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Clinical outcomes of potential coeliac disease: a systematic review and meta-analysis

Mohamed G Shiha[1,2], Annalisa Schiepatti[3,4], Stiliano Maimaris[3,4], Nicoletta Nandi[1,5], Hugo A Penny[1,2], David S Sanders[1,2]

[1]Academic Unit of Gastroenterology, Sheffield Teaching Hospitals, Sheffield, UK

[2]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK

[3]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

[4]Gastroenterology Unit of Pavia Institute, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy

[5]Department of Pathophysiology and Organ Transplantation, University of Milan, Milan, Italy

Corresponding author

Dr Mohamed Shiha, Academic Unit of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK; Mohamed.shiha1@nhs.net

Abstract

Objective

Potential coeliac disease (PCD) is characterised by positive serological and genetic markers of coeliac disease with architecturally preserved duodenal mucosa. The clinical outcomes and rates of progression to overt coeliac disease in patients with PCD remain uncertain. In this systematic review and meta-analysis, we aimed to evaluate the clinical outcomes of patients with PCD.

Design

We searched MEDLINE, EMBASE, Scopus, and Cochrane Library from 1991 through May 2024 to identify studies evaluating the clinical outcomes of PCD patients. The progression rates to villous atrophy, seroconversion and response to a gluten-free diet (GFD) were analysed. A random-effects meta-analysis was performed, and the results were reported as pooled proportions with 95% confidence intervals (CIs).

Results

Seventeen studies comprising 1010 patients with PCD were included in the final analyses. The pooled prevalence of PCD among patients with suspected coeliac disease was 16% (95% CI, 10% - 22%). The duration of follow-up in most of the studies was at least 1 year, with follow-up periods within individual studies ranging from 5 months to 13 years. During follow-up, 33% (95% CI, 18% - 48%; I^2=96.4%) of patients with PCD on a gluten-containing diet developed villous atrophy, and 33% (95% CI, 17% to 48%; I^2 = 93.0%) had normalisation of serology. Among those who adhered to a GFD, 88% (95% CI 79 – 97%; I^2 = 93.2%) reported symptomatic improvement.

Conclusion

Almost a third of patients with PCD develop villous atrophy over time, whereas a similar proportion experience normalisation of serology despite a gluten-containing diet. Most symptomatic patients benefit from a GFD. These findings highlight the importance of structured follow-up and individualised management for patients with PCD.

Keywords

Coeliac disease, diagnosis, gluten

Significance of this study

What is already known on this topic

- Coeliac autoimmunity affects approximately 1% of the population worldwide.
- Potential coeliac disease (PCD) is characterised by positive serological and genetic markers of coeliac disease without evidence of intestinal villous atrophy on duodenal biopsies.
- The outcomes and optimal management for patients with PCD remain unknown.

What this study adds

- Approximately 16% of people with positive coeliac-specific antibodies have PCD.
- Almost a third of patients with PCD who continue to eat gluten develop overt coeliac disease over time, but a similar proportion experience normalisation of serology.
- Most symptomatic patients with PCD benefit from a gluten-free diet.

How this study might affect research, practice or policy

- Future research should focus on identifying clinical and molecular predictors of progression from PCD to overt coeliac disease.
- This study provides data to inform shared decision-making between clinicians and patients regarding the management of PCD.

Introduction

Coeliac autoimmunity affects approximately 1.4% of the global population [1]. Yet, not all individuals with positive coeliac disease-specific antibodies, such as tissue transglutaminase (tTG) or endomysial antibodies (EMA), have intestinal villous atrophy, the histopathological hallmark of coeliac disease diagnosis. Potential coeliac disease (PCD) is characterised by the presence of these specific antibodies and a positive HLA-DQ2 or HLA-DQ8 genotype with no or minor small intestinal changes [2]. Data on the natural history of PCD remains poorly defined. While some patients with PCD may progress to overt coeliac disease with villous atrophy on a gluten-containing diet, many remain asymptomatic or have mild symptoms without developing intestinal damage [3].

