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# Association of anti-nuclear matrix protein 2 antibody with complications in patients with idiopathic inflammatory myopathies: A meta-analysis of 20 cohorts

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ABSTRACT

*Background:* Several complications like calcinosis, interstitial lung disease (ILD) or malignancy, are primary causes leading to poor outcomes in idiopathic inflammatory myopathies (IIM) patients. Specific antibodies might help to indicate the occurrence or absence of these complications.

*Objective:* The aim of this study was to evaluate the association of anti-nuclear matrix protein 2 antibody (anti-NXP2) with calcinosis, ILD and malignancy in IIM patients.

*Methods:* Two investigators independently searched literature about the relation of anti-NXP2 with calcinosis, ILD, malignancy in IIM patients in PubMed, EMBASE, Web of Science databases, then selected eligible articles and extracted data from the included studies. The association between anti-NXP2 and these complications was assessed by odds ratios (OR) and 95% confidence intervals (95% CI). Further quantitative meta-analysis, subgroup analysis, sensitivity analysis and publication bias analysis were conducted with STATA 14.0 software (Stata Corp.; College Station, Texas, USA). A fixed-effects model (the Mantel-Haenszel method) was employed when $I^2 < 25\%$, otherwise a random-effects model (the Mantel-Haenszel method) was used.

*Results:* Twenty cohorts with 3064 IIM patients were included in this meta-analysis, among which 9 were about calcinosis in adults, 6 about calcinosis in juvenile patients, 9 about ILD in adults, 3 about ILD in juvenile patients, while 13 about malignancy in adult patients. Anti-NXP2 was more common in patients with calcinosis than those without calcinosis (pooled OR = 4.00, 95% CI: 2.65–6.06 in adults; pooled OR = 1.62, 95% CI: 1.14–2.30 in juvenile patients). On the contrary, this antibody was less common in adult patients with ILD than those without ILD (pooled OR: 0.33, 95% CI: 0.19–0.56). No significant difference concerning the incidence of anti-NXP2 antibody was found in IIM patients between those with and without cancer (pooled OR = 1.42, 95% CI: 0.69–2.91).

*Conclusion:* The present study indicates that anti-NXP2 autoantibody is a risk factor for development into calcinosis both in adult and juvenile patients, while a protective factor for ILD in adult patients. Anti-NXP2 had no relation with malignancy in adult patients.

## 1. Introduction

Idiopathic inflammatory myopathies (IIM) or myositis is a cluster of diseases characterized by inflammation in muscular and vascular tissues. The incidence of IIM as a whole ranged from 1.16 to 19/million per year and its prevalence ranged from 2.4 to 33.8 per 100,000 inhabitants [1]. Although it is rare, IIM patients would end up with poor outcome when some complications occurred, such as interstitial lung disease (ILD), as well as malignancy [2–5], which required a more aggressive therapy. The mortality rate was quite high in adult patients, especially those with ILD and cancer, ranging from 6% to 60% of patients [4–7]. In juvenile onset IIM, calcinosis occurs up to 40% of patients and predicts a more severe and chronic disease course [8]. Earlier initiation of more aggressive treatments can improve the outcome of IIM patients to some extent. Therefore, it's crucial to predict or identify these severe complications as soon as possible.

In recent years, detection of autoantibodies has become an increasingly popular and helpful tool to classify different complications of IIM, among which malignancy, calcinosis and ILD were most widely studied. It gradually came to light that myositis patients with positive anti-transcriptional intermediary factor 1 γ antibody (anti-TIF1γ) were prone to coexist with malignancy [9], while those with anti-melanoma

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differentiation-associated protein 5 antibody (anti-MDA5) are more likely to develop into rapidly progressive ILD [10]. Detection of the above myositis specific antibodies helps to identify cancer or indicate rapidly progressive ILD, thus guiding clinicians in diagnosis and treatments and reflecting prognosis. Nowadays, increasing attention was paid to another autoantibody, anti-nuclear matrix protein 2 antibody (anti-NXP2).

A number of studies have investigated the association of anti-NXP2 with malignancy and calcinosis in IIM patients, but conclusions are uncertain and controversial. The relationship between anti-NXP2 and ILD was seldom analyzed separately before, although related data has been published. For the first time, Yang et al. [11] proposed that anti-NXP2-positive patients were less likely to develop ILD. Given the facts above, we aim to comprehensively study the association of anti-NXP2 with several complications, namely, calcinosis, ILD and malignancy in IIM patients. To our knowledge, this is the first meta-analysis evaluating the association between the anti-NXP2 and complications in IIM patients.

## 2. Results

### 2.1. Selection of eligible studies

A total of 287 articles were acquired from the three databases (i.e., PubMed: 65, EMBASE: 158, Web of Science: 64). Another 5 studies [12–16] were identified by cross-reference. One newly published article [17] during the period of revising the manuscript was also included. Then 126 duplicates were initially excluded. After review of the titles and abstracts, 138 irrelevant records were also ruled out. The remaining 29 articles were reviewed in full text, then 8 records were excluded, among which one [18] lacks adequate data that allowed for the calculation of the OR with 95% CI, while another seven [19–25] were conducted by the same researchers as the six included studies in the meta-analysis [11,26–30] for more detailed information in the latter. Another study [15] was excluded for no anti-NXP2 antibody found. Ultimately, 20 cohorts were included in the present meta-analysis. The process of study selection is illustrated in Fig. 1.

