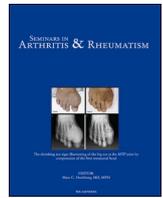




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Serum ferritin as a significant biomarker for patients with idiopathic inflammatory myopathy-associated interstitial lung disease: A systematic review and meta-analysis[☆]

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ABSTRACT

Objective: The biomarkers for predicting the occurrence, progression, and death of idiopathic inflammatory myopathy-associated interstitial lung disease (IIM-ILD) remain unclear. Serum ferritin (SF) is a potential candidate and this systematic review and meta-analysis aimed to reveal the clinical significance of SF in IIM-ILD. **Methods:** Eligible English studies were selected from PubMed, Embase, Web of science and Scopus up to 9 June 2023. The SF levels in patients with IIM-ILD were extracted and pooled. Subgroup analysis was performed based on disease types, sensitivity analysis was conducted by excluding one class of literature at a time, and publication bias was assessed by funnel plot and Egger's test.

Results: Pooled analysis of 1,933 patients with IIM from 19 studies showed that SF levels were significantly higher in IIM-ILD group (WMD=263.53ng/mL, 95% CI: 146.44-380.62, $p < 0.001$) than IIM without ILD, subgroup analysis showed that SF levels in DM-ILD (WMD = 397.67ng/mL, 95% CI:142.84-652.50, $p = 0.002$) and PM/DM-ILD (WMD = 117.68 ng/mL, 95% CI: 86.32-149.04, $p < 0.001$) were significantly higher compared to those without ILD. SF levels were significantly higher in rapidly progressive interstitial lung disease group (RP-ILD) (WMD = 484.99 ng/mL, 95% CI: 211.12-758.87, $p = 0.001$) than chronic ILD(C-ILD) group, subgroup analysis showed that SF levels in DM-RP-ILD (WMD= 509.75 ng/mL, 95% CI: 215.34-804.16, $p = 0.001$) were significantly higher than those in DM-C-ILD group. SF levels were significantly higher in death group (WMD= 722.16 ng/mL, 95% CI: 572.32-872.00, $p < 0.001$) compared to the survival group, subgroup analysis showed that death patients with DM-ILD(WMD= 735.62 ng/mL, 95% CI:574.92-896.32, $p < 0.001$) and PM-ILD (WMD= 632.56 ng/mL, 95% CI:217.92-1047.19, $p = 0.003$) had significantly higher SF levels than survival group respectively.

Conclusion: Increased SF levels can serve as a biomarker for predicting the occurrence, progression and death of patients with IIM-ILD, which can provide early warning sign for intervention and prognosis evaluation for IIM-ILD patients.

Introduction

As a heterogeneous group of connective tissue diseases (CTD), idiopathic inflammatory myopathies (IIM) comprise of dermatomyositis (DM), polymyositis (PM) and other subtypes. IIM may affect multiple

organs, with interstitial lung disease (ILD) being the most common clinical manifestation of IIM involvement in lungs. Approximately 41% of PM/DM patients suffer from ILD [1], and the annual mortality rate of patients with PM/DM-related ILD is 0.23/1,000,000 [2]. With the characteristic of progressive development, IIM-ILD increases the risk of