Unlike overt coeliac disease, which mandates a strict gluten-free diet (GFD), the approach to managing patients with PCD is less clear. Current clinical guidelines recommend regular monitoring and assessment rather than immediate dietary restrictions in patients with PCD [4,5]. In practice, asymptomatic individuals with PCD do not often receive any dietary interventions, while symptomatic patients may benefit from a GFD. However, the decision to start a GFD is controversial due to the limited evidence on the natural history of PCD and the risk of progression to overt coeliac disease [6].

The nomenclature of “potential coeliac disease” reflects the intermediate state of patients who are at risk of developing overt coeliac disease but do not currently meet the histological criteria for diagnosis. However, the term “potential” can sometimes lead to confusion regarding the appropriate clinical approach to manage these patients. Many patients with PCD remain unsure whether to continue eating gluten or to adhere to a life-long GFD. Given these uncertainties, we aimed to perform a systematic review and meta-analysis of studies evaluating the clinical outcomes of patients with PCD.

Methods

Study reporting and protocol registration

This systematic review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[7]. The study protocol was prospectively registered on the International Prospective Register of Systematic Reviews (CRD42024541847; May 2nd, 2024).

Search strategy

The search strategy was developed in collaboration with medical librarians at Sheffield Teaching Hospitals. We conducted a systematic literature search on MEDLINE, Embase, Scopus, and Cochrane Library for studies reporting the clinical outcomes of patients with PCD. The search was restricted to include studies published from January 1991, coinciding with the publication of the first modern guidelines for the diagnosis of coeliac disease by the European Society of Gastroenterology, Hepatology, and Nutrition in 1990[8]. There were no language restrictions. Both studies on paediatric and adult cohorts were considered. To identify any other relevant studies not captured by our database search, we performed a recursive search of the bibliographies of all eligible articles and relevant reviews. The full search strategy for each database is provided in the supplementary materials.

Study selection and inclusion criteria

The search results were exported to EndNote 20 (Clarivate Analytics, London, United Kingdom), and duplicate records were removed. Two reviewers (MGS & NN) independently screened the titles and abstracts of all citations for potentially eligible studies. The full-text articles of all potentially eligible studies were retrieved and evaluated in more detail. Any

disagreements between reviewers were resolved by consensus. We included observational or randomised controlled trials that reported the clinical outcomes of patients with PCD who continued to consume a gluten-containing diet or started a GFD. Conference abstracts, case reports, case series, reviews, editorials, practice guidelines and studies lacking specific data on outcomes relevant to PCD were excluded. Where there were overlapping studies from the same cohort, we selected the most recent and most comprehensive report.

Study outcomes

The primary outcome of this study was the proportion of patients with PCD who continued to consume gluten and developed overt coeliac disease during follow-up. Secondary outcomes included the proportion of patients with PCD who adhered to a GFD, the rates of symptomatic improvement and normalisation of serology on a gluten-containing diet or a GFD.

Data extraction

Two reviewers (MGS & SM) independently extracted all the data onto a standardised Excel spreadsheet (Microsoft Corp, Redmond, WA). The following data were extracted from each study, where available: study country, study design, number of patients, patient demographic characteristics (age and sex), diagnostic criteria, serology used, biopsy protocol, follow-up duration and outcomes data. Any discrepancies were resolved by consensus.

Risk of bias assessment

Two reviewers (MGS & NN) independently assessed the risk of bias in the included studies using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane risk-of-

bias (ROB) tool for randomised trials [9,10]. The NOS tool evaluates studies based on the selection of the study groups, the comparability of the groups, and the comparability of study outcomes. Each study is judged based on these elements and awarded a maximum of 9 stars, with more stars indicating a lower risk of bias. We considered studies having ≥7 stars to have a low risk of bias [11]. The ROB tool evaluates the risk of bias in randomised trials based on the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance and detection bias), incomplete data (attribution bias), and selective reporting (reporting bias). Each domain was rated as "low risk", "high risk" or "unclear risk" of bias based on the information reported in each study. Any disagreements between reviewers were resolved by consensus.