### 2.2. Characteristics of included studies

Twenty cohorts with 3064 IIM patients were included in this meta-analysis, among which 9 were about calcinosis in adults, 6 about calcinosis in juvenile patients, 9 about ILD in adults, 3 about ILD in juvenile patients, while 13 about malignancy in adult patients. These records were published between 2009 and 2018. On the whole, the involved studies cover different populations and regions, such as Asia, the north America, Europe and Latin America. The characteristics of each study are presented in Table 1.

### 2.3. Anti-NXP2 autoantibody and calcinosis

A total of 15 cohorts with 2519 IIM patients evaluated the association between anti-NXP2 and calcinosis, including 1629 adult IIM patients and 890 juvenile IIM patients. As age has been shown to be an independent factor in the development of calcinosis [24], we separately analyzed the association of anti-NXP2 with calcinosis in adult and pediatric IIM patient. A total of 261 (29.33%) pediatric and 143 (8.78%) adult patients developed calcinosis during the follow-up period. And 180 (20.22%) pediatric and 165 (10.13%) adult patients were detected with positive anti-NXP2. Low heterogeneity was identified by the Q-test and $I^2$ statistics ($I^2$ = 0.0%, $P$ = .564 in adult group; $I^2$ = 0.0%, $P$ = .756 in juvenile group); therefore, a fixed-effects model was adopted for the analysis (pooled OR = 4.00, 95% CI: 2.65–6.06 in adult group; pooled OR = 1.62, 95% CI: 1.14–2.30 in juvenile group) (Figs. 2–3). As you can see in Fig. 2B, adult patients from Asia had significantly higher OR (about 7) than that from other regions. Subgroup analysis based on detection methods and regions was also performed both in adult (Fig. 2A and B respectively) and pediatric patients (Fig. 3A and B respectively). In adult cohorts, anti-NXP2 was more common in calcinosis than non-calcinosis patients in all subgroups, whether analyzed based on detection methods or regions.

### 2.4. Anti-NXP2 autoantibody and interstitial lung disease

The association of anti-NXP2 with ILD was investigated in 12 independent studies, including nine adult cohorts and three juvenile cohorts. No significant heterogeneity was identified by the Q-test and $I^2$ statistics ($I^2$ = 17.0%, $P$ = .277); therefore, a fixed-effects model was adopted for the analysis (pooled OR = 0.33, 95% CI: 0.19–0.56) (Fig. 4). Subgroup analysis based on age group of disease onset showed a OR of 0.27 with 95%CI from 0.17 to 0.42 in adults. Subgroup analysis based on detection methods and regions was also conducted in adults (see Fig. 5).

### 2.5. Anti-NXP2 autoantibody and malignancy

Thirteen adult cohorts assessed the relationship between anti-NXP2 and malignancy altogether. A random-effects model was applied to estimate the overall OR and 95% CI (pooled OR = 1.42, 95% CI: 0.69–2.91) (Fig. 6), as moderate significant heterogeneity was found by the Q-test and $I^2$ statistics ($I^2$ = 39.1%, $P$ = .073). Subgroup analysis based on detection methods and regions was showed in the forest plot.

### 2.6. Publication bias and sensitivity analysis

A Begg's funnel plot was created to recognize potential publication bias. No significant asymmetry was discovered in the funnel plot (Fig. 7). Next, an Egger's test was performed, and also indicated an absence of potential publication bias with $p$-values > .10 (calcinosis: $p$ = .346 in adults, 0.391 in juvenile patients; ILD: $p$ = .963; malignancy: $p$ = .604). Furthermore, a similar conclusion was reached by sensitivity analysis, which suggested the results were stable and reliable (Fig. 8).

### 2.7. Discussion

Anti-NXP2 autoantibody was firstly discovered by Oddis et al. in 1997 [31], and then was classified as the myositis-specific autoantibodies. Gunawardena H's study showed, for the first time, that anti-NXP2 autoantibody was a major autoantibody subset in juvenile DM, and that it was associated closely with calcinosis [25]. Subsequently, increasing studies explored the relation of anti-NXP2 with complications in IIM patients [11–15,23,24,26,27,29,32–44], among which calcinosis, ILD and malignancy were most commonly studied. However, no consistent conclusions were reached. As the fact that IIM is a rare disease, meta-analysis could be a powerful tool not only for increasing the statistical power but also for getting more accurate and reliable conclusions. Fortunately, we did obtain some exciting results.

In this meta-analysis, 20 eligible cohorts with 3064 IIM patients were analyzed. The incidence of anti-NXP2 in IIM patients varies greatly, ranging from 0% to 39.13% (including Sato S's study [15]), which may be attributed to difference in sample size. The primary findings of this meta-analysis are as follows. First of all, the presence of anti-NXP2 autoantibody increases the risk of calcinosis both in adult and juvenile IIM patients. Calcinosis is a refractory complication mainly occurring in juvenile DM with mean prevalence of 40%, due to delay to diagnosis and initiation of therapy [8]. Notably, adult patients from Asia had significantly higher OR (about 7) than that from other regions, which might be attributed to longer delay in diagnosis and initiation of treatment especially in China. Patients with positive anti-NXP2 could develop calcinosis from the illness onset to as long as several years later [24,25,39]. Therefore, the presence of this antibody could alert the

