Systematic Review and Meta-Analysis

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Elevated plasma/serum levels of prolactin in patients with systemic sclerosis

A systematic review and meta-analysis

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Abstract

Background: Prolactin (PRL), an inflammatory hormone with cytokine properties, has long been considered to play a crucial role in the pathogenesis of autoimmune diseases, including systemic sclerosis (SSc). However, the plasma/serum levels of PRL in SSc were inconsistent in published studies. The aim of this study was to evaluate the plasma/serum levels of PRL in patients with SSc accurately.

Methods: Electronic databases, including PubMed, EMBASE, Cochrane Library, CNKI, VIP and WANFANG databases, were searched up to October 15, 2019. Pooled standard mean difference (SMD) with 95% confidence interval (CI) was calculated by fixed-effect or random-effects model analysis. All statistical analyses were conducted with STATA 12.0.

Results: Fifty three articles were obtained after searching databases, and 9 studies with 293 SSc patients and 282 controls were finally included. The meta-analysis showed that the plasma/serum PRL level in SSC patients was significantly increased compared with the healthy controls, with the SMD of 1.00 and 95% CI (0.56, 1.43). Subgroup analysis showed that female patients had higher plasma/serum PRL levels. However, no significant change in plasma/serum PRL levels was observed in male patients ($P = .318$). In subgroup analysis by detection type, electrochemiluminescence immunoassay (ECLIA) group and enzyme-linked immunosorbent assay (ELISA) group showed higher PRL levels among SSc patients.

Conclusions: In summary, our meta-analysis showed a significantly higher plasma/serum PRL level in SSc patients than healthy controls, and it was associated with gender and detection method.

Abbreviations: 95% CI = 95% confidence interval, ACR = American College of Rheumatology, CLIA = chemiluminescence immunoassay, dcSSc = diffuse cutaneous SSc, ECLIA = electrochemiluminescence immunoassay, ELISA = enzyme-linked immunosorbent assay, EULAR = European League Against Rheumatism, lcSSc = limited cutaneous SSc, NOS = Newcastle-Ottawa Quality Assessment Scale, PRL = prolactin, RIA = radioimmunoassay, SD = standard deviation, SMD = standard mean difference, SSc = systemic sclerosis.

Keywords: autoimmune, hormone, meta-analysis, prolactin, systemic sclerosis

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by alterations of the microvasculature, disturbances of the immune system, and massive deposition of collagen and other matrix substances in the skin and internal organs.[1] At present, the exact cause of SSc is not clear, but studies have shown that its pathogenesis may be related to genetic and environmental factors. It occurs in 2 main clinical forms, namely, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), and the classification is based on the extent and localization of skin involvement.[2] It is distributed worldwide as 2 to 10 per million. The prevalence rate of this disease is around 5/100,000 with an incidence of 1/100,000.[3] It is more common in women than men with a ratio of 3:1 to 6:1, according to the geographical region.[4,5] Women are more frequently affected, perhaps because sexual hormones are implicated in modulating the immune response.[6,7] SSc does not occur randomly in the populations. However, It carries the highest standardized mortality ratio among all systemic rheumatic diseases.[8] Therefore, it is urgent to identify and verify the accurate and feasible pathogenic factors in order to better prevent the occurrence of disease, guide personalized treatment and improve patient outcomes.

Prolactin (PRL) is a polypeptide hormone produced by the lactotrophs of the pituitary gland, but the immune cells can

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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produce PRL as well. The PRL receptor is a member of the type 1 cytokine/hematopoietic receptor superfamily and is widely expressed through the immune system, including monocytes, lymphocytes, macrophages, natural killer cells, granulocytes, and thymic epithelial cells.[7] Hence, the binding of PRL to its receptor activates downstream signaling pathways that will manipulate immune cells proliferation, differentiation, secretion, and survival.[9,10] This molecule is an integral member of the immune-neuroendocrinology network and has been largely associated with autoimmune diseases.[11] Hyperprolactinemia has been reported in 13% to 59% of patients with systemic sclerosis.[12]

The role of PRL in SSc has been widely studied and remains controversial. Previous studies have shown that SSc patients have altered serum PRL values.[13–16] A research demonstrated abnormally high PRL serum levels in SSc patients with a high number of disease manifestations.[13] Nevertheless, no significant difference in SSc has also been reported.[17,18] To the authors knowledge, no systematic review on this topic has been published so far. Therefore, the meta-analysis was performed to derive a more precise evaluation on plasma/serum PRL levels in SSc patients.

