aims 1 and 2, the period prevalence of RA and RA-ILD for 1 January 2006–31 December 2008 will be calculated using CDHB catchment area population data from the 2006 New Zealand census, and the period prevalence for 1 January 2011–31 December 2013 will be calculated using data from the 2013 New Zealand Census. Average annual incidence for each of the two time periods will be calculated. Prevalence and incidence rates will be age-adjusted and sex-adjusted to a standard population (e.g., US 2010) to facilitate comparisons with rates from other populations. Development of ILD among all people with RA will be determined by reviewing the clinical notes of patients with RA during longitudinal follow-up. The cumulative incidence of RA-ILD among patients with incident RA during each of the two time periods will be calculated.

For aim 3, clinical characteristics of persons with RA-ILD will be described. The association between the development of ILD and demographic characteristics (age at RA diagnosis, sex, ethnicity), clinical characteristics (seropositivity for rheumatoid factor, anticyclic citrullinated peptide, baseline C reactive protein, radiographic erosions) and environmental exposures (smoking, others if enough information available) will be examined using Cox-proportional hazard models adjusting for age, sex and smoking status. HRs and 95% CIs for different risk factors will be calculated.

For aim 4, Kaplan-Meier methods will be used to estimate mortality rates for patients with RA-ILD. Mortality for people with RA and RA-ILD will also be compared with the general population of the CDHB and standardised mortality ratios will be determined. Pulmonary function data will be collated to identify individuals in whom a clinically significant decline is found.

**Patient and public involvement statement**

This research does not involve direct patient or public involvement.

**ETHICS AND DISSEMINATION**

Ethical approval was obtained from the University of Otago Human Research Ethics Committee (REF: H18/079). This project does not involve experimentation on human subjects. It involves retrospective review of information obtained from medical records. Data on individual patients will not be released, and all results will only be published in aggregate. Data will be recorded onto a paper case record form and then entered in a timely fashion using the unique study identification number for each participant. Deidentified data will be housed in the Canterbury Rheumatology Immunology Research Group database, a secure web-based database. Deidentified data will not be made publicly available at the conclusion of the trial. Findings from this research will be published in peer-reviewed academic journals and presented at relevant scientific conferences.

**DISCUSSION**

Important gaps in our knowledge of the epidemiology and aetiopathogenesis of RA-ILD remain, particularly in New Zealand. Further research is needed to understand the changing trends in RA frequency, and the reasons underlying them. Studying the epidemiology of RA, and RA-ILD, in different populations and geographic contexts allows increased understanding of the underlying pathophysiology as well as the burden of these conditions. This work will add to the current body of international literature about prevalence of and risk factors for RA-ILD. It has the potential to generate new hypotheses regarding novel risk factors not previously reported. This study will endeavour to determine a valid and accurate measure of the frequency of RA-ILD, an essential first step in understanding the burden of this condition in New Zealand. Analysis of long-term outcomes of persons with RA-ILD from this study will allow greater understanding of the implications that a diagnosis of RA-ILD carries for the individual patient and the healthcare system. In addition, having an estimate of the frequency of RA based on clinical criteria will be valuable for understanding the burden of this condition in New Zealand and assist with
appropriate planning for the healthcare needs of patients with RA.

Strengths
The proposed study has a number of strengths. The population-based sampling method means that findings will be generalisable to a broad range of settings. Because the CDHB serves a well-defined population, and there are only a small number of rheumatologists caring for persons with RA in the private sector, our estimates of prevalence and incidence of disease are likely to be accurate. There will be some individuals with RA who are not seen by a rheumatologist, or who are cared for by a rheumatologist outside of the CDHB catchment area, but this is likely to be a relatively small number of individuals. The ability to use the NHI system prevents inclusion of individuals in duplicate and facilitates linkage of clinical data present on CDHB internal patient information systems. In addition, New Zealand represents a unique setting to undertake epidemiological research into RA and RA-ILD, due to population characteristics as well as differences in environmental risk factors and in access to RA therapy compared with other countries.

Limitations
The main limitation of our study is the retrospective design. Our study will be reliant on the completeness of medical record keeping. We expect data regarding demographics, laboratory tests, RA and RA-ILD characteristics, comorbidities and treatments to be nearly complete. It is likely that information about environmental exposures may be incomplete. This may limit our ability to identify and draw conclusions about the magnitude of risk for different exposures for the development RA-ILD. It could also mean that there are confounding factors we are not able to identify. Another limitation is that for persons with RA who do not meet our criteria for RA-ILD, we will abstract CT chest data from reports based on usual care, and these will not have been done in a standardised manner. This will limit our ability to detect changes associated with subclinical disease. Another limitation is that we are not collecting data on respiratory symptoms. The rationale for not collecting this data is that respiratory symptoms will not have been recorded in a systematic way and the conclusions that could be made from such data would be limited.

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Contributors
HF, LB, AE, EM and LS contributed to the conception and design of the study. HF if the principal investigator and is responsible for the overall content of this work. RT and EG specifically contributed to the content of the methods for analysing CT scans for people with RA-ILD. HF and LS wrote the first draft of the manuscript. All authors reviewed the manuscript, contributed to subsequent drafts and approved the final version of the manuscript.

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Competing interests
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Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication
Not applicable.

Provenance and peer review
Not commissioned; externally peer reviewed.

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