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REVIEW ARTICLE

Assessment of diagnostic utility, clinical phenotypic associations, and prognostic significance of anti-NXP2 autoantibody in patients with idiopathic inflammatory myopathies: a systematic review and meta-analysis

Liubing Li[1] · Chenxi Liu[1] · Linlin Cheng[1] · Songxin Yan[1] · Haizhen Chen[1,2] · Yongzhe Li[1]

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Abstract

The objectives of this study are to analyze the association between anti-nuclear matrix protein 2 (NXP2) autoantibody and idiopathic inflammatory myopathies (IIMs) and to assess the diagnostic and prognostic relevance of anti-NXP2 autoantibody in patients with IIMs. A systematic search was performed in PubMed, Web of Science, EMBASE, the Cochrane Library, and Scopus to identify studies published as of February 29, 2020. Data was analyzed using Stata 12.0 and Meta-DiSc 1.4. Twenty-eight studies (4764 patients with IIMs and 1981 controls) were included in the meta-analysis. Anti-NXP2 autoantibody showed a significant association with IIMs (odds ratio (OR) = 26.36, 95% confidence interval (CI): 12.05–57.67, $P < 0.001$), especially juvenile IIMs (OR = 62.48, 95% CI: 16.97–229.98, $P < 0.001$). The pooled sensitivity, specificity, and area under the curve were 0.19 (95% CI = 0.16–0.21), 1.00 (95% CI = 1.00–1.00), and 0.95 for patients with juvenile IIMs versus controls. Anti-NXP2 autoantibody was associated with an increased risk of developing five characteristics (edema, muscle weakness, myalgia/myodynia, dysphagia, and calcinosis) and reduced risk of interstitial lung disease (ILD) ($P < 0.001$). Anti-NXP2 autoantibody showed no association with increased risk of death in IIMs ($P = 0.463$). These findings suggest that anti-NXP2 autoantibody is specially related to IIMs and is related to edema, muscle weakness, myalgia/myodynia, dysphagia, calcinosis, and ILD in patients with IIMs. However, there is no evidence to suggest that the presence of anti-NXP2 autoantibody confers a poor prognosis with respect to overall survival.

Key Points

- *This study summarized the diagnostic and prognostic accuracies of anti-NXP2 autoantibody for patients with IIMs. Anti-NXP2 autoantibody is related to edema, muscle weakness, myalgia/myodynia, dysphagia, calcinosis, and ILD in patients with IIMs.*

Keywords Anti-NXP2 autoantibody · Idiopathic inflammatory myopathies · Meta-analysis

Liubing Li and Chenxi Liu contributed equally to this work.

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✉ Yongzhe Li
yongzhelipumch@126.com

[1] Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, People's Republic of China

[2] Department of Medical Laboratory, The First Hospital of Jilin University, Changchun 130021, People's Republic of China

Introduction

Idiopathic inflammatory myopathies (IIMs) refer to a rare group of heterogeneous autoimmune disorders, including polymyositis, immune-mediated necrotizing myopathy, dermatomyositis, and inclusion body myositis (IBM) [1]. Autoimmunity is known to play a key role in the pathogenesis of IIMs and autoantibodies have been found in over 50% of patients [2]. Conventionally, autoantibodies found in patients with IIMs are classified into myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies. MSAs

are clinically useful biomarkers with diagnostic and prognostic relevance [3].

Anti-nuclear matrix protein 2 (NXP2) autoantibody, originally termed as anti-MJ autoantibody, is one of the MSAs. The reported frequency of anti-NXP2 autoantibody in juvenile and adult IIMs ranges from 2 to 20% [3]. To date, results pertaining to the diagnostic accuracy of anti-NXP2 autoantibody for IIMs have been largely inconsistent. In addition, there is no clear consensus on the association between anti-NXP2 autoantibody and the clinical signs of IIMs. For example, Bodoki et al. found an association between anti-NXP2 autoantibody and malignancy [4]; however, some studies have found no significant difference in the prevalence of malignancy between patients with and without anti-NXP2 autoantibody [5, 6].

There is no consensus on the diagnostic and prognostic relevance of anti-NXP2 autoantibody for IIMs, as well as on the association between anti-NXP2 autoantibody and the clinical manifestations of patients with IIMs. Therefore, we performed a meta-analysis of studies to assess the correlation of anti-NXP2 autoantibody with IIMs and to assess the diagnostic and prognostic relevance of this autoantibody in the context of IIMs. Moreover, we also investigated the relationship of anti-NXP2 autoantibody with the demographic, clinical, and laboratory characteristics of patients with IIMs.

Methods

Search strategy

The PICO strategy was used to develop the search strategy. A systematic search was performed independently on PubMed, Web of Science, EMBASE, the Cochrane Library, and Scopus databases to identify English-language studies published as of February 29, 2020, by L Li and C Liu. A combination of the following keywords was used to retrieve studies: "myositis," "myopathy," "polymyositis," "immune-mediated necrotizing myopathy," "inclusion body myositis," "dermatomyositis," "nuclear matrix protein 2," "NXP2," "MJ," and "p140." The reference lists of the retrieved articles were also manually screened independently to identify additional relevant studies (L Li and C Liu). Any discrepancies in selecting articles will be resolved by a third author (L Cheng).

