Association of anti-Ro52 autoantibody with interstitial lung disease in autoimmune diseases: a systematic review and meta-analysis

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ABSTRACT
Objectives Interstitial lung disease (ILD) is an important manifestation of autoimmune diseases that can lead to morbidity and mortality. Although several autoantibodies have been linked with ILD presentation and adverse outcomes, the association of anti-Ro52 antibody with ILD is less studied. Hence, we investigated this association in various autoimmune diseases in the current study.

Design We designed a systematic review and meta-analysis and did a comprehensive search from inception until 2 January 2023.

Data sources A systematic search was conducted in four electronic databases: PubMed, Web of Science, Scopus and Embase.

Eligibility criteria Observational studies that reported ILD diagnosis (outcome) and anti-Ro antibody (exposure) status in any autoimmune conditions (population) were included. The association between rapidly progressive ILD (RP-ILD) and anti-Ro52 was studied in idiopathic inflammatory myopathies (IIM).

Data extraction and synthesis Collected data included study characteristics and ORs with 95% CIs. Quality assessment was performed using a modified version of the Newcastle-Ottawa Scale for cross-sectional studies. Random effects meta-analysis was used to pool the effect estimates.

Results A total of 2353 studies were identified, from which 59 articles met the eligibility criteria. Anti-Ro52/SSA positivity was associated with ILD in all autoimmune disease subgroups: IIM (OR=3.08; 95% CI: 2.18 to 4.35; p value<0.001; I2=49%), systemic lupus (OR=2.43; 95% CI: 1.02 to 5.79; p=0.046; I2=71%), Sjogren (OR=1.77; 95% CI: 1.09 to 2.87; p=0.021; I2=73%), systemic sclerosis (OR=1.71; 95% CI: 1.04 to 2.83; p=0.036; I2=43%), mixed connective tissue disease (OR=3.34; 95% CI: 1.82 to 6.13; p<0.001; I2=0%). Additionally, anti-Ro52-positive myopathy patients were more likely to have simultaneous RP-ILD (OR=2.69; 95% CI: 1.50 to 4.83; p<0.001; I2=71%).

Conclusion Anti-Ro52/SSA positivity is associated with a higher frequency of ILD diagnosis in various autoimmune diseases. Anti-Ro52/SSA is also linked with a more severe lung involvement (RP-ILD). Future studies can investigate the benefits of screening for anti-Ro52 and its association with ILD development.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Anti-Ro52/SSA positivity has been associated with a higher prevalence of interstitial lung disease (ILD), primarily in idiopathic inflammatory myositis.

WHAT THIS STUDY ADDS
⇒ Anti-Ro52/SSA positivity was associated with ILD presence in various autoimmune conditions other than myositis.
⇒ Anti-Ro52/SSA positivity was associated with a higher prevalence of rapidly progressive ILD in myositis patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Future prospective studies are required to investigate the possible association of anti-Ro52/SSA with ILD development and progression.

INTRODUCTION
Interstitial lung disease (ILD) may occur as a manifestation of many autoimmune diseases, such as idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc) and systemic lupus erythematosus (SLE).1–3 The prognosis of ILD depends on its subtype and the associated autoimmune disease.4,5 Nevertheless, ILD can be a major cause of morbidity and mortality.4,5 Despite its significance, many associated diagnostic markers and predictors of ILD development remain unknown.

One particular biomarker that may be associated with ILD is the antibody to tripartite motif protein-21, also known as Ro52. Ro52 is an intracellular ubiquitin ligase that helps the cells defend against viruses that have escaped the extracellular immune system and entered the cells. In an autoimmune disease state, where tolerance mechanisms mistakenly identify self-antigens as non-self, autoantibodies can develop against the Ro52

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Conclusion Anti-Ro52/SSA positivity is associated with a higher frequency of ILD diagnosis in various autoimmune diseases. Anti-Ro52/SSA is also linked with a more severe lung involvement (RP-ILD). Future studies can investigate the benefits of screening for anti-Ro52 and its association with ILD development.