2. Materials and methods

2.1. Ethical approval

Since this study was a meta-analysis of published studies, no ethical approval or patient consent was required.

2.2. Search strategy

Two authors (YW and MLL) independently performed a comprehensive literature retrieval using PubMed, EMBASE, Cochrane Library, CNKI, VIP and WANFANG databases. The last search was conducted on October 15, 2019. The following keywords were used in the search: ("Systemic sclerosis" OR "Scleroderma, Systemic" OR "SSc") AND ("prolactin" OR "PRL"). The references of the retrieved relevant articles were manually scanned to identify additional studies.

2.3. Eligibility criteria

Studies meeting the following inclusion criteria were included: date: up to October 15, 2019; study design: case-control, cohort or cross-sectional study; species: humans; population: adults diagnosed with SSc; SSc diagnostic criteria: the American College of Rheumatology (ACR) 1980 classification criteria or ACR/ the European League Against Rheumatism (ACR/EULAR) 2013 criteria; comparison group description: matching criteria (age, gender, and reproduction), healthy control subjects; data: fasting plasma/serum PRL levels in both SSc patients and healthy controls; language: English/Chinese. Studies that did not meet the inclusion criteria and reported in reviews, editorials, non-research letters, case reports, or case-only design were excluded. Patients with hypothyroidism, hepatic insufficiency or advanced chronic renal failure, as well as those who were pregnant, nursing, or taking any drug known to influence plasma/serum prolactin levels (bromocriptine, chloroquine, metoclopramide, cimetidine, etc.) were excluded. Only the study with the newest and most related information was included when duplicate publications from the same center were identified.

2.4. Study selection

Two independent authors (YW and MLL) deleted duplicate records, screened the titles and abstracts of the retrieved articles, and reviewed the full text if necessary. The studies that were potentially relevant according to the eligibility criteria were selected. Disagreements were resolved by discussion with the third reviewer (LJH).

2.5. Data extraction and quality assessment

Using a standardized protocol and data recording form, 2 authors (YW and MLL) independently extracted the following information from each eligible study: first authors name, year of publication, country, sample size, gender, age, disease duration, detection method, the mean and standard deviation (SD) of PRL concentrations of cases and controls, and quality assessment score. In cases where mean and SD were not reported, methods described by Hozo et al[19] were used to estimate mean and SD. If the original vital data was unavailable, we e-mailed the corresponding authors to obtain the further details. Discrepancies were resolved by discussion with the third reviewer (LJH).

Two authors (YW and MLL) independently assessed the quality of eligible studies using the Newcastle-Ottawa Quality Assessment Scale (NOS). Disagreements were resolved by discussion with the third reviewer (LJH). The highest NOS score is 8 points, and studies greater than 5 were classified as high-quality.

2.6. Statistical methods

In order to supply quantitative evidence of all included studies and minimize the variance, the standard mean difference (SMD) and its corresponding 95% confidence interval (95% CI) were calculated. The results were displayed graphically in a forest plot. The statistical significance of pooled SMDs was estimated with Z test. Statistical heterogeneity among studies was evaluated using the Chi-Squared test and I^2 statistic. Random-effects model was performed when significant heterogeneity ($I^2 > 50\%$ or $P < .05$) was detected. To assess the potential sources of heterogeneity, further subgroup analysis was conducted. Sensitivity analysis was used to determine the stability and reliability of the results. Publication bias was evaluated using Begg's funnel plot and Egger's regression test. This meta-analysis was conducted with STATA 12.0 (StataCorp LP, College Station, TX). $P < .05$ was considered statistically significant.

3. Results

3.1. Search results

A total of 53 potentially relevant publications were retrieved using the above search strategy. Twenty seven articles were ultimately obtained by removing duplicate studies. After screening the titles and abstracts, 13 articles were excluded and 14 potentially eligible studies were retrieved for full text evaluation. Nine articles with 293 SSc patients and 282 healthy controls were incorporated according to the mentioned criteria. Details of the screening process are described in Figure 1.