Inclusion and exclusion criteria

Original research articles that qualified the following eligibility criteria were included: (1) patients with IIMs fulfilled the Bohan and Peter criteria [7, 8], Sontheimer criteria [9], the criteria of the European Neuromuscular Centre (ENMC) workshop [10], the 2017 European League Against Rheumatism/American College of Rheumatology classification criteria [11], Griggs diagnostic criteria [12] for inclusion body myositis (IBM), or Connors diagnostic criteria [13] for antisynthetase syndrome; (2) availability of data pertaining to the anti-NXP2 autoantibody status of patients with IIMs; (3) availability of adequate data to calculate the odds ratios (OR) or weighted mean differences and the corresponding 95% confidence intervals (CI); (4) adequate data to evaluate the utility of anti-NXP2 autoantibody in the diagnosis of IIMs. Literature reviews, case reports, commentaries, letters, and meeting abstracts were excluded.

Data extraction

The full texts of potentially eligible articles were reviewed and data from the selected studies were extracted independently using a standardized form by two reviewers (L Li and C Liu). The form included the following information: first author, publication year, diagnosis, age at disease onset, age at disease diagnosis, follow-up period, country or region, ethnicity, detection method, total number of cases and controls, frequency of anti-NXP2 autoantibody in cases and controls, demographics, clinical characteristics, laboratory results, and prognostic information of patients with IIMs. Discrepancies, if any, were resolved through discussion and consensus.

Quality assessment

The Newcastle-Ottawa Scale with a star rating system (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to evaluate the quality of the included studies. A study is judged based on three criteria: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest for studies. Studies awarded 7–9 stars, 4–6 stars, and $\leq$ 3 stars were regarded as high-quality, moderate-quality, and low-quality studies, respectively.

Data analysis

This meta-analysis was performed using Stata 12.0 software (Stata Corporation, College Station, TX, USA). The overall odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to evaluate the association between anti-NXP2 autoantibody and IIMs, as well as characteristics. The overall relative risk (RR) with 95% CIs was calculated to evaluate the prognostic value. Heterogeneity among the included studies was evaluated using the Cochrane Q test and I^2 statistics. In the event of significant heterogeneity ($P \leq 0.1$ for the Cochrane Q test or $I^2 \geq 50\%$), a sensitivity analysis was conducted to assess the stability of the combined results by sequential omission of individual studies, and the random-effects model was used to calculate the summary ORs and corresponding 95% CIs; otherwise, a fixed-effects model

was used. The pooled sensitivity, specificity, and area under the curve (AUC) of anti-NXP2 autoantibody for IIMs were assessed using the Meta-DiSc statistical software (version 1.4, Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).

Results

Characteristics and quality of the included studies

As shown in Fig. 1, a total of 2143 studies were retrieved on search of the databases. Twenty-eight studies [4–6, 14–38] with a combined study population of 4764 patients with IIMs and 1981 controls (including 369 healthy controls, 183 systemic lupus erythematosus, 577 systemic sclerosis, 414 juvenile idiopathic arthritis, 27 muscular dystrophies, 25 rheumatoid arthritis, 25 Sjögren syndrome, 124 idiopathic pulmonary fibrosis, 47 genetic muscle disease, 45 Behcet's disease, 145 psoriatic arthritis) qualified the inclusion criteria and were included in the meta-analysis. Fourteen studies [16–18, 22, 23, 26, 27, 29–31, 34, 36–38] with a combined study population of 2877 patients with IIMs and 1981 controls were assessed for the association between anti-NXP2 autoantibody and IIMs, as well as the diagnostic accuracy of anti-NXP2 autoantibody for IIMs. Twenty-three studies [4–6, 14–22, 24–26, 28, 30–36] (3538 patients with IIMs) were evaluated for the correlation of anti-NXP2 autoantibody with two demographic (male and female), 18 clinical (edema, muscle weakness, myalgia/myodynia, arthritis/arthralgia, interstitial lung disease, dysphagia, malignancy, heliotrope rash, Gottron's sign or papules, mechanics hand, skin ulcers, calcinosis, alopecia, Raynaud's phenomenon, lateral hip rash, facial erythema, palmar papules, and heart involvement), and one laboratory (elevation of creatine kinase (CK)) characteristics. Two studies [19, 33] enrolling 74 patients with IIMs were used to assess the prognostic value of anti-NXP2 autoantibody for IIMs. The characteristics of the 28 eligible studies are presented in Table 1. All the included studies showed moderate-quality or high-quality scores.