PROSPERO registration number CRD42022381447.
It is understood that anti-Ro52 and anti-Ro60 antibodies have distinct associations with different autoimmune conditions. It is thought that the first detected antibody, while anti-Ro52 is primarily associated with other autoimmune diseases, such as primary Sjögren’s syndrome (pSS). In fact, positivity for anti-Ro/SSA antibodies is a major criterion for diagnosing pSS. Beyond acting as a diagnostic marker for pSS, IIM patients with anti-Ro52 positivity might have a higher prevalence of ILD. Additionally, it has been suggested that anti-Ro52 may be associated with a more severe phenotype of ILD in IIM patients called rapidly progressive ILD (RP-ILD), but conclusive evidence is lacking.

While most studies have focused on the effects of anti-Ro52 in IIM patients, the role of this antibody in ILD development in other autoimmune conditions, such as SSC, SS or SLE, is less known. Due to a lack of systematic literature analysis, we explored the association of anti-Ro52 positivity and ILD presence in different autoimmune conditions in the current systematic review and meta-analysis.

METHODS

This systematic review and meta-analysis was written according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. It was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42022381447). Due to the cross-sectional design of the included studies, the quality assessment tool was changed from the risk of bias in non-randomised studies to the Newcastle-Ottawa Scale in the protocol stage.

Eligibility criteria

Observational studies that reported ILD diagnosis (outcome) and anti-Ro antibody (exposure) status in any autoimmune conditions (population) were included. We excluded studies that only reported anti-Ro60 status. However, studies that did not differentiate between anti-Ro52 and anti-Ro60 antibodies and reported the antibody status as anti-Ro or anti-SSA were included. These studies were included to reduce publication bias. The distinction between anti-Ro52 and anti-Ro52/SSA was later addressed by subgroup analysis.

We also excluded case reports, case series and reviews. In addition, studies with any of the following criteria were also excluded: (1) population consisting of juvenile autoimmune disease patients, (2) having no comparison based on ILD or anti-Ro status, (3) not providing ORs or 2×2 contingency table data and finally, (4) published in languages other than English.

Due to the diverse methodology of different studies in diagnosing ILD, and measuring anti-Ro levels, we did not set any eligibility criteria for these items. However, they were evaluated in the quality assessment section. Conference abstracts were included if they provided the relevant information. In addition, we included studies that compared the presence of RP-ILD in anti-Ro+ and anti-Ro− IIM patients to explore the association of anti-Ro positivity with ILD severity. RP-ILD was defined as either of the following criteria in 1 month: (1) progressive worsening of dyspnoea; (2) decrease in forced vital capacity by more than 10% or decrease in diffusing capacity of the lungs for carbon monoxide by more than 15%; (3) increase in the severity of interstitial pneumonia on high-resolution CT (HRCT); (4) arterial blood gases showing respiratory failure or decrease in partial pressure of oxygen more significant than 10 mm Hg. Studies that used a longer timeframe (>1 month) for RP-ILD definition were also included but were given a lower quality score.

Search strategy

A systematic search was conducted from inception to 2 January 2023 in four electronic databases: PubMed, Web of Science, Scopus and Embase. Keywords such as ‘interstitial lung disease’, ‘interstitial pneumopathy’, ‘Interstitial Pneumonia’, ‘Ro antibody’, ‘anti-ro’, ‘anti-ro52’ and ‘anti-ssa/ro52’ were used in conducting the search. No restrictions and filters were used for searching. The full search strategy for all databases is presented in online supplemental file 1.

Study selection and data collection

Four investigators (HY-K, AM, MJ and KF) screened the articles based on their titles/abstracts to exclude the irrelevant articles. Then, two independent reviewers (SN and AM) assessed the full texts of the remaining articles. Any inconsistencies were resolved by consulting with a third reviewer (HK).

Data extraction was carried out independently by MJ and HY-K. Collected data included study characteristics such as author name, country, year of publication, type of autoimmune disease in the patients, ORs with respective 95% CI, 2×2 contingency table data, ILD diagnosis method, the average age of the target population, female (%) and proportion of patients with anti-histidyl transfer RNA synthetase (anti-Jo1), anti-melanoma differentiation-associated gene 5 (anti-MDA5), anti-threonyl-tRNA synthetase (anti-PL-7) and anti-alanyl-tRNA-synthetase (anti-PL-12) autoantibodies.