Data synthesis and statistical analysis

We calculated the pooled estimates and 95% confidence intervals (CI) of the main study outcomes using a random-effects meta-analysis model to account for variability across studies. Heterogeneity between studies was assessed using the Cochrane Q and I^2 statistics, where I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively. Potential publication bias was assessed by visual inspection of funnel plots and formally using Egger's regression asymmetry test. To determine the influence of each study on the overall effect size estimate, we performed a leave-one-out analysis by excluding each study one at a time and recalculating the pooled estimates. Subgroup analyses were also conducted based on key study characteristics, such as study design, participants' age, and biopsy protocol. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 18 (StataCorp, College Station, Texas, USA).

Results

Study Selection and Study Characteristics

The systematic literature search yielded a total of 975 citations, of which 41 articles were eligible for full-text screening. One study that met the eligibility criteria was excluded as most patients underwent jejunal biopsies using Watson capsules [12]. Additionally, 3 studies were excluded as they reported duplicated data from the same group of participants reported in other studies [13–15]. A total of 17 studies comprising 1010 patients were included in the final analyses [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] (Figure 1).

The characteristics of the included studies are summarised in Table 1. All the studies were cohort studies except the study by Kurppa et al., which was a randomised controlled trial comparing a GFD with a gluten-containing diet in patients with PCD[18]. Ten studies were conducted in a paediatric setting, and 7 studies included adult patients. Almost half of the included studies were conducted in Italy. Most studies included patients with Marsh 0 or 1 histology. However, 3 studies defined PCD by the absence of villous atrophy and included patients with Marsh 2 histology [18] [19] [23]The duration of follow-up in most of the studies was at least 1 year, with follow-up periods within individual studies ranging from 5 months to 13 years. There were 8 prospective studies and 9 retrospective studies. Auricchio et al. (2014)[22] included the original cohort from Auricchio et al. (2019)[28] in their analysis, but the outcomes of patients who followed a GFD were not reported in the latter study. The pooled prevalence of PCD among patients with suspected coeliac disease, reported in 9 studies, was 16% (95% CI, 10% - 22 %) (Supplementary Figure 1).

Outcomes of patients on a gluten-containing diet

Fifteen studies reported the rates of developing villous atrophy in patients with PCD who underwent a repeat biopsy while on a gluten-containing diet. Overall, 65% (95% CI, 49% - 80%) of patients with PCD continued a gluten-containing diet, of whom 73% (95% CI, 58% - 87%) underwent follow-up biopsy. The pooled proportion of patients developing villous atrophy during follow-up was 33% (95% CI, 18% - 48%), with high heterogeneity between studies (I^2 = 96.4%) (Figure 2). There was evidence of funnel plot asymmetry (Egger z = 2.26, p=0.02) (Supplementary Figure 2), indicating possible publication bias or small study effects. The leave-one-out sensitivity analysis (Supplementary Figure 3) indicated that no single study disproportionately influenced the overall results, with pooled estimates remaining consistent between 28% and 35%. Excluding studies that included patients with Marsh 2 histology did not significantly alter the results but showed lower heterogeneity between studies (I^2 = 87.4%) (Supplementary Figure 4).

On subgroup analysis, studies where duodenal bulb biopsies were obtained showed lower rates of progression to villous atrophy (19%, 95% CI 11% - 26%) and lower heterogeneity (I^2 = 65.6%) compared with studies where only distal duodenal biopsies were obtained (44%, 18% - 70%; I^2 = 96.7%) (Figure 3). The rates of progression to villous atrophy were also higher in adults (39%; 95% CI, 13% - 65%) than in children (28%; 95% CI, 10% - 45%). However, the difference between the groups was not statistically significant (p=0.50) (Figure 4). Similarly, no statistically significant differences were found between studies according to study design (Supplementary Figure 5), serological tests (Supplementary Figure 6) and follow-up duration (Supplementary Figure 7).

The pooled proportion for serology normalisation on a gluten-containing diet was 33% (95% CI, 17% to 48%), with high heterogeneity between studies (I^2 = 93.0%) (Figure 5).