Heterogeneity test

The results of the heterogeneity tests are summarized in Table 2. No significant heterogeneity ($I^2 < 50\%$ and $P > 0.1$) was observed during the assessment of the association between anti-NXP2 autoantibody and IIMs (including subgroup analysis according to control group, age, and region); the relationship between anti-NXP2 autoantibody and two demographic features, 15 clinical manifestations, and one laboratory result; and the correlation between anti-NXP2 autoantibody and mortality. Significant heterogeneity ($I^2 \geq 50\%$ and $P \leq 0.1$) was observed for three clinical manifestations (arthritis/arthralgia, malignancy, and calcinosis). Owing to no significant heterogeneity, a fixed-effects model was used to calculate the overall ORs or the overall RR. A random-effects model was used to calculate the overall ORs between anti-NXP2 autoantibody and arthritis/arthralgia, malignancy, and calcinosis, respectively (Table 2). Sensitivity analyses showed that the combined results of association between anti-NXP2 autoantibody and arthritis/arthralgia, malignancy, and calcinosis were stable (data not shown).

Association between anti-NXP2 autoantibody and IIMs

On comparing 2877 patients with IIMs and 1981 controls from 13 studies, the frequency of anti-NXP2 autoantibody in patients with IIMs was significantly greater than that in controls (OR = 26.36, 95% CI: 12.05–57.67, $P < 0.001$) (Table 3).

Subgroup analyses were performed disaggregated by the type of control group (healthy control and disease control), age (adult and juvenile), and region (Asia, Europe, and North America) (Table 3). In the subgroup analysis disaggregated by the type of control group, 11 studies (2268 IIMs versus 369 healthy controls) as well as 7 studies (1449 IIMs versus 1612 disease controls) were assessed. The overall OR was 10.72 (95% CI: 4.55–25.22, $P < 0.001$) for the healthy control subgroup and 40.39 (95% CI: 13.62–119.80, $P < 0.001$) for the disease control subgroup. On subgroup analysis disaggregated by age, the overall OR from eight studies of 1251 adult IIMs versus 1284 controls was 11.81 (95% CI: 4.01–34.78, $P < 0.001$), and the overall OR from six studies of 874 juvenile IIMs versus 1373 controls was 62.48 (95% CI: 16.97–229.98, $P < 0.001$). Subgroup analysis disaggregated by region involved six studies of 1631 IIMs versus 963 controls in Asia, five studies of 942 IIMs versus 951 controls in Europe, and two studies of 304 IIMs versus 67 controls in North America. The frequency of anti-NXP2 autoantibody in IIMs was significantly greater than that in controls in Asia (OR = 11.03, 95% CI: 3.40–35.76, $P < 0.001$), in Europe (OR = 58.70, 95% CI: 15.85–217.33, $P < 0.001$), and in North America (OR = 14.35, 95% CI: 1.96–105.28, $P = 0.009$).

Diagnostic ability of anti-NXP2 autoantibody for IIMs

The pooled sensitivity, specificity, and AUC of the summary receiver operating characteristic curve of anti-NXP2 autoantibody for IIMs versus controls were 0.11 (95% CI = 0.10–0.12), 1.00 (95% CI = 1.00–1.00), and 0.91, respectively (Table 3).

The diagnostic accuracy of anti-NXP2 autoantibody for IIMs versus controls was calculated in the subgroup analysis disaggregated by the type of control group (healthy control