Quality assessment

Two reviewers (MJ and KF) conducted the quality assessment independently using the adapted version of the
Synthesis methods and reporting bias assessment

Separate meta-analyses were performed with ORs and 95% CIs to assess the association of anti-Ro52 with ILD and anti-Ro52 with RP-ILD (specifically in IIM patients). The 2×2 contingency table data were used to calculate the ORs and 95% CI using the MedCalc online calculator for the studies that did not provide OR. Due to heterogeneity among the included studies, a random effect meta-analysis was used. Subgroup analysis was done based on autoimmune disease type and whether or not studies differentiated between anti-Ro52 and anti-SSA antibodies. I² was used as a measure of heterogeneity. The effects of age, gender (%), anti-Jo1, anti-MDA5, anti-PL-7 and anti-PL-12 on heterogeneity were measured with a restricted maximum likelihood estimator meta-regression model. Meta-analysis based on quality scores and outlier removal were used as sensitivity analyses. In addition, subgroup analysis based on disease type was also performed on the studies that distinguished anti-Ro52.

Funnel plots and Egger’s test were used to assess reporting bias. All analyses were performed with R V.4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio, Boston, Massachusetts, USA), using [metafor] and [dmetar] packages.

Patient and public involvement

There were no patients involved in this study.

RESULTS

Study characteristics

We identified 2355 results by searching four databases: PubMed, Embase, Web of Science and Scopus. After removing duplicates, 1147 articles were excluded in the title/abstract screening due to not meeting the eligibility criteria. We reviewed the full texts of the 242 remaining articles for eligibility, after which 183 were excluded. A list of the excluded articles and reasons for exclusion is provided in online supplemental file 3.

Eventually, 59 articles were included in our systematic review and meta-analysis, with 51 studies used for ILD meta-analysis (20 in the myositis, four in the SLE, 11 in the pSS, 7 in the SSc, 2 in mixed connective tissue disease (MCTD) and 7 in the other autoimmune diseases groups) and 11 for RP-ILD. The PRISMA flowchart in figure 1 demonstrates the selection process. The characteristics of the included studies are shown in online supplemental tables 1 and 2.

The quality assessment of the studies by the adapted version of the Newcastle-Ottawa Scale showed that among the ILD articles, 12 had very good, 18 had good, 19 had satisfactory and 2 had unsatisfactory qualities. In the RP-ILD studies, two had very good, six had good, two had satisfactory and one had unsatisfactory qualities. The results of the quality assessment are presented in online supplemental table 3.

Meta-analysis results and heterogeneity exploration

Our results showed that anti-Ro52/SSA positivity was associated with concomitant ILD in all autoimmune disease subgroups: IIM (OR=3.08; 95% CI: 2.18 to 4.35; p value<0.001; I²=49%), SLE (OR=2.43; 95% CI: 1.02 to 5.79; p=0.046; I²=71%), pSS (OR=1.77; 95% CI: 1.09 to 2.87; p=0.021; I²=73%), SSc (OR=1.71; 95% CI: 1.04 to 2.83; p=0.036; I²=43%), MCTD (OR=3.34; 95% CI: 1.82 to 6.13; p<0.001; I²=60%) and in the other autoimmune diseases category which consisted of patients with a plethora of connective tissue diseases (OR=2.20; 95% CI: 1.49 to 3.26; p<0.001; I²=34%). The overall random
effect model also showed a positive association between anti-Ro52/SSA and ILD (figure 2A).

The subgroup analysis based on whether studies differentiated between anti-Ro52 and anti-SSA showed that studies specifically measuring anti-Ro52 had a higher overall OR (figure 3).

Furthermore, anti-Ro52/SSA-positive IIM patients were more likely to have simultaneous RP-ILD (OR=2.69; 95% CI: 1.50 to 4.83; $I^2=71%$; p<0.001, figure 4A). The funnel plots for both ILD and RP-ILD studies had slight asymmetries, but Egger’s test was insignificant regardless. (coefficient=0.60; 95% CI: -0.34 to 1.55; t=1.25; p=0.217 for ILD and coefficient=-2.36; 95% CI: -5.69 to 0.97; t=-1.388; p=0.198 for RP-ILD, online supplemental figures 1 and 2).