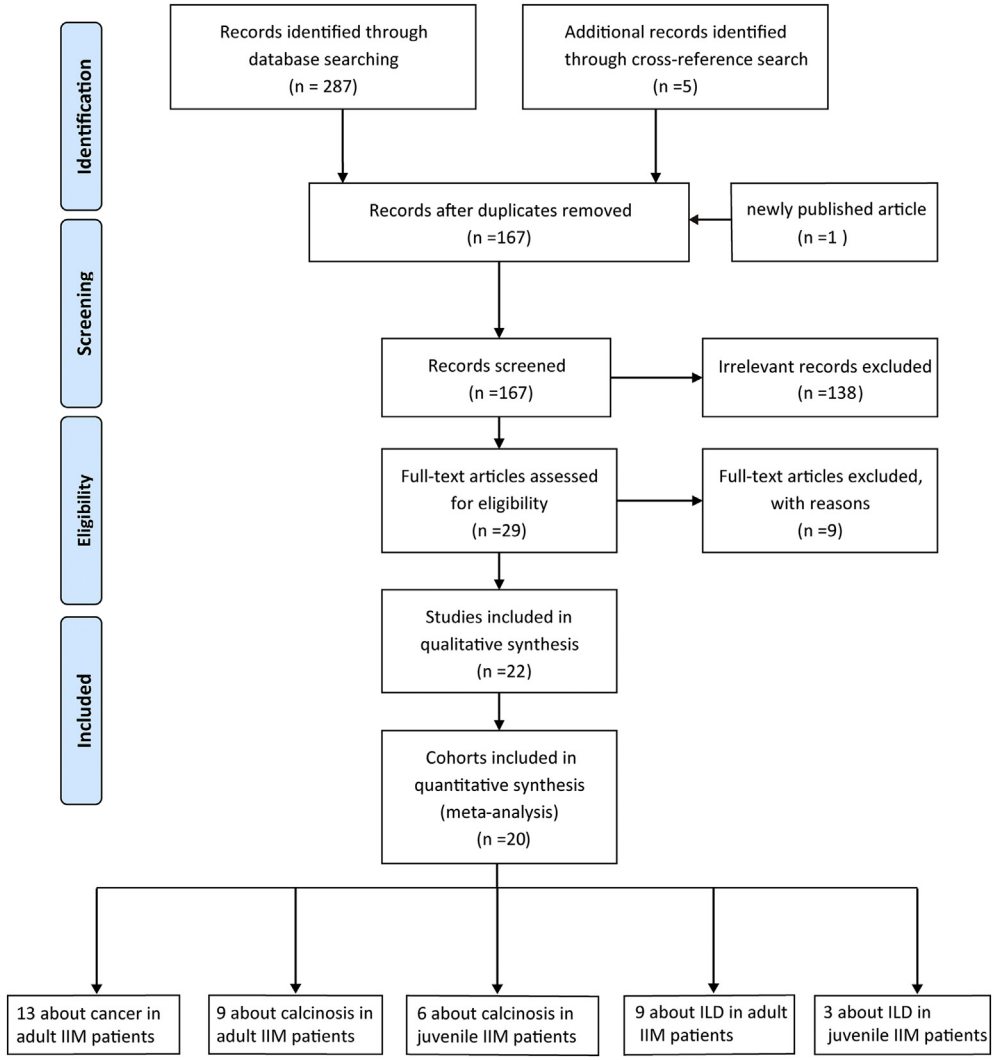


**Fig. 1.** Flowchart of the selection of eligible studies in the meta-analysis. Two hundred and eighty-seven records were obtained through the original search strategy and another five were added by cross-reference search. One newly published article during the period of revising the manuscript was also included. After titles, abstracts and full texts (when necessary) reviewed, 29 articles were assessed for eligibility and 20 cohorts were included in the meta-analysis.

physicians to strengthen the treatment for IIM patients.

Inspiringly and unexpectedly, the positivity of anti-NXP2 indicates a protective role on ILD in adult IIM patients. In fact, Yang et al. [11] previously proposed that anti-NXP2-positive patients were less likely to develop ILD. Traditionally, it's believed that formation of autoantibodies interferes the corresponding molecules' physiological functions, thus to prompt occurrence of diseases. This theory was proved by the role of anti-ARS and anti-MDA5 antibodies on predicting the onset and prognosis in IIM-ILD patients [45]. For better understanding of this result, confounding factors like other autoantibodies should be taken into consideration, which requires for further well-designed studies. Meanwhile, it's necessary to find out the effect of anti-NXP2 on NXP2 to illustrate this fantastic result. After all, it is still unclear whether this antibody have a pathogenic role or just an epiphenomenon.

The anti-NXP2 antibody have been believed to share similar phenotype with anti-TIF1γ antibody, such as malignancy. Actually, previous studies [23,27] did show that anti-NXP-2-positive subjects had an increased risk of cancer compared to the general population. However, in this overall analysis, no evident relation was discovered between anti-NXP2 and malignancy in adult IIM patients. That is to say, no significant difference concerning the incidence of anti-NXP2 antibody was found in IIM patients between those with and without cancer. Additional large scale and reasonably designed research studies are required to find out its relationship with malignancy.

However, there are several limitations in this meta-analysis. The primary challenge is in comparing the anti-NXP2 autoantibody data from different laboratories, using different methods with varying sensitivity and specificity. But we don't think detection methods have decisive impact on the results of this meta-analysis, as we can see in the forest plots of subgroup analysis. The second problem is to combine data of IIM patients without having each subset analyzed separately. Thirdly, some confounders influencing the antibody positivity have not be taken into consideration in this meta-analysis. For example, the positive rate might be understated because the collection time of blood samples in different studies were always after treatment. Another concern is the small sample sizes of some studies, which may have caused the statistical power to be inadequate. Despite of the above shortcomings, we believe that our meta-analysis really gave us some indications on the association between the anti-NXP2 antibody and several complications in IIM patients.