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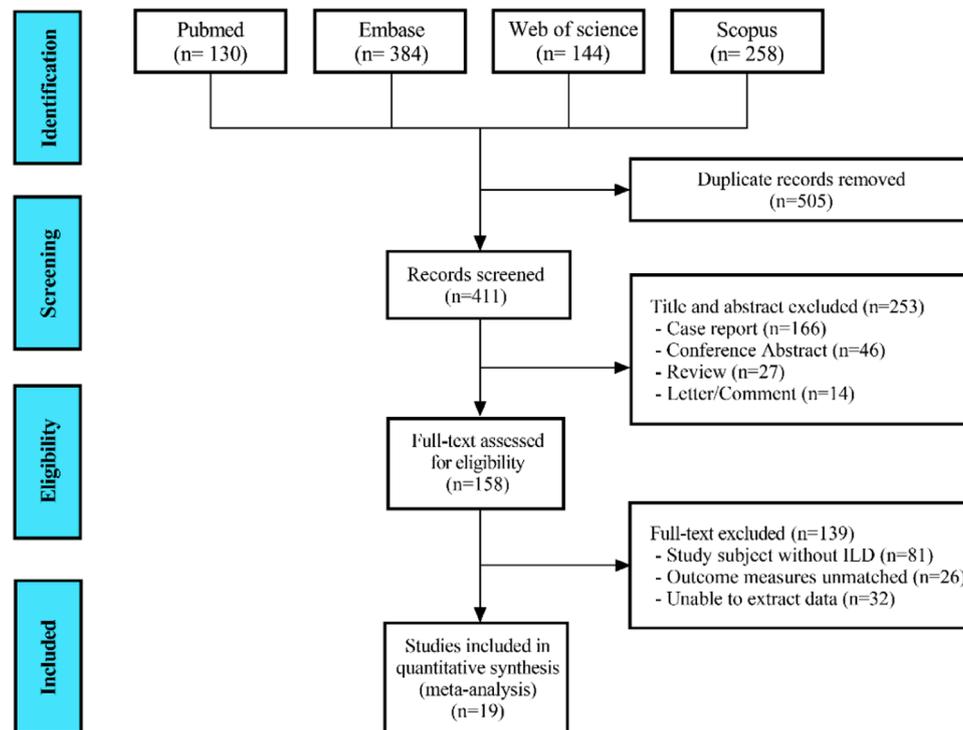


Fig. 1. Diagram of the preferred reporting items for systematic review and meta-analysis (PRISMA).

death in patients[3], while early IIM-ILD often is easy to be ignored without noticeable clinical symptoms. Furthermore, there is a lack of biomarkers for identifying the occurrence, progression and death of ILD in IIM patients at an early stage.

Ferritin, an important iron-containing protein in human body, plays a crucial role in cellular and systemic iron homeostasis and is also an acute-phase reactant in inflammatory responses, involved in the occurrence and progression of infection and cancer[4]. Hyperferritinemia is considered to reflect disease progression and prognosis[5]. It has been reported that SF can serve as a predictor for ILD occurrence and prognosis in IIM patients[6], while it is still controversial with no pooled analysis of quantitative data.

Therefore, we conducted this systematic review and meta-analysis to explore the clinical significance of SF levels in the occurrence, progression, and death in IIM-ILD patients, using quantitative methods for pooled studies.

Materials and methods

Search strategy

The study was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7], and registered with INPLASY (<http://INPLASY.com>) under registration number INPLASY 2023110008. A systematic literature search of the PubMed, Embase, web of science and Scopus was performed up to 9 June 2023, with the following terms “Myositis”, “Idiopathic Inflammatory Myopathy”, “Dermatomyositis”, “Polymyositis”, “anti-synthetase syndrome”, “Interstitial Lung Disease” and “Ferritin”(Supplementary Table 1).

Eligibility criteria

The inclusion criteria were as follows: (1) case-control studies, cohort studies, and cross-sectional studies; (2) IIM-ILD was diagnosed by clinical features and high-resolution computed tomography (HRCT).

Rapidly progressive interstitial lung disease (RP-ILD) was defined as an acute worsening of dyspnea secondary to ILD, requiring hospitalization, supplemental oxygen, or intubation for respiratory failure within 3 months of ILD diagnosis[8]. Chronic ILD (C-ILD) was defined as asymptomatic or gradually progressive ILD with a duration exceeding 3 months; (3) availability of quantitative data; (4) English literature.

The exclusion criteria were as follows: (1) Review, case report, letter/comment and conference abstract; (2) other connective tissue disease-associated ILD (CTD-ILD); (3) studies that SF was not a study index; (4) inability to obtain quantitative data on SF or to be converted by algorithms.