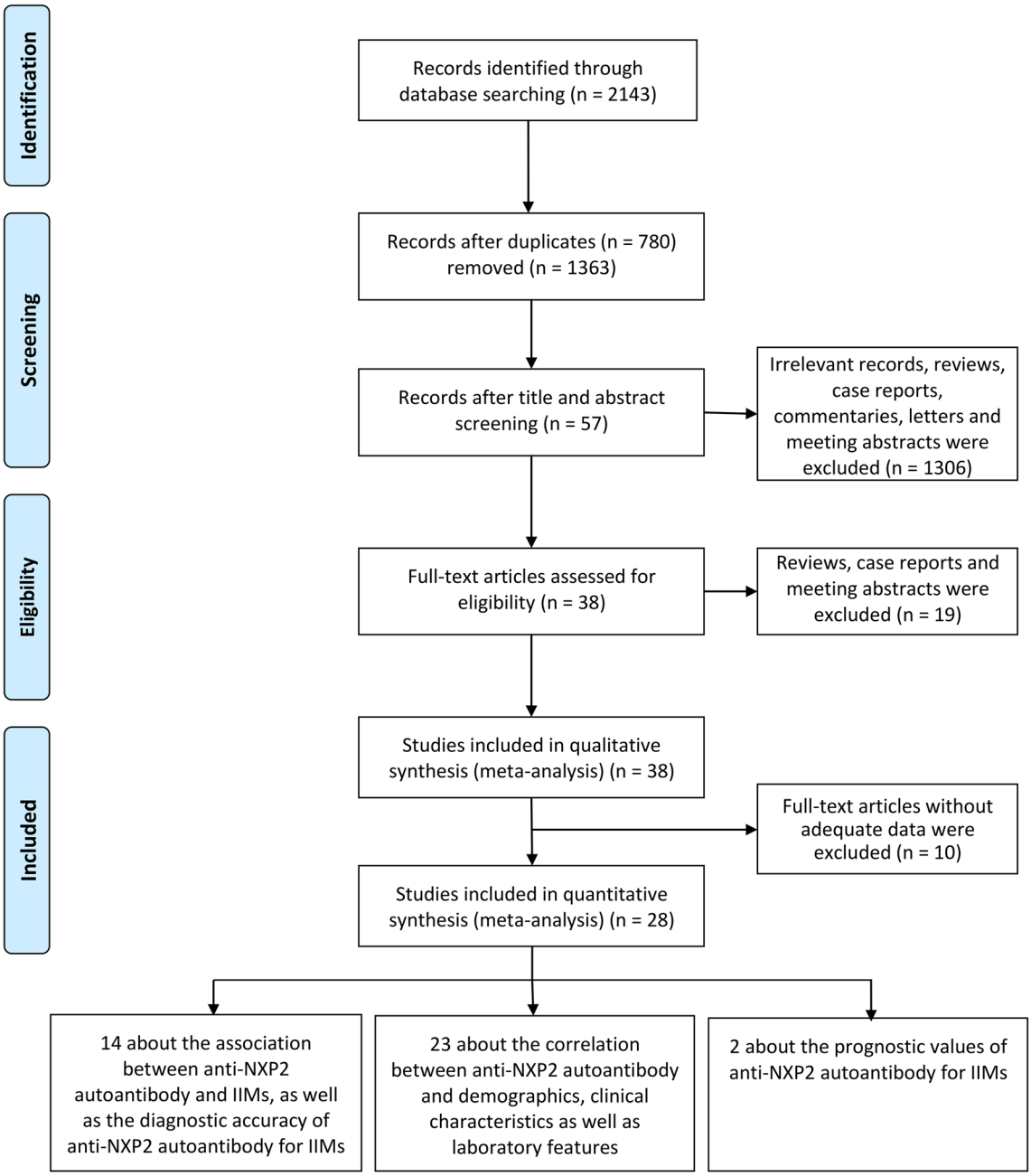

Fig. 1 Illustration of the literature search and study selection criteria

and disease control), age (adult and juvenile), and region (Asia, Europe, and North America) (Table 3). In the subgroup analysis by control group, the pooled sensitivity, specificity, and AUC values of anti-NXP2 autoantibody were 0.13 (95% CI = 0.11–0.14), 1.00 (95% CI = 0.99–1.00), and 0.83 in IIMs versus healthy controls, and 0.10 (95% CI = 0.08–0.11), 1.00 (95% CI = 1.00–1.00), and 0.93 in IIMs versus disease controls, respectively. On subgroup analysis disaggregated by age, the pooled sensitivity, specificity, and AUC values of anti-NXP2 autoantibody, respectively, were 0.07 (95% CI = 0.06–0.09), 1.00 (95% CI = 1.00–1.00), and 0.84 in adult IIMs versus controls, and 0.19 (95% CI = 0.16–0.21), 1.00 (95% CI = 1.00–1.00), and 0.95 in juvenile IIMs versus controls. On subgroup analysis disaggregated by region, the pooled sensitivity for diagnosing IIMs was 0.06 (95% CI = 0.05–0.07) in Asia, 0.17 (95% CI = 0.15–0.20) in Europe, and 0.18 (95% CI = 0.14–0.23) in North America. The pooled specificity for diagnosis of IIMs was 1.00 (95% CI = 1.00–1.00) both in Asia and Europe, and 1.00 (95% CI = 0.95–1.00) in North America. The AUC values were 0.83 and 0.95 for IIM diagnosis in Asia and Europe, respectively. The AUC value for diagnosis of IIMs in North America was not evaluated due to the small sample size of participants examined.

Table 1 The main characteristics of the 28 studies included in this meta-analysis

First author and year	PMID	Diagnosis	Age at disease onset	Age at disease diagnosis	Country or region	Ethnicity	Newcastle-Ottawa Scale
Ye 2019	[14]	Adult DM	Mean age ± SD: 47.26 ± 11.44 years	–	China	Chinese	8
Li 2019	[15]	Adult and juvenile PM/DM	–	–	China	Chinese	8
Li 2018	[16]	Adult PM/DM	–	Mean age ± SD: 46.27 ± 13.01 years	China	Chinese	8
Wang 2018	[17]	Adult PM/DM	–	–	China	Chinese	6
Ueki 2018	[19]	Juvenile IIMs	Mean age: 6.04 years (range 1–14 years)	–	Japan	Japanese	8
Aouizerate 2018	[20]	Juvenile DM	Median age: 129 months (IQR 75.5–149.5 years)	–	France	–	8
Best 2018	[21]	Adult DM	–	–	France	Caucasian, African, Asian, Caribbean, others	7
Yang 2018	[18, 22]	Adult and juvenile IIMs	–	–	China	Chinese	8
Tansley 2017	[23]	Juvenile IIMs	Median age: 6.8 years (Q1–Q3 3.9–10.1 years)	–	UK	–	6
Rogers 2017	[5]	Adult and juvenile DM	–	Median age: 48.3 years (IQR 4.6–86.9 years)	USA	White, Latino, Pacific Islander, Asian, African American	8
Albayda 2017	[6]	DM	–	–	USA	White, African American, other	5
Merlo 2017	[24]	Adult DM	Mean age: 56.4 years (range 31–79 years)	–	Italy	–	8