### 2.8. Conclusions

In summary, anti-NXP2 is helpful to indicate some complications of IIM. The present study indicates that anti-NXP2 autoantibody is a risk factor for development into calcinosis both in adult and juvenile IIM

**Table 1**
The characteristics of studies included in the present meta-analysis.

| Author | Year | Country | Length of Follow-up (months) | Methods for detection of antibody | Complications studied | NOS | Age group of disease onset | Total no. of IIM patients |
|---|---|---|---|---|---|---|---|---|
| Ceribelli [32] | 2012 | Italy | 56 (1–288) | IP&WB | CAM, calcinosis, ILD | 6 | Adult | 58 |
| Ceribelli [33] | 2016 | Italy | N/M | IP&WB | CAM, ILD | 6 | Adult | 38 |
| Espada [34] | 2009 | Argentina | 36 | IP&WB | Calcinosis, ILD | 8 | Juvenile | 64 |
| Yang [11,23] | 2017 | China | 33 (13–61) | ELISA + IP&WB | CAM, calcinosis, ILD | 8 | Adult | 709 |
| Rogers [26] | 2017 | the US | 29 | IP | CAM, calcinosis, ILD | 8 | Adult | 178 |
| Tansley [30] | 2017 | the UK | 112 | IP | Calcinosis | 6 | Juvenile | 379 |
| Merlo [36] | 2016 | Italy | 120 (24–180) | WB | CAM | 8 | Adult | 19 |
| Albayda [27] | 2017 | the US | N/M | IP | CAM, calcinosis, ILD | 8 | Adult | 235 |
| Best [37] | 2017 | France | 42 | immunodot assay | CAM, calcinosis, ILD | 8 | Adult | 97 |
| Petri [14] | 2013 | Mexico | N/M | IP | CAM | 6 | Adult | 95 |
| Yu [13] | 2014 | China | N/M | WB | CAM, calcinosis | 6 | Juvenile | 25 |
| Troyanov [38] | 2014 | France | 181 (4–552) | IP | CAM, calcinosis | 8 | Adult | 100 |
| Fredi [39] | 2017 | Italy | 56 (1–288) | IP | Calcinosis | 8 | Adult | 74 |
| Kang E H[12,44][a] | 2010 | Korea | 59.1 ± 51.9 | IP | CAM, ILD | 8 | Adult | 49 |
| Bodoki [28] | 2014 | Hungary | N/M | IP | CAM | 5 | Adult | 337 |
| Ishikawa [41] | 2012 | Japan | N/M | IP | CAM, calcinosis, ILD | 8 | Adult | 106 |
| Rider [29] | 2013 | the US | N/M | IP&WB | Calcinosis, ILD | 6 | Juvenile | 374 |
| Aouizerate [42] | 2018 | France | 18.6 (10.9–32.0) | Immunodot assay | Calcinosis | 6 | Juvenile | 23 |
| Ueki [43] | 2018 | Japan | 2–307 | IP&WB | Calcinosis, ILD | 8 | Juvenile | 25 |
| Wang L | 2018 | China | N/M | IP&WB | CAM, calcinosis, ILD | 8 | Adult | 120 |

NOS = Newcastle Ottawa Scale; DM = dermatomyositis; IIM = idiopathic inflammatory myopathies; IP = immunoprecipitation; WB = western blot; CAM = cancer-associated myositis; ILD = interstitial lung disease; N/M = not mentioned; ELISA = enzyme-linked immunosorbent assay.
[a] Reference #44 indicates two out of the nine anti-140 antibody was anti-MJ/NXP-2.

patients, while a protective factor for ILD in adult IIM patients. No significant difference concerning the incidence of anti-NXP2 antibody was found in IIM patients between those with and without cancer.

## 3. Materials and methods

### 3.1. Data sources

A comprehensive literature search was performed in the PubMed, EMBASE, and Web of Science databases up to the date of March 31, 2018. Full text searches were used in the PubMed and EMBASE databases, while medical subject headings (MeSH) search was applied in the Web of Science database. The keywords used for search were (anti-NXP2 OR NXP2 OR NXP-2 OR "nuclear matrix protein 2" OR "nuclear matrix protein-2" OR anti-MJ OR MORC3) and ("idiopathic inflammatory myopathies" or myositis or dermatomyositis). A cross-reference search of eligible articles was performed to identify studies not found in the computerized search. No restrictions were imposed on the type of studies. Newly published papers during the period of revising the manuscript are also traced in PubMed database for update.

### 3.2. Inclusion and exclusion criteria

The included studies meet the following criteria: 1) articles published in English; 2) studies concerning the correlation between the anti-NXP2 and calcinosis, malignancy or ILD in IIM patients; and 3) studies with adequate data that allowed for the calculation of the odds ratio (OR) with 95% confidence interval (CI). The exclusion criteria were as follows: 1) case reports or case series; 2) studies without available data; and 3) duplicate studies.