Quality assessment and data extraction

Two investigators (XH and JJ) independently reviewed literatures thoroughly that met the inclusion criteria, evaluating the quality of studies by Newcastle-Ottawa Quality Assessment Scale (NOS)[9]. The following data was extracted: the first author, year of publication, country, study type, study object, sample size, and mean and standard deviation (or calculated by algorithms)[10,11]. When any discrepancy arose during the review, it could be discussed with a third investigator (LG).

Statistical analysis

The weighted mean difference (WMD) with 95% confidence interval (95% CI) was calculated to evaluate the differences in SF between groups, and heterogeneity is assessed by Cochran's Q statistic and inconsistency value (I^2). If $p < 0.05$ or $I^2 \geq 50\%$, it was considered significant heterogeneity, and the Dersimonian-Laird method should be used to pool the results; otherwise, inverse-variance method would be used. Subgroup analysis was performed according to IIM subtypes. The sensitivity analysis was carried out by excluding one category of literature at a time. If the exclusion of a category had no significant effect on the pooled results, it reflected that our results were statistically stable and reliable. Heterogeneity was analyzed by funnel plot and Egger's test

Table 1
Characteristics of studies included in the meta-analysis.

No.	Author	Time	Country	Study type	Object	Effect size(n)	Effect size(Mean±SD,ng/ml)
1	Wanlong Wu,	2022	China	cohort	DM-ILD	Survival=109 Death=75	Survival=1214±1750 Death=2614±3580
2	Sei-ichiro Motegi,	2019	Japan	retrospective	DM(ADM)-ILD	C-ILD=12 RP-ILD=16 Survival=9 Death=7	C-ILD=453±133 RP-ILD=849±172 Survival=514.6±187 Death=1183.6±238.7
3	Kaiwen Wang,	2019	China	cohort	IIM-ILD	PM=4 PM-ILD=17 DM=8 DM-ILD=25 ADM=7 ADM-ILD=43 Survival=68 Death=17	PM=358.03±398.49 PM-ILD=536.19±944.29 DM=487.35±450.09 DM-ILD=938.51±1108.23 ADM=189.68±198.49 ADM-ILD=1238.72±1430.43 Survival=670.91±810.98 Death=1100.65±1297.97
4	Toshinori Takada,	2018	Japan	cross-sectional	ADM-ILD	Survival=17 Death=9	Survival=420.1±326.3 Death=855.3±592.9
5	Mizuho Nara,	2014	Japan	retrospective	ADM-ILD	Survival=6 Death=6	Survival=372.6±227.4 Death=701.9±645.3
6	Yuhui Li,	2020	China	retrospective	DM(ADM)-ILD	Survival=19 Death=9 C-ILD=8 RP-ILD=28	Survival=806.1±717.8 Death=2028.5±1176.2 C-ILD=54.4±65.5 RP-ILD=1417.3±1113.8
7	Hideaki Tsuji,	2020	Japan	historical controlled	DM(ADM)-ILD	Survival=23 Death=4	Survival=459.9±516.3 Death=2050.3±1772.7
8	Masanori Hanaoka,	2019	Japan	retrospective	PM/DM-ILD	PM/DM=16 PM/DM-ILD=39	PM/DM=229±140 PM/DM-ILD=373±463
9	Chenghua Weng,	2023	China	retrospective case-control	DM-ILD	DM=40 DM-ILD=38	DM=560.9±627.9 DM-ILD=707.7±636.7
10	Norimoto Kobayashi,	2014	Japan	retrospective	JDM-ILD	JDM=24 JDM-ILD=8 JDM=24 JDM-ILD=19 C-ILD=19 RP-ILD=8	JDM=131.2±160.4 JDM-ILD=355.4±136.8 JDM=131.2±160.4 JDM-ILD=222.8±129.3 C-ILD=222.8±129.3 RP-ILD=355.4±136.8
11	Jinghao Lu,	2021	China	retrospective	DM-ILD	DM=54 DM-ILD=153 CILD=131 RP-ILD=22	IIM=153.9±210.93 IIM-ILD=806.2±653.87 C-ILD=725.19±625.27 RP-ILD=1041.11±711.63
12	Pei Zhou	2023	China	retrospective	PM/DM-ILD	PM/DM =196 PM/DM -ILD=343	PM/DM =296.81±228.76 PM/DM -ILD=425.84±210.09
13	Tingting Yan,	2023	China	retrospective case-control	PM/DM-ILD	PM/DM=19 PM/DM-ILD=14	PM/DM=383.64±519.83 PM/DM-ILD=787.97±920.12
14	Satoshi Takanashi,	2019	Japan	retrospective	PM/DM -ILD	PM/DM=20 PM/DM-ILD=52	PM/DM=101.43±94.15 PM/DM-ILD=189.17±140.29
15	Lifang Ye,	2022	China	retrospective	DM-ILD	C-ILD=21 RP-ILD=13	C-ILD=443.26±875.9 RP-ILD=1122.18±1139.02
16	T. Shimizu,	2021	Japan	retrospective observational	PM/DM-ILD	C-ILD=8 RP-ILD=20	C-ILD=847.99±872.78 RP-ILD=1121.93±807.1
17	Shogo Matsuda,	2020	Japan	retrospective	PM/DM-ILD	Survival=29 Death=10	Survival=281.7±333.94 Death=1056.04±849.68
18	Yasuoki Horiike,	2019	Japan	retrospective	DM(ADM)-ILD	Survival=23 Death=10	Survival=472.71±592.63 Death=1350.56±1309.18
19	Takahisa Gono,	2010	Japan	retrospective	DM(ADM)-ILD	Survival=9 Death=5	Survival=396.89±437.34 Death=1835.03±512.87