3.2. Study characteristics

The basic characteristics of the eligible studies are summarized in Table 1.[13–15,17,18,20–23] The studies were generally high-quality, with all NOS scores more than 5. Of note, the article by La Montagna et al[20] provided 2 independent comparisons based on the serum PRL levels of post-menopausal women and women of

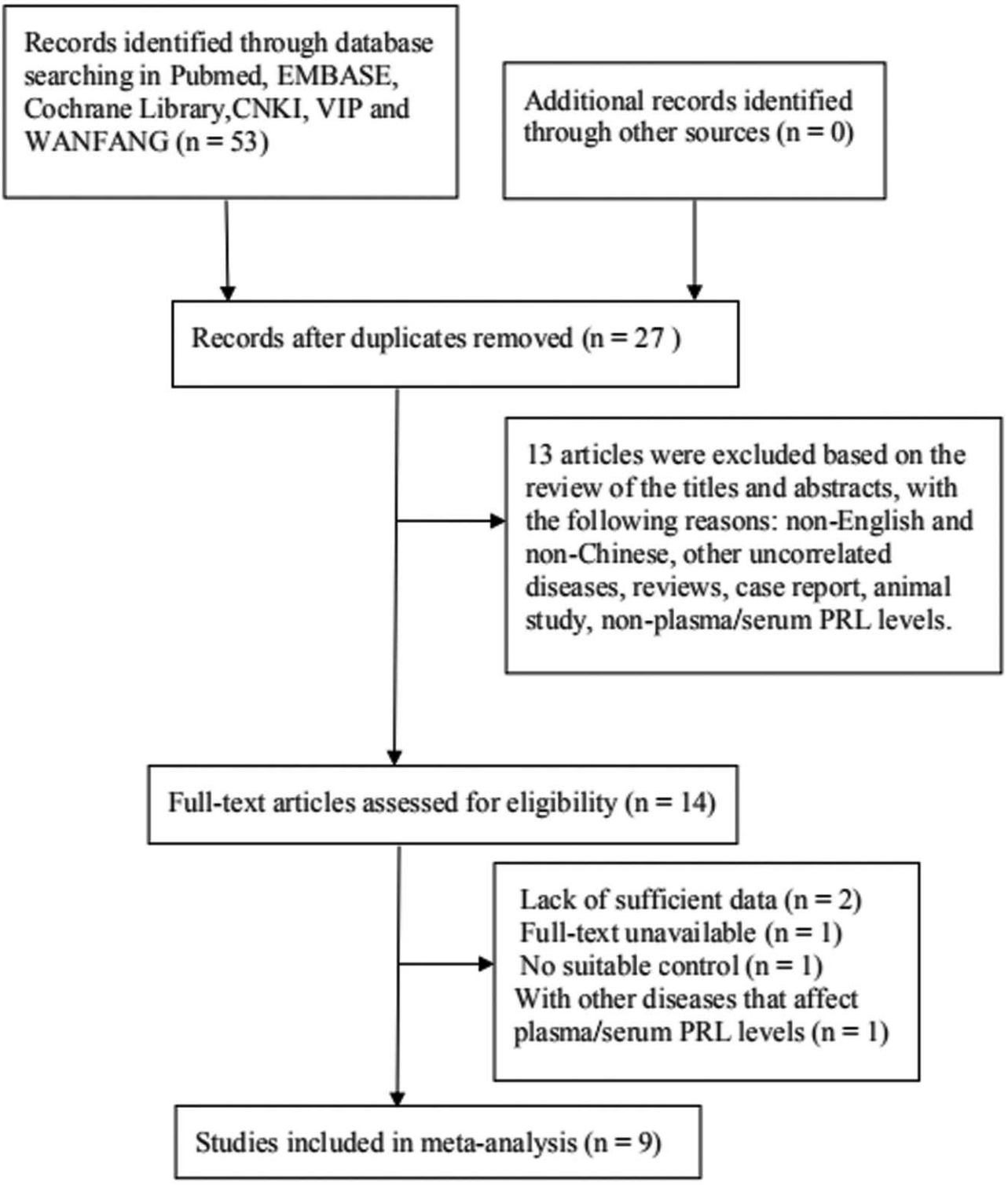

Figure 1. Flow diagram of selected articles.

childbearing age respectively. The article by Czuwara-Ladykowska et al[22] provided 2 independent comparisons based on male and female serum PRL levels separately. The article by Mirone et al[23] provided 3 independent comparisons on the basis that the serum PRL levels of post-menopausal women, women of childbearing age and man were determined and reported respectively. Thus, in total, 13 comparisons (from 9 articles) comprising 293 patients were included in the pooled analysis. The studies were conducted in 7 countries (the United States, Poland, Germany, Switzerland, Italy, Egypt and Sweden) and published from 1986 to 2017. All of 13 case-control studies were incorporated in the meta-analysis. Among them, cases of all

Table 1

Characteristics of abstracted studies.