### 3.3. Data extraction

The following items were extracted independently by two

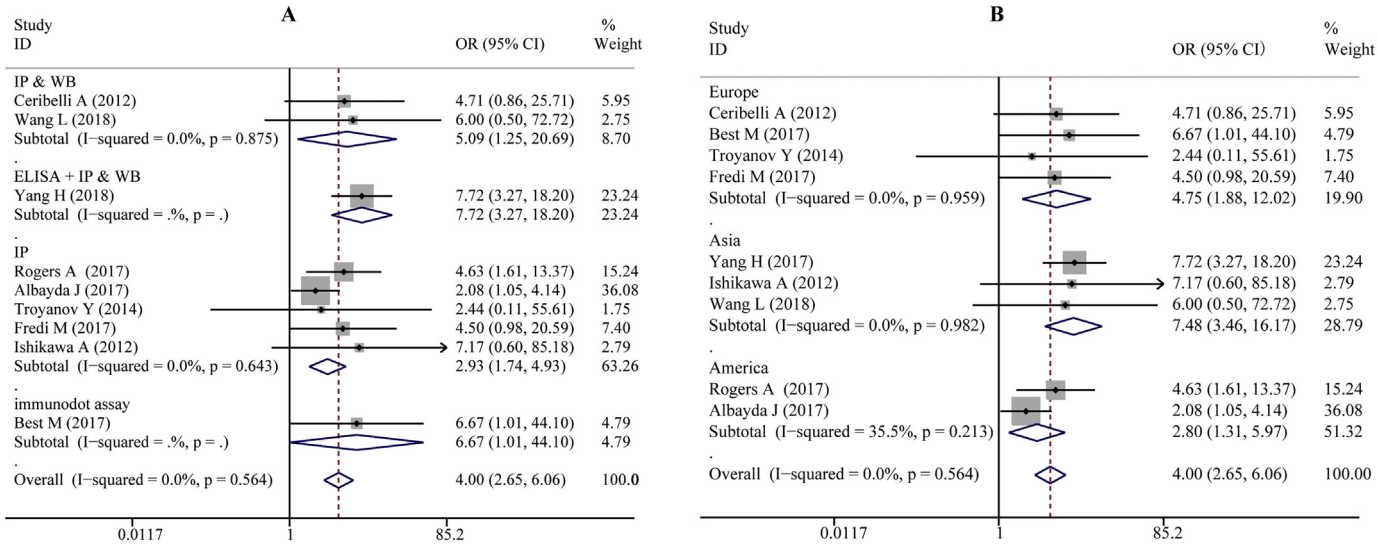


**Fig. 2.** Forest plot of the association of anti-NXP2 with calcinosis in adult IIM patients. (A) Subgroup analysis based on detection methods; (B) Subgroup analysis based on regions.

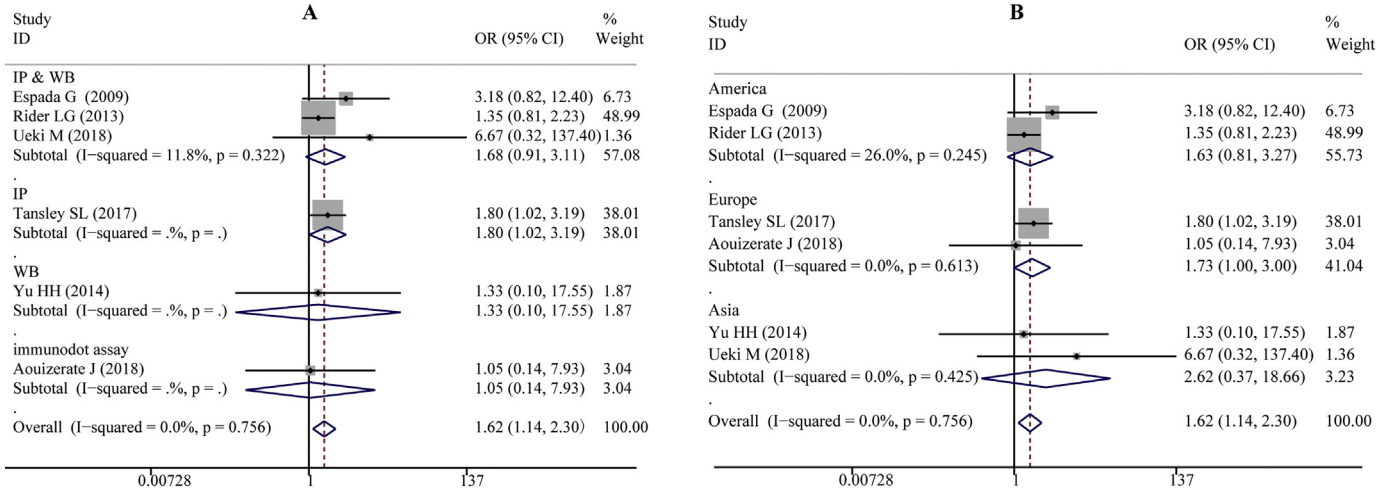


**Fig. 3.** Forest plot of the association of anti-NXP2 with calcinosis in juvenile IIM patients. (A) Subgroup analysis based on detection methods; (B) Subgroup analysis based on regions.