Table 1 (continued)

First author and year	PMID	Diagnosis	Age at disease onset	Age at disease diagnosis	Country or region	Ethnicity	Newcastle-Ottawa Scale
Fredi 2017	[25]	Adult IIMs	Mean age ± SD: 43 ± 17.4 years	–	Italy	Caucasian, African, Asian	8
Ceribelli 2016	[26]	Adult and juvenile IIMs	–	–	Italy	–	6
Mammen 2015	[27]	Adult DM	Median age: 45 years (Q1–Q3 34–58 years)	–	USA	White, black, other	8
Troyanov 2014	[28]	Adult IIMs	–	–	Canada	French Canadian	8
Bodoki 2014	[4]	Adult and juvenile IIMs	–	–	Hungary	Caucasian	8
Ceribelli 2014	[29]	Adult IIMs	Mean age ± SD: 44.5 ± 18 years	Mean age ± SD: 55.2 ± 14.5 years	Italy	European Caucasian	8
Yu 2014	[30]	Juvenile DM	Mean age ± SD: 6.3 ± 3.2 years	Mean age ± SD: 6.9 ± 3.3 years	Taiwan	–	6
Tansley 2014	[31]	Juvenile IIMs	Mean age: 6.2 years (IQR 4–10 years)	–	UK	–	8
Valenzuela 2014	[32]	Adult DM	–	Mean age ± SD: 50.0 ± 14.8 years	USA	White, Asian, Hispanic, African American, other	8
Kang 2014	[33]	Adult IIMs	–	Mean age ± SD: 45.4 ± 14.6 years	Korea	Korean	6
Fiorentino 2013	[34]	Adult DM	–	Mean age ± SD: 48.0 ± 16 years	USA	White, Asian, African American, other	8
Ceribelli 2012	[35]	Adult IIMs	Mean age ± SD: 43 ± 17.4 years	Mean age ± SD: 52 ± 16 years	USA	Italian	8
Ishikawa 2012	[36]	Adult and juvenile IIMs	–	–	Japan	Japanese	8
Ichimura 2012	[37]	Adult and juvenile IIMs	–	–	Japan	Japanese	7
Gunawardena 2009	[38]	Juvenile IIMs	Median age: 6 years (IQR 3–9 years)	Median age: 7 years (IQR 4–10 years)	UK	–	7
First author and year	Detection method	Controls	TP	FP	TN	FN	Features
Ye 2019	Commercial immunoblot assay	–	6	0	0	43	Interstitial lung disease

Table 1 (continued)

First author and year	PMID	Diagnosis	Age at disease onset	Age at disease diagnosis	Country or region	Ethnicity	Newcastle-Ottawa Scale
Li 2019	Commercial immunoblot assay	–	26	0	0	471	Muscle weakness, interstitial lung disease, dysphagia, malignancy, Gottron's sign or papules, skin ulcers, calcinosis, heart involvement
Li 2018	Commercial immunoblot assay	50 healthy individuals; 25 adult RA; 25 adult SLE; 25 adult SSc; 25 adult SS	6	0	150	124	Interstitial lung disease
Wang 2018	Immunoprecipitation and immunoblot	20 healthy controls	10	0	20	110	Male, female, arthritis/arthralgia, interstitial lung disease, dysphagia, malignancy, heliotrope rash, Gottron's sign or papules, calcinosis, Raynaud's phenomenon, elevation of CK
Ueki 2018	Immunoprecipitation-immunoblotting	–	3	0	0	22	Male, female, edema, arthritis/arthralgia, interstitial lung disease, heliotrope rash, Gottron's sign or papules, skin ulcers, calcinosis
Aouizerate 2018	Immunodot assay	–	9	0	0	14	Calcinosis
Best 2018	Commercial dot immunoassays	–	8	0	0	109	Arthritis/arthralgia, interstitial lung disease, malignancy, mechanics hand, skin ulcers, calcinosis, alopecia, Raynaud's phenomenon, lateral hip rash, palmar papules, elevation of CK
Yang 2018	ELISA and immunoprecipitation-western blot and commercial line blot assay	50 healthy subjects	56	0	50	653	Male, female, edema, muscle weakness, myalgia/myodynia, arthritis/arthralgia, interstitial lung disease, dysphagia, malignancy, skin ulcers, calcinosis, Raynaud's phenomenon
Tansley 2017	Immunoprecipitation and ELISA	48 healthy children; 21 juvenile SLE; 318 juvenile idiopathic arthritis; 27 muscular dystrophies	59	0	414	320	–
Rogers 2017	Immunoprecipitation	–	20	0	0	158	Male, female, edema, myalgia/myodynia, arthritis/arthralgia, interstitial lung disease, dysphagia, malignancy, heliotrope rash, Gottron's sign or papules, skin ulcers, calcinosis, alopecia, Raynaud's phenomenon, lateral hip rash, facial erythema, palmar papules
Albayda 2017	Immunoprecipitation	–	56	0	0	179	Male, female, edema, myalgia/myodynia, interstitial lung disease, dysphagia, malignancy, calcinosis