First author, year [reference]	Country	Patients with SSc				Control			Criteria for the classification of SSc	Detection method	Study design	NOS
		No.	Gender (F/M)	Age (mean ± SD) (years)	Duration (mean ± SD) (years)	No.	Gender (F/M)	Age (mean ± SD) (years)				
Nowlin, 1986[17]	US	10	0/10	35–69 *	NA	10	0/10	NA	ACR 1980	RIA	Case-Control	7
Kucharz, 1996[13]	Poland	17	17/0	32–49 *	NA	10	10/0	NA	ACR 1980	RIA	Case-Control	6
Straub, 1997[14]	Germany	31	26/5	19–78 *	NA	42	28/14	50.3 ± 2.3 †	ACR 1980	ELISA	Case-Control	8
Hilty, 2000[15]	Switzerland	73	57/16	56 ± 11	NA	73	57/16	NA	ACR 1980	ELISA	Case-Control	7
La Montagna-1, 2001[20]	Italy	12	12/0	34.8 ± 2.4 †	7.7 ± 1.3 †	12	12/0	NA	ACR 1980	RIA	Case-Control	7
La Montagna-2, 2001[20]	Italy	6	6/0	46.8 ± 2.4 †	12.2 ± 3.1 †	6	6/0	NA	ACR 1980	RIA	Case-Control	7
Shahin, 2002[21]	Egypt	24	23/1	37.7 ± 12.7	7.4 ± 5.8	15	15/0	35.6 ± 8.2	ACR 1980	ELISA	Case-Control	8
Czuwara- Ladykowska-1, 2006[22]	Poland	8	0/8	43.75 ± 8.77	7.56 ± 7.49	8	0/8	NA	ACR 1980	ELISA	Case-Control	7
Czuwara- Ladykowska-2, 2006[22]	Poland	44	44/0	46.40 ± 10.6	11.03 ± 9.18	44	44/0	NA	ACR 1980	ELISA	Case-Control	7
Mirone-1, 2006[23]	Italy	12	12/0	35.3 ± 5.2	5.1 ± 5.6	14	14/0	NA	ACR 1980	ECLIA	Case-Control	8
Mirone-2, 2006[23]	Italy	22	22/0	55.7 ± 8.9	9.3 ± 8.2	23	23/0	NA	ACR 1980	ECLIA	Case-Control	8
Mirone-3, 2006[23]	Italy	5	0/5	51.4 ± 13.6	6.4 ± 3.4	8	0/8	NA	ACR 1980	ECLIA	Case-Control	8
Arnaud, 2017[18]	Sweden	29	0/29	60 (38–80) ‡	4.9 (0.9-23.9) ‡	17	0/17	61 (41–86) ‡	ACR/EULAR 2013	CLIA	Case-Control	7

NA = not available.

* range.

† mean ± SEM.

‡ median (range).

ACR = American College of Rheumatology criteria for SSc, CLIA = chemiluminescence immunoassay, dcSSc = diffuse cutaneous SSc, ECLIA = electrochemiluminescence immunoassay, ELISA = Enzyme-linked immunosorbent assay, EULAR = European League Against Rheumatism criteria for SSc, lcSSc = limited cutaneous SSc, NOS = Newcastle-Ottawa Scale, RIA = radioimmunoassay, SSc = systemic sclerosis.

studies were diagnosed with SSc by ACR 1980 classification criteria or ACR/EULAR 2013 criteria. Age and sex matched between SSc patients and controls in all included studies. The detection methods for PRL concentrations were as follows: 5 comparisons measured by ELISA (enzyme-linked immunosorbent assay); 4 comparisons measured by RIA (radioimmunoassay); 1 comparison measured by CLIA (chemiluminescence immunoassay); 3 comparisons measured by ECLIA (electrochemiluminescence immunoassay). The results of quality evaluation by NOS for these studies are depicted in Table 1. The quality of the studies was evaluated as high quality, ranging from 6 to 8 stars.