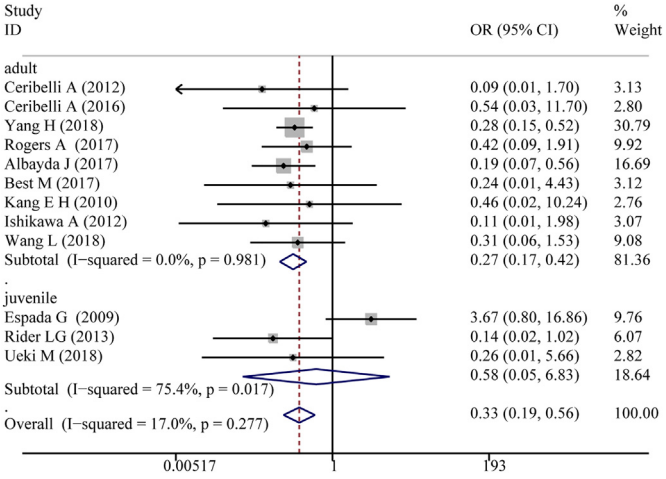


**Fig. 4.** Forest plot of the association of anti-NXP2 with ILD in IIM patients. Subgroup analysis was done based on age group of disease onset.

researchers (Linqing Zhong and Zhongxun Yu): 1) characteristics of included studies, i.e., the first author, publication year, sample size, country, length of follow-up, age group of disease onset and methods for detection of antibody; and 2) the data for quantitative meta-analysis, i.e., number of IIM patients with calcinosis (or malignancy, or ILD), number of IIM patients with positive anti-NXP2, number of IIM patients with positive anti-NXP2 who developed calcinosis (or malignancy, or ILD). Discrepancies were resolved by discussion.

### 3.4. Quality assessment

The two researchers (Linqing Zhong and Zhongxun Yu) independently evaluated the qualities of the included studies with the Newcastle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS form includes the following 3 sections: the selection of subjects, the comparability between the groups (whether developing into calcinosis, ILD and malignancy or not), and the ascertainment of exposure. A star rating system was applied, and each could be awarded a maximum of nine stars altogether.

### 3.5. Statistical methods

The meta-analysis was performed with STATA 14.0 software (Stata

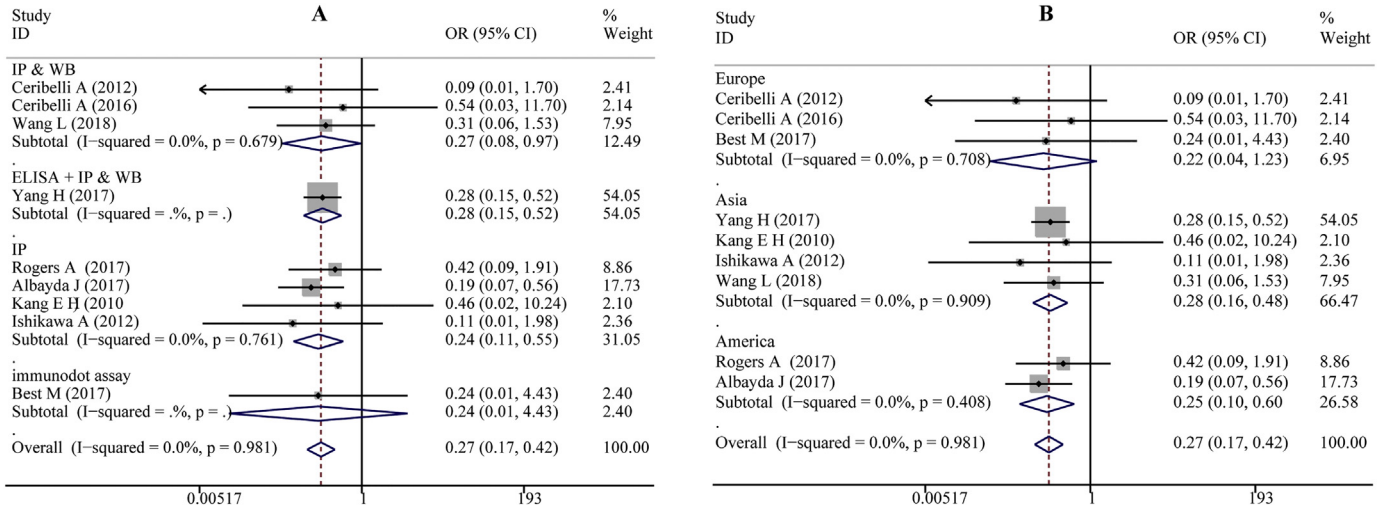


**Fig. 5.** Forest plot of the association of anti-NXP2 with ILD in adult IIM patients. (A) Subgroup analysis based on detection methods; (B) Subgroup analysis based on regions.