Outcomes of patients on a gluten-free diet

Ten studies reported the clinical outcomes of patients with PCD who followed a GFD. Overall, 50% (95% CI, 34% - 65%) of patients with PCD in these studies started a GFD. The pooled proportion of symptomatic improvement after adhering to a GFD was 88% (95% CI, 79%—97%), with high heterogeneity between studies (I^2 = 93.25%) (Figure 6). Seven studies [17] [18] [20] [23] [24] [25] [26] reported the rates of serology normalisation on a GFD, and as expected, all patients achieved normalisation of their serological markers.

Risk of bias assessment

The overall risk of bias in the included studies was low. The total scores of these studies, using the NOS, ranged between 6 and 8, with a median score of 7 (Table 1). The randomised controlled trial by Kurppa et al. had a low risk of bias across all domains except for blinding of participants (Supplementary Figure 8).

Discussion

In this systematic review and meta-analysis, we found that PCD is common among patients with suspected coeliac disease, with a pooled prevalence of 16%. Approximately a third of patients with PCD who continued to consume gluten developed villous atrophy during follow-up, and a similar proportion of patients experienced normalisation of serology over time. Most symptomatic patients with PCD benefited from a GFD.

PCD is variably defined across studies. Many groups of authors consider PCD to include asymptomatic patients with normal duodenal mucosa (Marsh 0, <25 intraepithelial lymphocytes), permissive genetics, and positive serology or elevated γδ lymphocytes. Additionally, some authors suggest that having first-degree relatives with coeliac disease also supports the diagnosis of PCD [2][5][33][34]. These variations highlight the challenges and complexity in diagnosing PCD. In the current study, we included patients with positive serology and no evidence of villous atrophy on duodenal biopsies. Accurate diagnosis of PCD relies on using validated serological assays, ensuring patients consume enough gluten before testing, and adhering to the recommended biopsy protocols [5]. Failure to follow these standards can result in false-negative results, leading to delayed diagnosis of coeliac disease. We found that 33% of patients with PCD who continued to consume gluten developed villous atrophy during follow-up. Interestingly, these progression rates were lower in studies where duodenal bulb biopsies were performed. This may be because ultra-short coeliac disease, characterised by villous atrophy confined to the duodenal bulb, can easily be misdiagnosed as PCD if bulb biopsies are not performed [35]. Adding duodenal bulb biopsies has been shown to increase the sensitivity of coeliac disease detection by approximately 10% [36]. Therefore, in studies where duodenal bulb biopsies were not

performed, some patients may have had ultra-short coeliac disease that was misdiagnosed as PCD.

Several studies attempted to identify factors associated with the progression of PCD to overt coeliac disease with villous atrophy. Key factors include the presence of symptoms, persistent positive serology, age at diagnosis and positive anti-TG2 intestinal deposits [13][24][28]. We found slightly higher rates of progression to villous atrophy in adults compared with children, although this was not statistically significant. This finding is consistent with previous studies showing that children younger than 3 years diagnosed with PCD have a very low chance of progression to overt coeliac disease, whereas older children and adults who remain on a gluten-containing diet are more likely to develop villous atrophy over time [28][18].

Asymptomatic patients with PCD are often identified through screening of high-risk populations, such as patients with Type 1 diabetes and first-degree relatives of people with coeliac disease [37]. In these groups, IgA-tTG levels can elevate transiently and normalise without any dietary changes [38][39]. Our results support this notion, as almost a third of patients with PCD had seroconversion while on a gluten-containing diet. Therefore, it is crucial to consider the clinical context and monitor serological trends over time before advising patients to adhere to a lifelong GFD. This approach helps avoid unnecessary dietary restrictions and the associated burden on patients [40].