3.3. Meta-analysis results

3.3.1. Heterogeneity test results. Heterogeneity was assessed using the Chi-Squared test and I^2 measure. In this study, the random-effects model was performed for the following analyses due to statistically significant heterogeneity ($I^2 = 80.2\%$, $P = .000$) among studies (Fig. 2).

3.3.2. Overall effects and subgroup analysis. The results indicated that SSc patients had significantly higher plasma/serum PRL levels than healthy controls (SMD = 1.00, 95% CI: 0.56–1.43, $P < .001$) (Fig. 2). When stratified by gender, female patients with SSc showed higher PRL levels (SMD = 1.47, 95% CI: 0.83–2.11). However, there was no significant difference in male patients (SMD = 0.21, 95% CI: −0.21 to 0.63). When stratified by average age, both age ≥45 years group and age <45 years group showed higher PRL levels (SMD = 1.05, 95% CI: 0.41–1.69, $I^2 = 87.1\%$; SMD = 1.02, 95% CI: 0.60–1.43, $I^2 = 0.0\%$). When stratified by disease duration, both disease duration ≥7.5 years and disease duration <7.5 years showed elevated plasma/serum PRL levels (SMD = 1.44, 95% CI: 0.65–2.23, $I^2 = 78.4\%$; SMD = 0.53, 95% CI: 0.16–0.90, $I^2 = 36.8\%$). For the groups which measured by ECLIA and ELISA, higher PRL levels were found in the SSc patients (SMD = 1.10, 95% CI: 0.64–1.57; SMD = 1.27, 95% CI: 0.56–1.98). The results of the subgroup analysis are detailed in the Table 2.

3.3.3. Sensitivity analyses and publication bias. To evaluate the stability of our results, sensitivity analysis was performed by omitting one study at a time and checking the consistency of the overall effect estimate. The results demonstrated that no study had an excessive impact on the pooled SMDs and our conclusion was relatively stable ($P > .05$) (Fig. 3). Publication bias was evaluated by Beggs funnel plot and Eggers regression test. Beggs funnel plot revealed no asymmetry (Begg $P = .760$) (Fig. 4A). The Eggers test also did not identify the publication bias (Egger $P = .507$) (Fig. 4B).

4. Discussion

This study included 13 comparisons from 9 articles involving 293 SSc patients. The result showed that SSc patients appeared to have significantly higher plasma/serum PRL levels than healthy controls ($P < .001$), meaning that the increased PRL may play a pathogenic role in the development of SSc. Due to significant heterogeneity among the studies, the subgroup analysis was conducted to minimize the potential influence factors. Subgroup analysis based on gender showed that PRL levels were higher in the female SSc patients. In subgroup analysis by detection type, the ECLIA group and ELISA group showed higher PRL levels among SSc patients. Subgroup analysis based on age, both age ≥45 years group and age <45 years group showed higher PRL levels. Subgroup analysis based on disease duration, both disease duration ≥7.5 years and disease duration <7.5 years showed elevated plasma/serum PRL levels. To test the stability of the results of the meta-analysis, sensitivity analysis was conducted