Meta-regression demonstrated that mean age, the proportion of females, anti-Jo1, anti-MDA5, anti-PL-7, and anti-PL-12 had no significant effects on the association between anti-Ro52/SSA and ILD. Additionally, as suggested by the small $R^2$ values, these factors did not account for significant heterogeneity (table 1).

Sensitivity analysis
Among the articles with ILD as an outcome, studies by Al Nokhatha et al.,22 Huang et al.,23 Srivastava et al.,24 Li et al.25 and Gao et al.26 were identified as outliers. Performing sensitivity analysis by removing these studies increased the overall OR to 2.47. Nevertheless, the direction and strength of the association remained approximately the
same, suggesting that outliers did not heavily bias our results (figure 2B). Heterogeneity was reduced ($I^2=23\%$, $p=0.09$), and the prediction interval narrowed to 95% CI of 1.51 to 4.02. Both figures strongly associate anti-Ro52/SSA and ILD (figure 4B).

Sensitivity analysis based on quality assessment demonstrated that studies with a better quality had a higher OR for the association of anti-Ro52/SSA and ILD (OR=2.77; 95% CI: 1.81 to 4.02). Meta-regression analysis showed that levels of several other autoantibodies, including anti-Jo1, anti-MDA5, anti-PL-7 and anti-PL-12, did not change the association between anti-Ro52/SSA and ILD. In addition, SLE and SSC subgroups lost statistical significance as there were fewer articles than the meta-analysis of all included studies. All included studies in this meta-analysis had satisfactory or better quality assessment scores (online supplemental figure 4).

DISCUSSION
There has been previous controversy on the association of anti-Ro52/SSA and ILD, with some studies demonstrating that ILD prevalence may not be significantly higher in anti-Ro52-positive patients compared with anti-Ro52/SSA negative subjects. However, the current meta-analysis showed that patients with positive anti-Ro52 were more likely to have simultaneous RP-ILD. A higher OR shows that patients with positive anti-Ro52 were more likely to have simultaneous RP-ILD. 12 13 16 27 34 35 40 47 77–79

Figure 3 Subgroup meta-analysis of articles with interstitial lung disease based on whether studies differentiated between anti-Ro52 and anti-SSA.

Figure 4 Overall and subgroup meta-analysis (A) and the sensitivity analysis (B) of articles with rapidly progressive interstitial lung disease (RP-ILD). A higher OR shows that patients with positive anti-Ro52 were more likely to have simultaneous RP-ILD. 12 13 16 27 34 35 40 47 77–79

DISCUSSION
There has been previous controversy on the association of anti-Ro52/SSA and ILD, with some studies demonstrating that ILD prevalence may not be significantly higher in anti-Ro52-positive patients compared with anti-Ro52/SSA negative subjects. However, the current meta-analysis showed that autoimmune disease patients with positive anti-Ro52/SSA antibodies had more than two times the odds (OR=2.34) of having concurrent ILD than anti-Ro52/SSA negative patients. The sensitivity analysis confirmed this finding as the overall OR only changed minimally. Meta-regression analysis showed that levels of several other autoantibodies, including anti-Jo1, anti-MDA5, anti-PL-7 and anti-PL-12, did not change the association between anti-Ro52/SSA and ILD. In addition,
we demonstrated that anti-Ro52/SSA was associated with RP-ILD in IIM subjects. The association between anti-Ro52/SSA and ILD was strongest in the MCTD (OR=3.34) group, followed by IIM (OR=3.08), SLE (OR=2.43), pSS (OR=1.77) and SSc (OR=1.71) patients. This disparity in the magnitude of effect in different autoimmune diseases might have several explanations. First, the methods used for anti-Ro52 screening have different specificity and sensitivity, with line-blot immunoassay having an edge compared with ELISA.30-32 This can inevitably influence the number of anti-Ro52-positive patients in different studies, leading to heterogeneous results.