DM: dermatomyositis; PM: polymyositis; ADM: amyopathic dermatomyositis; JDM: juvenile dermatomyositis; IIM: idiopathic inflammatory myopathy

was combined to determine publication bias. Meta-analysis was conducted by Stata software(package meta, version 16.0) and $p < 0.05$ was considered statistically significant.

Results

Study selection and study characteristics

A total of 916 studies were identified through comprehensive search and 19 studies (1933 patients) were included in this systematic review after full-text screening, which adhered to the PRISMA guidelines (Fig. 1). All studies were conducted in Asia, including 8 studies showing the comparison of SF levels between IIM patients and IIM-ILD patients [12–19], 6 studies presenting the difference of SF levels between patients with RP-ILD and C-ILD [15,19–23], and 10 studies evaluating the

SF levels between survivals and deaths in patients with IIM-ILD[16, 22–30]. The detailed information of each included study was showed in Table 1. Based on NOS evaluation, all 19 studies were considered high quality (Supplementary Table 2).

The analysis between IIM and IIM-ILD patients

In eight studies, there was significant heterogeneity ($I^2 = 89.6\%$, $p < 0.001$) between 412 patients with IIM and 751 patients with IIM-ILD, so DerSimonian–Laird method was used for the meta-analysis, demonstrating that the SF levels in IIM-ILD were significantly higher than those without ILD (WMD = 263.53 ng/mL, 95% CI: 146.44–380.62, $p < 0.001$) (Fig. 2). Subgroup analysis based on the IIM subtypes showed that SF levels in DM-ILD were significantly higher compared to those without ILD (WMD = 397.67ng/mL, 95% CI:142.84–652.50, $p = 0.002$) and SF