Table 1 (continued)

First author and year	PMID	Diagnosis	Age at disease onset	Age at disease diagnosis	Country or region	Ethnicity	Newcastle-Ottawa Scale
Merlo 2017	Immunoassay	–	1	0	0	18	Malignancy
Fredi 2017	Immunoprecipitation	–	8	0	0	66	Calcinosis
Ceribelli 2016	Immunoprecipitation-western blot	12 healthy subjects; 79 adult SSc; 45 Behcet's disease; 145 psoriatic arthritis	3	0	281	37	Male, female, arthritis/arthralgia, interstitial lung disease, malignancy, Raynaud's phenomenon
Mammen 2015	Immunoprecipitation	47 genetic muscle disease	17	0	47	74	–
Troyanov 2014	Immunoprecipitation	–	2	0	0	98	Arthritis/arthralgia, interstitial lung disease, malignancy, mechanics hand, calcinosis, Raynaud's phenomenon
Bodoki 2014	Immunoprecipitation	–	4	0	0	333	Malignancy
Ceribelli 2014	Immunoprecipitation	40 healthy adult control subjects	8	0	40	68	–
Yu 2014	Immunoblot	17 healthy control subjects	7	0	17	18	Male, female, muscle weakness, arthritis/arthralgia, malignancy, heliotrope rash, Gottron's sign or papules, calcinosis, facial erythema
Tansley 2014	Immunoprecipitation and ELISA	42 healthy adult control subjects	56	0	42	229	Male, female, calcinosis
Valenzuela 2014	Immunoprecipitation	–	14	0	0	112	Calcinosis
Kang 2014	Immunoprecipitation and immunoblotting	–	2	0	0	47	Male, female, interstitial lung disease, malignancy
Fiorentino 2013	Immunoprecipitation	20 healthy control subjects	37	0	20	176	Malignancy
Ceribelli 2012	Immunoprecipitation and western blot and ELISA	–	10	0	0	48	Male, female, arthritis/arthralgia, interstitial lung disease, malignancy, heliotrope rash, Gottron's sign or papules, calcinosis, Raynaud's phenomenon, facial erythema, heart involvement, elevation of CK
Ishikawa 2012	Immunoprecipitation	20 healthy adult control subjects; 21 adult SLE; 20 adult SSc	6	0	61	123	Male, female, interstitial lung disease, malignancy, heliotrope rash, Gottron's sign or papules, calcinosis, Raynaud's phenomenon, elevation of CK
Ichimura 2012	Immunoprecipitation and western blotting	108 adult SLE; 433 adult SSc; 124 idiopathic pulmonary fibrosis	10	0	665	508	–

Table 1 (continued)

First author and year	PMID	Diagnosis	Age at disease onset	Age at disease diagnosis	Country or region	Ethnicity	Newcastle-Ottawa Scale
Gunawardena 2009	Immunoprecipitation	50 healthy adult control subjects; 8 juvenile SLE; 20 juvenile SSc; 96 juvenile idiopathic arthritis	37	0	174	125	–

IIMs, idiopathic inflammatory myopathies; *DM*, dermatomyositis; *PM*, polymyositis; *IQR*, interquartile range; *SD*, standard deviation; *ELISA*, enzyme-linked immunosorbent assay; *SLE*, systemic lupus erythematosus; *SSc*, systemic sclerosis; *RA*, rheumatoid arthritis; *SS*, Sjögren syndrome; *NXP2*, nuclear matrix protein 2; *TP*, true positive; *FP*, false positive; *TN*, true negative; *FN*, false negative; *CK*, creatine kinase; *NOS*, Newcastle-Ottawa Scale

Association of anti-NXP2 autoantibody with demographic, clinical, and laboratory characteristics

The association of anti-NXP2 autoantibody with demographic, clinical, and laboratory characteristics is shown in Table 4. Five clinical features showed a positive association with anti-NXP2 autoantibody. The overall ORs, 95% CIs, and the associated *P* values were as follows: edema (four studies with 1147 IIMs patients) (OR = 3.94, 95% CI = 2.63–5.91, $P < 0.001$); muscle weakness (three studies with 1211 IIMs patients) (OR = 9.89, 95% CI = 4.55–21.50, $P < 0.001$); myalgia/myodynia (three studies with 1122 IIMs patients) (OR = 2.97, 95% CI = 1.97–4.46, $P < 0.001$); dysphagia (five studies with 1719 IIMs patients) (OR = 3.81, 95% CI = 2.71–5.36, $P < 0.001$); calcinosis (15 studies with 2633 IIMs patients) (OR = 4.19, 95% CI = 2.44–7.18, $P < 0.001$). Based on the analysis of 14 studies (2371 IIMs patients), anti-NXP2 autoantibody was negatively associated with interstitial lung disease (ILD) (OR = 0.26, 95% CI = 0.18–0.38, $P < 0.001$).