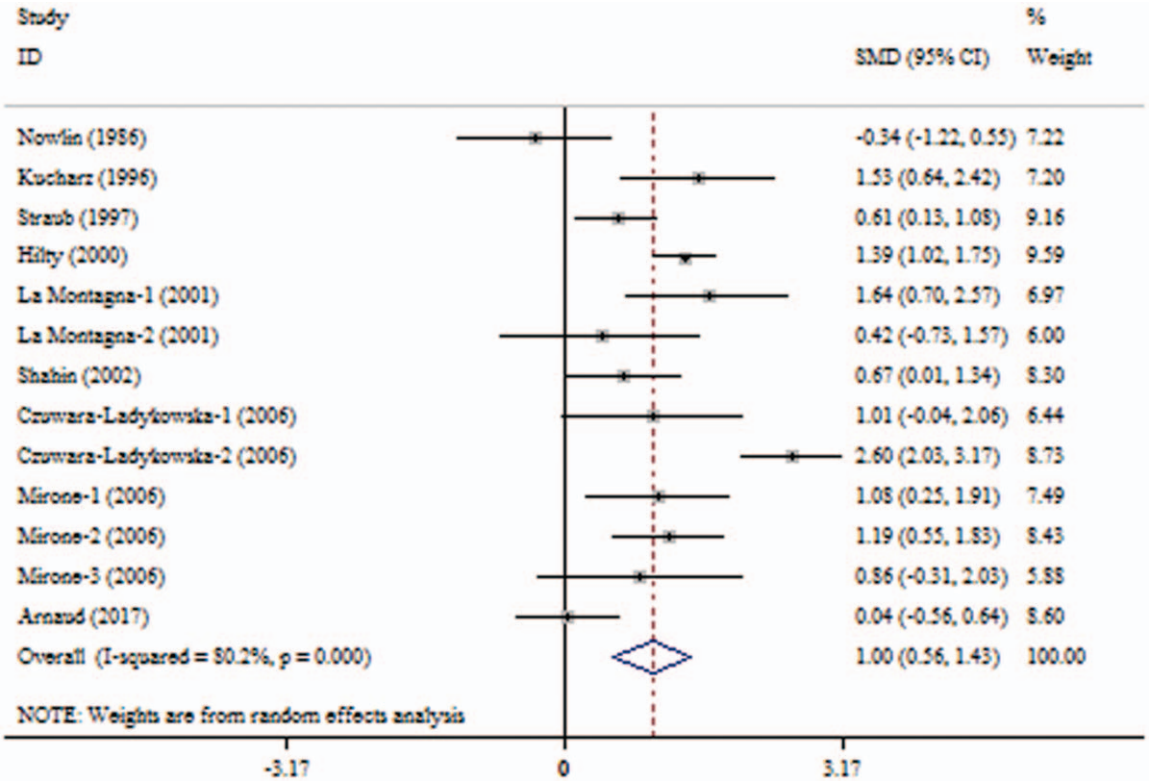

Figure 2. Meta-analysis of 13 comparisons reporting on PRL in SSc compared with controls.

and showed that the results of the meta-analysis were robust. Beggs test and Eggers test suggested no publication bias. In patients with dcSSc, PRL levels showed significant correlation with the severity of skin sclerosis, cardiovascular, and lung involvement.[21] Conversely, Arnaud et al[18] observed no association between the levels of PRL and SSc subtypes (lcSSc, dcSSc), modified Rodnan skin thickness score, or history of digital ulcers. La Montagna et al[24] revealed that no correlation was found between PRL levels and SSc subtypes, serological parameters, or the level of disease activity. However, due to the limited number of studies contained in the subgroup analysis, we could not discuss the possibility that positive findings may result from the subjects with different regions and disease manifestations.

SSc is a T cell-mediated connective tissue disease with high mortality and morbidity among the autoimmune rheumatic diseases.[23,25] PRL has a recognized immunostimulatory effect, specially increasing the synthesis of IFN-γ and IL-2 by Th1 lymphocytes and activating Th2 lymphocytes with autoantibody production. Moreover, PRL inhibits the negative selection of

Table 2

Subgroup analysis of PRL levels in SSc.

Subgroup	No. of studies	No. of patients	Heterogeneity	Statistical model used	SMD (95% CI)	Significance
Total	13	293	I^2 = 80.2%, P = .000	Random	1.00 (0.56, 1.43)	P = .000
Gender						
Male	4	52	I^2 = 42.2%, P = .158	Fixed	0.21 (-0.21, 0.63)	P = .318
Female	6	113	I^2 = 73.7%, P = .002	Random	1.47 (0.83, 2.11)	P = .000
Age						
Age ≥45	7	210	I^2 = 87.1%, P = .000	Random	1.05 (0.41, 1.69)	P = .001
Age <45	4	56	I^2 = 0.0%, P = .431	Fixed	1.02 (0.60, 1.43)	P = .000
Disease duration						
Disease duration ≥7.5	5	92	I^2 = 78.4%, P = .001	Random	1.44 (0.65, 2.23)	P = .000
Disease duration <7.5	4	70	I^2 = 36.8%, P = .191	Fixed	0.53 (0.16, 0.90)	P = .005
Assay method						
CLIA	1	29	NA	NA	0.04 (-0.56, 0.64)	P = .899
ECLIA	3	39	I^2 = 0.0%, P = .887	Fixed	1.10 (0.64, 1.57)	P = .000
ELISA	5	180	I^2 = 87.5%, P = .000	Random	1.27 (0.56, 1.98)	P = .000
RIA	4	45	I^2 = 75.9%, P = .006	Random	0.82 (−0.15, 1.79)	P = .099