Although PCD is thought to be associated with less severe nutritional and metabolic consequences compared with overt coeliac disease, this does not necessarily correspond to a milder symptom profile [31]. We found that 88% of patients with PCD who adhered to a GFD reported symptomatic improvement. This clinical response is comparable to what is seen in patients with overt coeliac disease, and much higher than what is typically observed

in patients with irritable bowel syndrome who follow a GFD [41][42][43]. Previous studies showed a poor correlation between symptoms and intestinal damage in patients with coeliac disease at diagnosis and during follow-up[44][45][46], suggesting that traditional histology may not adequately capture the range of intestinal dysfunction in coeliac disease. Other factors beyond villous atrophy, such as cytokines released by gluten-specific CD4+ T cells , alterations in gut microbiota and disturbances of gastrointestinal motility, may contribute to symptom generation in both PCD and coeliac disease [47][48][49]. Therefore, it is important to consider the broader spectrum of gluten-related disorders and the potential benefits of GFD in conditions like PCD, even in the absence of clear intestinal damage. Future guidelines should avoid confusion by revising the term “potential” with a more illustrative term that accurately represents the clinical and pathophysiological findings in these individuals. Moreover, the management of persistent symptoms after adhering to a GFD in patients with PCD should follow the same approach as in overt coeliac disease, given that additional underlying diagnoses, such as inflammatory bowel disease, irritable bowel syndrome and microscopic colitis, are often identified [31] [50].

Since 2012, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) has adopted a no-biopsy diagnostic pathway, whereby children with IgA-tTG ≥10 times the upper limit of normal (ULN) and positive confirmatory EMA could be diagnosed with coeliac disease without duodenal biopsies [51][4]. The decision to avoid biopsies was supported by a landmark study that confirmed the reliability of the no-biopsy approach in children with a positive predictive value of >99% [52]. A more recent systematic review and meta-analysis showed that the same approach could be extrapolated to selected adult patients with a moderate to high pre-test probability of coeliac disease [53]. However, there areconcerns about the lack of baseline duodenal biopsy during follow-up and the

possibility of false-positive serology results, which could lead to an unnecessary lifelong GFD [54]. Kori et al. found that patients with PCD and IgA-tTG ≥10x ULN had a nearly 20-fold higher risk of progressing to overt coeliac disease compared with those with IgA-tTG 1-3x ULN [32]. Furthermore, the results of the current meta-analysis suggest that most symptomatic patients with PCD benefit from a GFD. These findings could aid clinicians and patients in making informed decisions regarding serology-based diagnosis of coeliac disease and initiation of a GFD. .

Our study has several strengths. First, we conducted a comprehensive literature search across several databases to ensure that all eligible studies were included, and we analysed data on more than one thousand patients with PCD. Second, the study was conducted based on an a priori registered protocol with predefined outcomes and inclusion criteria to minimise the risk of bias. Third, we adhered to rigorous reporting standards and statistical methods, including extensive sensitivity and subgroup analyses to explore the causes of heterogeneity between studies. Fourth, the quality of the included studies was independently assessed by two reviewers using validated risk of bias tools. Finally, the relatively large sample size obtained by pooling the studies enhances the robustness of our findings.

Despite these strengths, the study also had limitations. There was evidence of publication bias suggesting that negative or inconclusive studies may be underrepresented in the current literature. We were also unable to evaluate predictors of progression to overt coeliac disease as we did not have access to individual patient data. Additionally, there was significant heterogeneity between studies in our analyses, which was only partially explained by our subgroup analyses. This variability stems from the differences in study populations, designs, biopsy protocols, and follow-up durations. It is also important to

consider the different performance of serological tests; tTG being slightly more sensitive and EMA more specific [55]. Although there were no statistically significant differences between studies using only EMA and those that used tTG with or without EMA confirmation, Kondala et al. study showed a lower rate of progression to overt coeliac disease when EMA was not used [23]. Another limitation is that most of the studies were conducted in Europe, which limits the generalisability of our findings to other populations. Importantly, not all patients who continued to consume gluten underwent follow-up biopsies, which may have led to an underestimation of the rates of progression to villous atrophy.

In conclusion, this systematic review and meta-analysis of 17 studies, including 1010 patients with PCD, demonstrates that almost a third of patients who continue to consume gluten progress to overt coeliac disease, while a similar proportion experience seroconversion over time. Most symptomatic patients benefit from a GFD. These findings could aid clinicians in making informed decisions about the management of patients with PCD.