Second, unknown pathophysiological mechanisms underlying separate autoimmune diseases may contribute to the different effect estimates. It is proposed that environmental, genetic and autoimmune dysregulation are all important components of ILD development, and based on the type of noxious stimuli and autoimmune response, different phenotypes of lung injury may occur. Repeated environmental injury leads to post-translational protein modifications and neutrophil activation. These neutrophils then release several enzymes that result in the loss of immune tolerance.33

Third, several studies have not distinguished between anti-Ro52 and anti-Ro60 antibodies.30 Ro60 and Ro52 antigens were initially believed to be part of the same protein complex named Ro; hence, the antibody was called anti-Ro/SSA. While anti-Ro52 has been associated with ILD, no such associations have been demonstrated for anti-Ro60 and ILD.31 Our results aligned with this observation as subgroup analysis revealed that studies distinctively measuring anti-Ro52 had a higher overall estimate (OR=2.62) for the presence of ILD compared with studies that reported anti-Ro52/SSA (OR=1.63). Anti-Ro52 and anti-Ro60 also appear to be elevated in different autoimmune diseases. A study by Robbins et al showed that SLE was the most common disease in Ro52–Ro60+ patients, whereas, in Ro52+Ro60+ subjects, pSS was the most likely disease.7 Isolated anti-Ro52 positivity was mostly associated with inflammatory myositis. They also reported that some laboratories in France no longer measured the anti-Ro52 levels. However, the findings of Robbins et al, coupled with the current study, show that the laboratories and researchers may need to report the anti-Ro52 and anti-Ro60 antibodies separately.

In addition to its association with ILD, several studies have linked anti-Ro52 with RP-ILD, a progressive subtype of ILD with a high mortality rate and resistance to treatment.12 We showed that anti-Ro52-positive patients had 2.69 times higher odds of having RP-ILD than anti-Ro52-negative subjects. All of the included studies demonstrated OR>1 except for Gan et al27 and Li et al.34 The number of patients in the Li et al study was small to reach a meaningful conclusion. Gan et al included subacute ILD patients in the definition of RP-ILD, which may have influenced its results.27 34

It has been proposed that in IIM, anti-Ro52, rather than acting as an independent risk factor, aggravates the clinical phenotypes associated with myositis-specific antibodies (MSA). For instance, in anti-MDA5-positive IIM patients, anti-Ro52 positivity has been linked to refractory RP-ILD, whereas IIM patients with isolated anti-MDA5 have been found to respond well to conventional therapies.35 Another example has been the co-occurrence of anti-Ro52 with anti-Jo1, in which ASS patients have demonstrated more severe myositis and ILD and decreased survival rate.36 Other than anti-Ro52, anti-PL-7 and anti-Jo1 have also been associated with a higher rate of simultaneous ILD diagnosis, with anti-Jo1 having a high concomitance rate with anti-Ro52.23 We performed a meta-regression analysis to investigate whether other antibodies affected the association between anti-Ro52 and ILD. The results showed that different frequencies of other antibodies in studies did not significantly change the OR between anti-Ro52 and ILD.