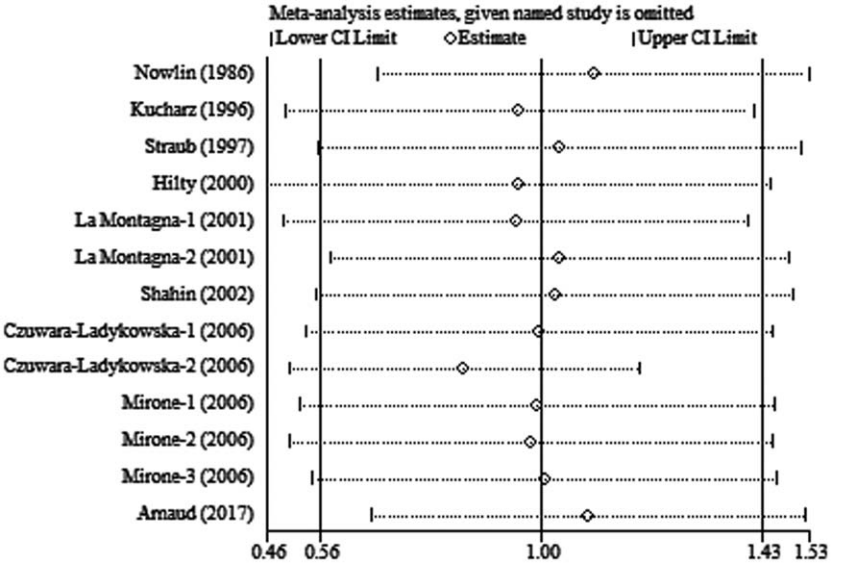

Figure 3. Sensitivity analysis by excluding one study at a time.