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Tables

Table 1 – Study characteristics

Author, year (Ref)	Country	Study design	Sample size	Study population	Mean/median* age (years)	Female (%)	Serology	Duodenal bulb biopsies	Follow-up duration	Newcastle-Ottawa score
Piccoli et al., 2002[16]	Italy	Prospective single-centre study	11	Children	8.7	63.6	tTG & EMA	No	1 – 4 years	6
Dickey et al., 2005[17]	Northern Ireland	Retrospective single-centre study	35	Adults	43	62.9	EMA	No	1 – 6 years	8
Kurppa et al., 2009[18]	Finland	Randomised controlled trial	23	Adults	50*	65.2	tTG & EMA	No	1 year	ǂ
Szaflarska-Popławska, 2009[19]	Poland	Retrospective single-centre study	30	Children	12.6	60.0	EMA	No	1 – 4 years	7
Kurppa et al., 2010[20]	Finland	Prospective single-centre study	17	Children	11*	58.8	tTG & EMA	No	1 year	8
Biagi et al., 2013[21]	Italy	Retrospective single-centre study	47	Adults	35	68.1	EMA	No	1 – 3 years	6
Auricchio et al., 2014[22]	Italy	Prospective single-centre study	210	Children	6.4*	67.1	tTG & EMA	Yes	Up to 9 years	8
Kondala et al., 2016[23]	India	Prospective single-centre study	57	Adults	28.7	59.6	tTG	No	1 year	8

Volta et al., 2016[24]	Italy	Prospective single-centre study	77	Adults	33	59.7	tTG & EMA	Yes	1-10 years(mean 3 years)	8
Imperatore et al., 2017[25]	Italy	Retrospective single-centre study	56	Adults	31.4	73.2	tTG & EMA	Yes	Up to 6 years	7
Mandile et al., 2018[26]	Italy	Prospective single-centre study	65	Children	7.3*	67.7	tTG & EMA	Not specified	2 – 5 years	6
Lionetti et al., 2019[27]	Italy	Prospective multi-centre study	26	Children	2*	50.0	tTG & EMA	Yes	Up to 10 years	8
Auricchio et al., 2019[28]	Italy	Prospective single-centre study	340	Children	Not specified	67.1	tTG & EMA	Yes	Up to 12 years (median 5 years)	8
Sakhuja et al., 2021[29]	USA	Retrospective single-centre study	40	Children	Not specified	Not specified	tTG & EMA	Yes	Median 1.1 years	7
Kröger et al., 2022[30]	Finland	Retrospective single-centre study	12	Children	Not specified	Not specified	tTG & EMA	No	6.1 – 13.3 years (median 10.1 years)	7
Newton et al., 2023[31]	England	Retrospective single-centre study	84	Adults	36.5*	63.1	tTG & EMA	Yes	Median 1.7 years	7
Kori et al., 2023[32]	Israel	Retrospective single-centre study	90	Children	7.2	71.1	tTG & EMA	Yes	5 months to 2.9 years (mean 1.4 years)	7

USA: United States of America; EMA: Endomysial antibodies; tTG: tissue transglutaminase
ǂLow risk of bias

Figures

Figure 1 – PRISMA flow diagram of study selection

Figure 2 – Forest plot of studies assessing the proportion of patients with PCD who developed villous atrophy on repeat duodenal biopsies

Figure 3 – Forest plot of studies assessing the proportion of patients with PCD who developed villous atrophy on repeat duodenal biopsies, sub-grouped according to obtaining duodenal bulb biopsies

Figure 4 – Forest plot of studies assessing the proportion of patients with PCD who developed villous atrophy on repeat duodenal biopsies, sub-grouped according to age

Figure 5 – Forest plot of studies assessing the proportion of patients with PCD who had normalisation of serology despite a gluten-containing diet

Figure 6 – Forest plot of studies assessing the proportion of patients with PCD who reported symptomatic improvement on a gluten-free diet

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Competing interests

None.

Availability of data

Data are available upon reasonable request.

Contributorship Statement

Conception and design: MGS & AS. Data collection and extraction: MGS, SM, NN. Data analyses and drafting the manuscript: MGS. Data interpretation and critical revisions of the manuscript: MGS, AS, SM, NN, HAP and DSS. All authors approved the final draft of the manuscript. MGS is the guarantor.

Patient and Public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.