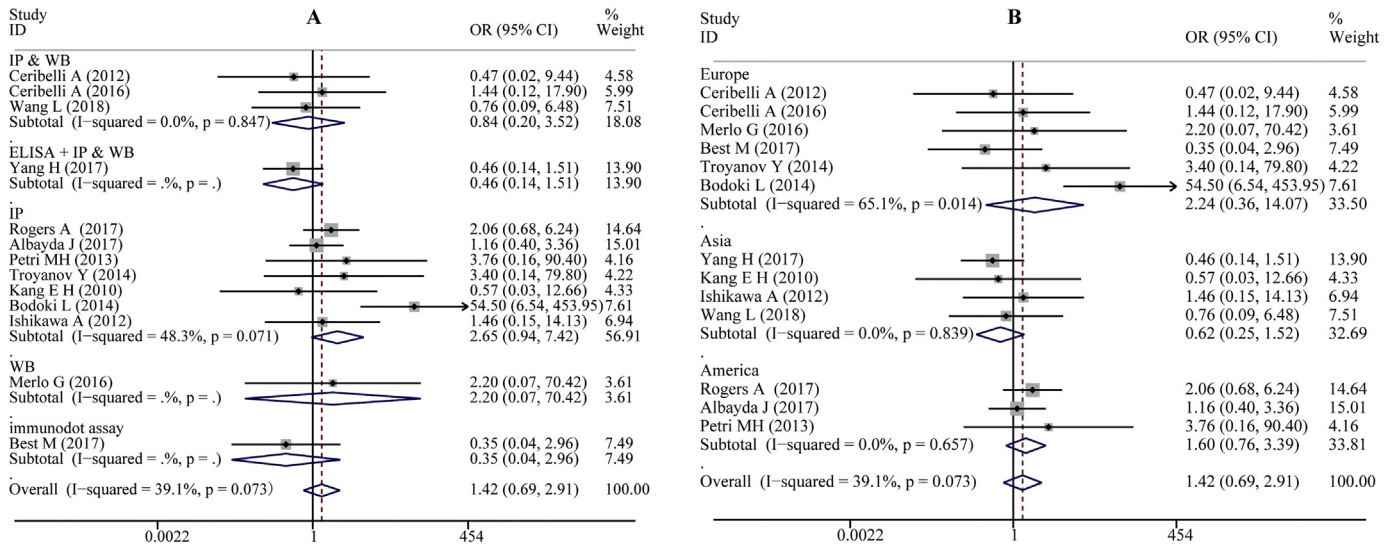


**Fig. 6.** Forest plot of the association of anti-NXP2 with malignancy in adult IIM patients. (A) Subgroup analysis based on detection methods; (B) Subgroup analysis based on regions.

Corp.; College Station, Texas, USA). The relevance of the anti-NXP2 with clinical subsets of IIM patients was assessed with the pooled ORs and 95% CIs. The heterogeneity between studies was estimated with the Q-test (statistically significant heterogeneity existed when the *p*-value < .10) and the $I^2$ statistic (25%, 50% and 75% were regarded as the cut-off points for low, moderate and high heterogeneity, respectively). A fixed-effects model (the Mantel-Haenszel method) was employed when $I^2$ < 25%, otherwise a random-effects model (the Mantel-Haenszel method) was used. Begg's funnel plots and Egger's test were applied to assess the risk of publication bias, and the p-value was set at 0.10. Sensitivity analysis was used to estimate whether the results were stable and reliable. Subgroup analysis was done based on