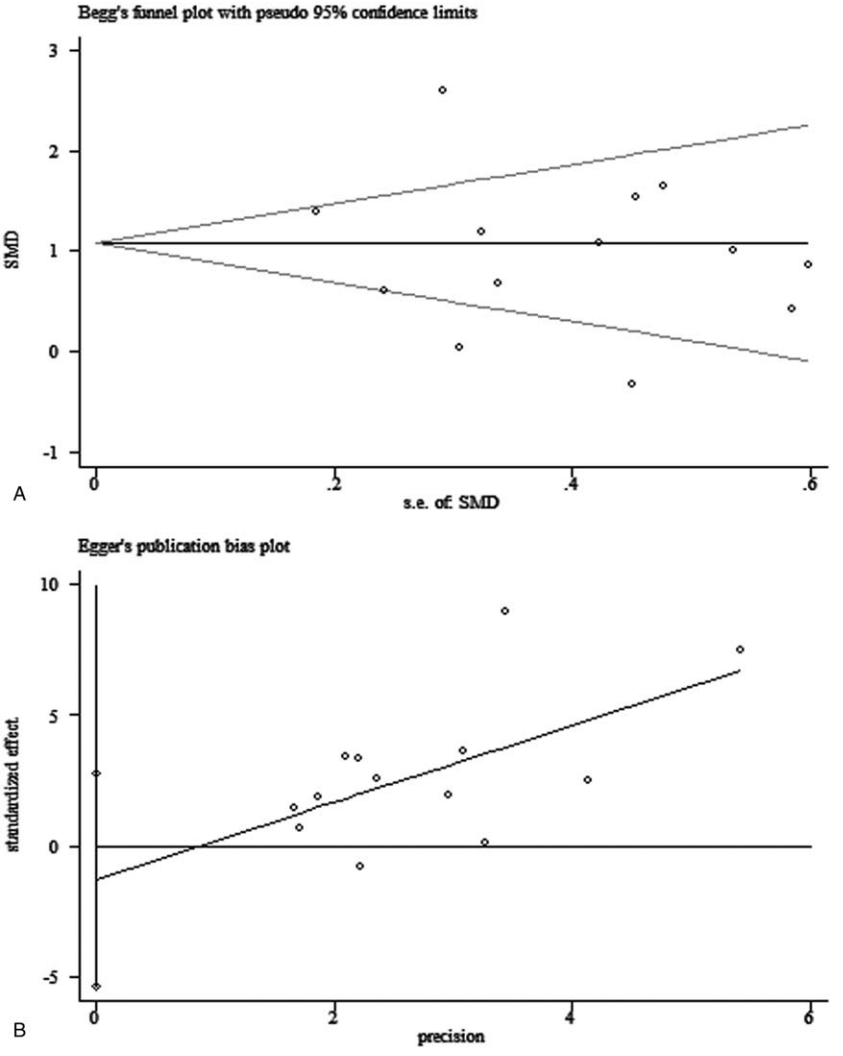

Figure 4. Beggs funnel plot and Eggers regression test for assessment of potential publication bias. (A) Beggs funnel plot; (B) Eggers regression test.

autoreactive B lymphocytes, promoting autoimmunity. In accordance, hyperprolactinemia has been associated with several autoimmune diseases, influencing their pathogenesis.[26,27] Although the mechanisms involving this interaction are not completely understood, it has been documented that PRL can influence the communication and regulation of immune cells.[28]

For SSc patients, the association between the plasma/serum level of PRL and disease manifestations was largely inconclusive. In the present analysis, several studies[13–15,20–23] showed that PRL was significantly correlated with SSc subtypes, disease duration and disease activity. For example, elevated PRL levels occurred significantly more often in patients with short disease duration.[21] Moreover, in a recent systematic review by Chairta et al,[29] STRING10 analysis clearly revealed that PRL in particular stood out as the main "hub" of interaction network of the non-HLA genes associated with SSc. The correlations between the "hub" genes and their interconnected genes are important parameters for the investigation of new interaction pathways, which may lead to developing new therapeutic approaches in the future. However, several studies found no significant difference in PRL values between SSc patients and healthy controls.[17,18,20,22–24] Our meta-analysis found a significantly higher PRL level in SSc patients compared to healthy controls, but with a gender difference. Therefore, the routine PRL assessment is necessary for these patients. A few controlled studies of dopamine agonist treatment in humans with autoimmune disease have suggested potential benefit in patients with SLE, RA, Reiters syndrome, and psoriasis.[30] Our findings may help to establish the rationale for clinical studies of dopamine agonist therapy in women with SSc.

Several limitations should be considered in the present study. First, this analysis was restricted to the studies published in English and Chinese. Second, due to the limitation of incorporated studies, most studies did not have clear disease activity reports. Thus, the association between PRL and disease activity was not assessed effectively by analysis. Third, in the incorporated studies, the sample size varied greatly and most of them were relatively small. Fourth, some data were approximated by conversion, which might lead to deviations in the results. Fifth, there was significant heterogeneity among the included studies. The reagent kits and assay conditions may be the reasons of heterogeneity. Future studies using more uniform detection methods will likely obtain more reliable results.

Despite these limitations, this meta-analysis has its advantages. To the best knowledge of the authors, this is the first meta-analysis to assess the association of plasma/serum PRL levels in patients with SSc. In addition, Subgroup analysis was performed to further explore the potential sources of significant heterogeneity. The results of sensitivity analyses indicated that the findings were stable. Moreover, no publication bias was detected.

5. Conclusions

In conclusion, this study showed a significantly higher plasma/serum PRL level in SSc patients than healthy controls, and it was associated with gender and detection method. Further larger sample studies using more uniform detection methods are necessary to confirm our results.

Author contributions

Conceptualization: Yang Wu, Meng-Lei Li, Hua-Jing Han, Li-Jun Huang.
Data curation: Yang Wu, Meng-Lei Li, Hua-Jing Han, Li-Jun Huang.
Formal analysis: Yang Wu, Meng-Lei Li.
Investigation: Yang Wu, Meng-Lei Li, Hua-Jing Han, Li-Jun Huang.
Methodology: Yang Wu, Meng-Lei Li, Li-Jun Huang.
Project administration: Yang Wu, Meng-Lei Li.
Resources: Yang Wu, Meng-Lei Li, Li-Jun Huang.
Software: Yang Wu, Meng-Lei Li, Li-Jun Huang.
Supervision: Yong He, Yang Wu.
Validation: Yang Wu, Hua-Jing Han.
Visualization: Yang Wu, Hua-Jing Han.
Writing – original draft: Yang Wu.
Writing – review & editing: Yong He, Yang Wu, Li-Jun Huang.

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