Anti-NXP2 autoantibody showed no correlation with sex, 12 clinical manifestations (arthritis/arthralgia, malignancy, heliotrope rash, Gottron's sign or papules, mechanics hand, skin ulcers, alopecia, Raynaud's phenomenon, lateral hip rash, facial erythema, palmar papules and heart involvement), and one laboratory characteristic (elevated CK level) (all $P > 0.05$).

Prognostic relevance of anti-NXP2 autoantibody for IIMs

The overall RR determined from two studies (74 patients with IIMs) was 1.83 (95% CI = 0.36–9.21, $P = 0.463$).

Discussion

Nuclear matrix protein 2 (NXP2) is a protein involved in the regulation of transcriptional and RNA metabolism [39]. Anti-NXP2 autoantibody was first identified in 1997 in childhood myositis [40] and was regarded as a key biomarker for diagnosis of IIMs. A previous meta-analysis evaluated the association of anti-NXP2 autoantibody with calcinosis, ILD, and malignancy in IIM patients [41]. However, the association of anti-NXP2 autoantibody with other demographic, clinical, and laboratory characteristics as well as the diagnostic and prognostic relevance of anti-NXP2 autoantibodies for IIMs is worth studying. Thus, we included a greater number of studies and performed a meta-analysis to analyze the diagnostic accuracy, clinical phenotypic association, and prognostic significance of anti-NXP2 autoantibody for IIMs.

This meta-analysis showed that the frequency of anti-NXP2 autoantibody was specific to IIMs. Based on the overall

Table 2 The results of the heterogeneity tests in this meta-analysis

	Heterogeneity		Calculation model	Calculation of OR or RR
	I^2 (%)	P		
Total	0	0.842	Fixed-effects	OR
Subgroup				
Control group				
Healthy control	0	0.956	Fixed-effects	OR
Disease control	0	0.640	Fixed-effects	OR
Age				
Adult	0	0.979	Fixed-effects	OR
Juvenile	0	0.557	Fixed-effects	OR
Region				
Asia	0	0.950	Fixed-effects	OR
Europe	0	0.629	Fixed-effects	OR
North America	0	0.644	Fixed-effects	OR
Demographics				
Male	11.2	0.337	Fixed-effects	OR
Female	11.2	0.337	Fixed-effects	OR
Clinical features				
Edema	48.7	0.119	Fixed-effects	OR
Muscle weakness	0.0	0.574	Fixed-effects	OR
Myalgia/myodynia	0.0	0.495	Fixed-effects	OR
Arthritis/arthralgia	51.6	0.035	Random-effects	OR
Interstitial lung disease	0.0	0.995	Fixed-effects	OR
Dysphagia	0.0	0.751	Fixed-effects	OR
Malignancy	42.0	0.050	Random-effects	OR
Heliotrope rash	29.7	0.212	Fixed-effects	OR
Gottron's sign or papules	0.0	0.841	Fixed-effects	OR
Mechanics hand	36.9	0.208	Fixed-effects	OR
Skin ulcers	22.8	0.269	Fixed-effects	OR
Calcinosis	57.2	0.003	Random-effects	OR
Alopecia	0.0	0.763	Fixed-effects	OR
Raynaud's phenomenon	0.0	0.782	Fixed-effects	OR
Lateral hip rash	0.0	0.374	Fixed-effects	OR
Facial erythema	15.4	0.307	Fixed-effects	OR
Palmar papules	0.0	0.886	Fixed-effects	OR
Heart involvement	6.6	0.301	Fixed-effects	OR
Laboratory				
Elevation of CK	24.8	0.262	Fixed-effects	OR
Prognostic significance				
Mortality	38.6	0.202	Fixed-effects	RR

OR, risk ratio; *RR*, relative risk

ORs, the anti-NXP2 autoantibody showed a stronger association with juvenile IIMs than adults IIMs (62.48 vs. 11.81). Anti-NXP2 autoantibody showed the strongest association with IIMs among European patients as compared with that in Asian and North American patients (overall ORs: 58.70 vs. 11.03 vs. 14.35). However, further studies are required to confirm the correlation between anti-NXP2 autoantibody and patients with IIMs in North America due to the small sample size. Additionally, related studies conducted in other regions are few or absent; therefore, we could not evaluate the association between anti-NXP2 autoantibody and IIMs in other geographical regions. Analysis of the diagnostic indices demonstrated that anti-NXP2 autoantibody had good specificity but low sensitivity for diagnosis of IIMs. The frequency of

Table 3 The summary of ORs in IIMs patients versus controls and in subgroup analysis