As most studies evaluating the association between anti-Ro52/SSA and ILD frequency were cross-sectional, no cause-and-effect relationship has been established. A study by Buivy et al in pSS patients suggested that patients positive for anti-Ro52 were more likely to develop ILD at 5-year follow-up compared with anti-Ro52-negative subjects.37 This finding shows that anti-Ro52 can be used as a screening marker. Currently, anti-Ro52 positivity is primarily checked in pSS, SLE and IIM patients.38 However, checking for this antibody in other autoimmune diseases may be beneficial as a cheap and available method alongside pulmonary function tests to identify patients that require HRCT examination.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studies, n</th>
<th>Coefficient</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
<th>R²</th>
<th>Residual i²</th>
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<tbody>
<tr>
<td>Age (mean)</td>
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<td>−0.0247</td>
<td>−0.0535</td>
<td>0.0041</td>
<td>0.0934</td>
<td>4.80%</td>
<td>62.62%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>48</td>
<td>0.0006</td>
<td>−0.0119</td>
<td>0.0132</td>
<td>0.9207</td>
<td>0.00%</td>
<td>53.39%</td>
</tr>
<tr>
<td>Anti-Jo1</td>
<td>21</td>
<td>−0.0063</td>
<td>−0.0179</td>
<td>0.0053</td>
<td>0.2900</td>
<td>7.04%</td>
<td>47.34%</td>
</tr>
<tr>
<td>Anti-MDA5</td>
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<td>0.0024</td>
<td>−0.0123</td>
<td>0.0170</td>
<td>0.7524</td>
<td>0.00%</td>
<td>52.89%</td>
</tr>
<tr>
<td>Anti-PL-7</td>
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<td>−0.1365</td>
<td>0.0710</td>
<td>0.5362</td>
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<td>60.04%</td>
</tr>
<tr>
<td>Anti-PL-12</td>
<td>13</td>
<td>−0.0682</td>
<td>−0.2404</td>
<td>0.1041</td>
<td>0.4379</td>
<td>1.18%</td>
<td>58.04%</td>
</tr>
</tbody>
</table>
Limitations

The current study has several limitations. First, the overall OR in the current meta-analysis should be interpreted cautiously, as it results from all autoimmune disease types and may not represent an accurate estimate for a particular subgroup. Second, the number of studies in the MCTD subgroup was small, and further studies are needed to confirm the results in MCTD patients. Meta-regression analysis of MSA antibodies was only performed in IIM patients, and results cannot be generalised to other autoimmune diseases.

Third, different studies used various techniques to measure anti-Ro52 levels, which may have different sensitivity and specificities. This can inevitably lead to heterogeneity among the included studies. Another source of heterogeneity may be the different criteria used for ILD and RP-ILD diagnosis in the studies. Nevertheless, our study is the first systematic investigation showing an association between anti-Ro52 and ILD in various autoimmune diseases. Fourth, some included studies did not differentiate between anti-SSA and anti-Ro52, which may have skewed our results slightly. However, they only comprised a small group, and most included studies distinctly measured anti-Ro52. Additionally, our subgroup analysis showed that studies measuring anti-Ro52 showed a significantly stronger association with ILD than those reporting anti-SSA. Thus, removing anti-SSA studies will only strengthen the association between anti-Ro52 and ILD.

Finally, most investigations researching the association between RP-ILD and anti-Ro52 only consisted of ILD patients, but some studies also had non-ILD subjects. Since anti-Ro52 is associated with concomitant ILD, the presence of non-ILD subjects in the study population may result in a slight overestimation of the OR of the study and, thus, the meta-analysis.

CONCLUSION

To summarise, anti-Ro52/SSA positivity was associated with a higher frequency of concomitant ILD diagnosis in various autoimmune diseases. The levels of several other autoantibodies, including anti-Jo1, anti-MDA5, anti-PL-7 and anti-PL-12, did not change the association between anti-Ro52/SSA and ILD. The association between anti-Ro52 and ILD was stronger than the association between anti-Ro52/SSA and ILD. This suggests that separate laboratory measurements to distinguish between anti-Ro52kD and anti-Ro60kD antibodies may prove beneficial both in clinical practice and research. Additionally, we showed that RP-ILD was more common among patients with positive Anti-Ro52/SSA. Future prospective studies are required to investigate the possible benefits of screening for anti-Ro52 and its association with ILD development.

Contributors

SN: conceptualisation of the work, full-text screening, data analysis and drafting of the manuscript. AM: title/abstract screening, full-text screening and drafting of the manuscript. HY-K: title/abstract screening and data extraction. MJameie: title/abstract screening, data extraction and quality assessment of the included articles. KE: title/abstract screening and quality assessment of the included articles. RA-Y: reviewing the manuscript. ZT: conceptualisation of the work. MJameie: reviewing the manuscript. AMM: reviewing the manuscript. HK: guarantor, supervision and final approval of the manuscript. All authors meet the authorship criteria, and all of them have read and approved the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

Not applicable.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request. The data supporting this study’s findings are available from the corresponding author upon reasonable request.

Supplemental material

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