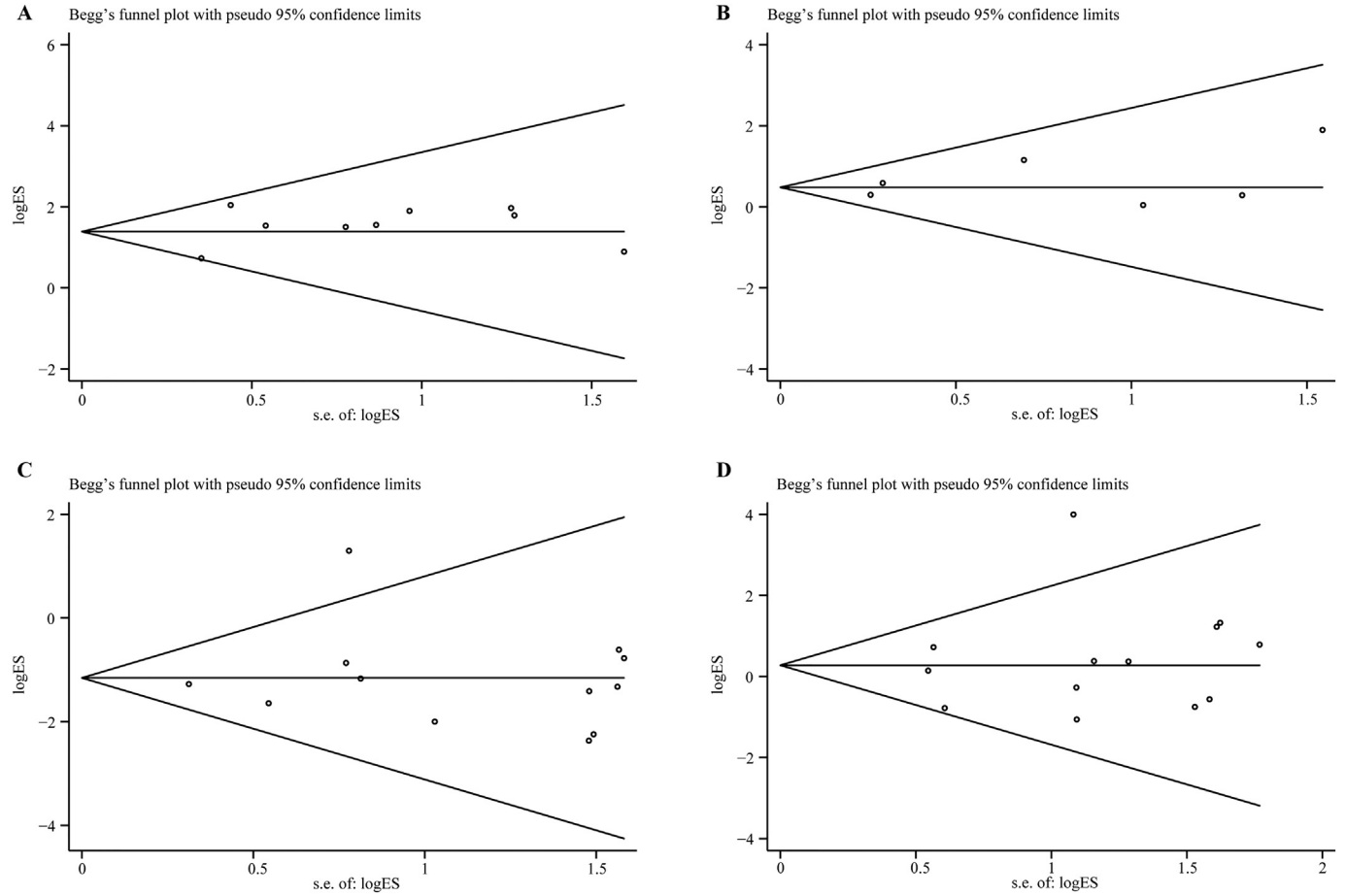


**Fig. 7.** Begg's funnel plots. (A) calcinosis in adult IIM patients; (B) calcinosis in juvenile IIM patients; (C) ILD in IIM patients; (D) malignancy in adult IIM patients. No significant asymmetry was discovered in these plots.

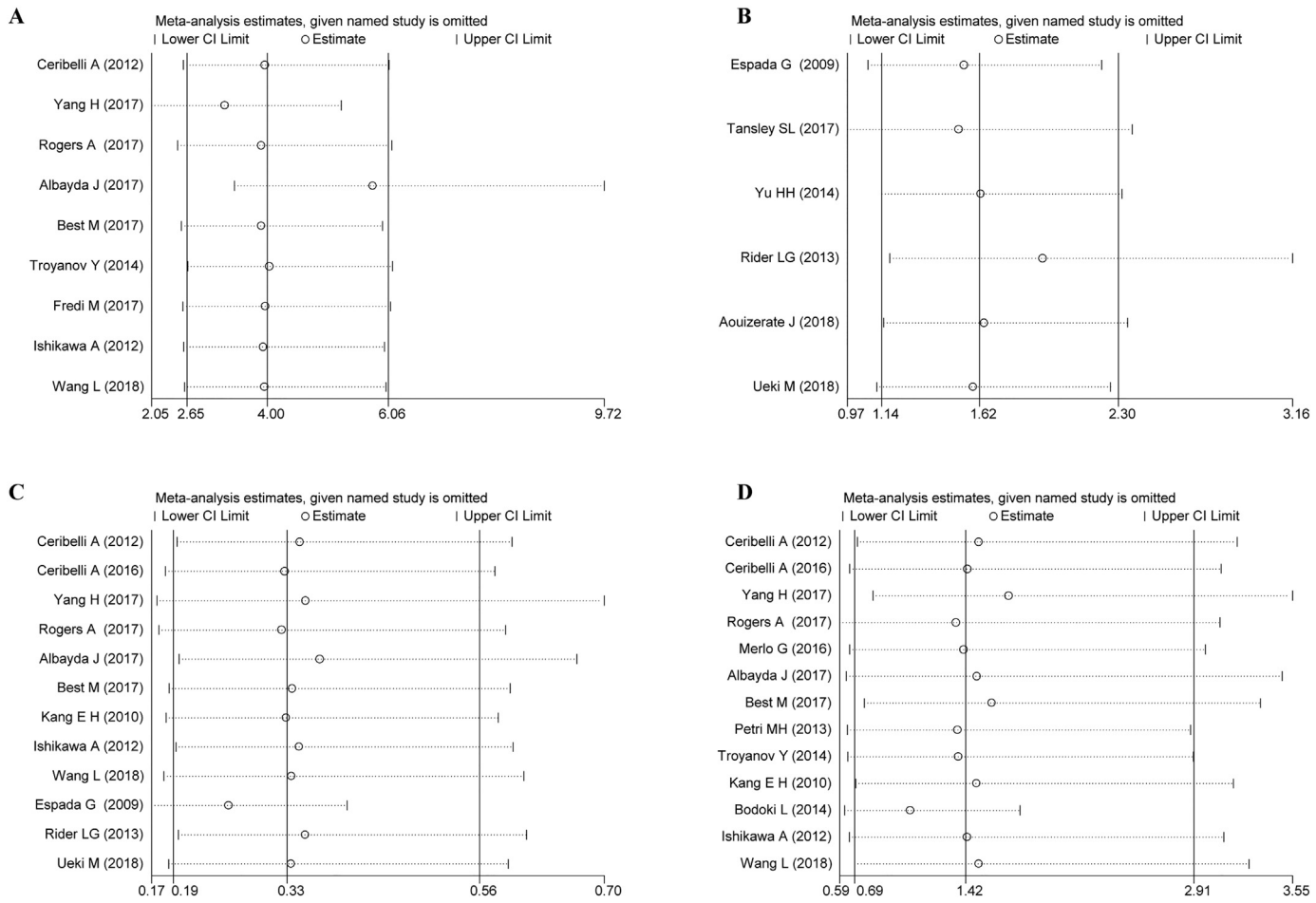


**Fig. 8.** Sensitivity analysis. (A) calcinosis in adult IIM patients; (B) calcinosis in juvenile IIM patients; (C) ILD in IIM patients; (D) malignancy in adult IIM patients. It shows that the results are stable and reliable.

detection methods of antibody and regions respectively. *P*-values < .05 were considered statistically significant.

## Conflict of interest

The authors declare that they have no conflict of interest.

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