	Studies	Cases	Controls	OR (95% CI)	*P*	The pooled sensitivity (95% CI)	The pooled specificity (95% CI)	AUC
Total	13	2877	1981	26.36 (12.05–57.67)	< 0.001	0.11 (0.10–0.12)	1.00 (1.00–1.00)	0.91
Subgroup								
Control group								
Healthy control	11	2268	369	10.72 (4.55–25.22)	< 0.001	0.13 (0.11–0.14)	1.00 (0.99–1.00)	0.83
Disease control	7	1449	1612	40.39 (13.62–119.80)	< 0.001	0.10 (0.08–0.11)	1.00 (1.00–1.00)	0.93
Age								
Adult	8	1251	1284	11.81 (4.01–34.78)	< 0.001	0.07 (0.06–0.09)	1.00 (1.00–1.00)	0.84
Juvenile	6	874	1373	62.48 (16.97–229.98)	< 0.001	0.19 (0.16–0.21)	1.00 (1.00–1.00)	0.95
Region								
Asia	6	1631	963	11.03 (3.40–35.76)	< 0.001	0.06 (0.05–0.07)	1.00 (1.00–1.00)	0.83
Europe	5	942	951	58.70 (15.85–217.33)	< 0.001	0.17 (0.15–0.20)	1.00 (1.00–1.00)	0.95
North America	2	304	67	14.35 (1.96–105.28)	0.009	0.18 (0.14–0.23)	1.00 (0.95–1.00)	–

ORs, odds ratios; *IIMs*, idiopathic inflammatory myopathies; *CI*, confidence interval; *AUC*, area under the curve of the summary receiver operating characteristic

anti-NXP2 autoantibody ranged from 1.2 to 64.3% [4–6, 14–38], but was absent in the sera of healthy controls and disease controls.

The association of anti-NXP2 autoantibodies with demographic, clinical, and laboratory features is conflicting. In particular, contradictory results have been reported with

Table 4 Results of the meta-analysis showing the association of anti-NXP2 antibody with demographic, clinical, and laboratory features

Features	Number of studies	Number of patients	OR (95% CI)	*P*
Demographics				
Male	11	1828	1.16 (0.86–1.57)	0.317
Female	11	1828	0.86 (0.64–1.16)	0.317
Clinical features				
Edema	4	1147	3.94 (2.63–5.91)	< 0.001
Muscle weakness	3	1211	9.89 (4.55–21.50)	< 0.001
Myalgia/myodynia	3	1122	2.97 (1.97–4.46)	< 0.001
Arthritis/arthralgia	9	1368	0.63 (0.27–1.45)	0.280
Interstitial lung disease	14	2371	0.26 (0.18–0.38)	< 0.001
Dysphagia	5	1719	3.81 (2.71–5.36)	< 0.001
Malignancy	15	2761	1.43 (0.76–2.70)	0.273
Heliotrope rash	6	512	1.36 (0.76–2.45)	0.306
Gottron's sign or papules	7	989	0.78 (0.47–1.27)	0.314
Mechanics hand	2	217	0.52 (0.07–4.03)	0.533
Skin ulcers	5	1506	1.10 (0.65–1.85)	0.726
Calcinosis	15	2633	4.19 (2.44–7.18)	< 0.001
Alopecia	2	295	0.78 (0.32–1.89)	0.576
Raynaud's phenomenon	8	1425	0.79 (0.43–1.47)	0.463
Lateral hip rash	2	295	0.71 (0.32–1.60)	0.411
Facial erythema	3	261	1.24 (0.56–2.77)	0.597
Palmar papules	2	295	0.17 (0.02–1.29)	0.087
Heart involvement	2	535	1.30 (0.60–2.79)	0.509
Laboratory				
Elevation of CK	4	398	1.52 (0.61–3.79)	0.371

OR, odds ratio; *CI*, confidence interval

respect to the relationship of anti-NXP2 autoantibody with malignancy and calcinosis [3]. Our meta-analysis showed that anti-NXP2 autoantibody increased the risk of calcinosis. However, there was no association between anti-NXP2 autoantibody and malignancy. These results are consistent with those of a previous study [41]. In addition, we also found a relation of anti-NXP2 autoantibody with edema, muscle weakness, myalgia/myodynia, dysphagia, and ILD.

The prognostic relevance of anti-NXP2 autoantibodies was also analyzed in the current meta-analysis. We found no connection between the presence of anti-NXP2 autoantibody and poor prognosis of patients with IIMs. However, due to the small number of patients examined, the result should be interpreted with caution and additional studies are required to confirm this outcome.

Some limitations of this meta-analysis should be acknowledged. Due to the small sample size of studies conducted in North America, further studies are required to obtain more definitive evidence. In addition, the relationship of anti-NXP2 autoantibody with other demographic, clinical, and laboratory characteristics was not investigated because of the limited number of studies available.

In conclusion, our findings indicate that anti-NXP2 autoantibody has a high specificity and low sensitivity for diagnosis of IIMs. Anti-NXP2 autoantibody is related to edema, muscle weakness, myalgia/myodynia, dysphagia, calcinosis, and ILD in patients with IIMs, but is not associated with overall survival of these patients.

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Compliance with ethical standards

Disclosures None.

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