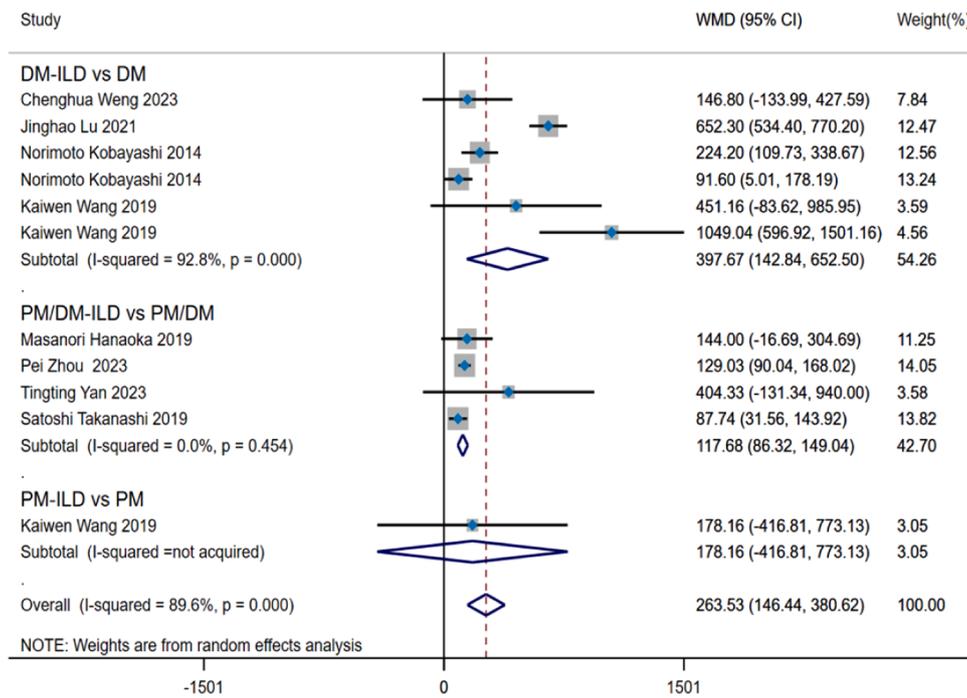


Fig. 2. The forest plot pooled the WMD (95% CI) of serum ferritin level between IIM and IIM-ILD.

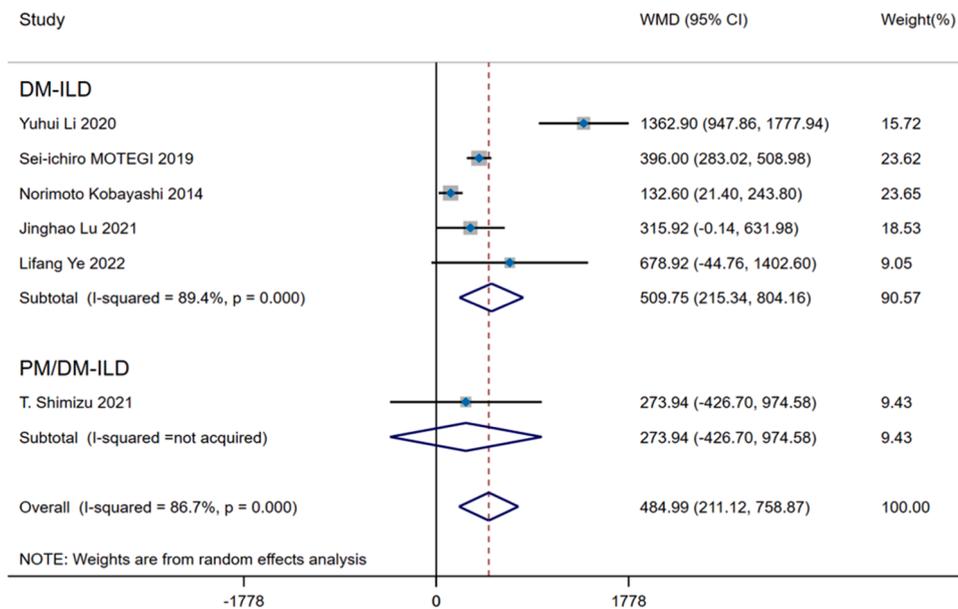


Fig. 3. The forest plot pooled the WMD (95% CI) of serum ferritin level between C-ILD and RP-ILD.

levels in PM/DM-ILD were remarkably higher compared to those without ILD (WMD = 117.68 ng/mL, 95% CI: 86.32-149.04, $p < 0.001$) (Fig. 2).

The analysis between C-ILD and RP-ILD patients

Between 199 C-ILD patients and 107 RP-ILD patients in six studies, there was significant heterogeneity ($I^2 = 86.7\%$, $p < 0.001$), so DerSimonian-Laird method was used for the meta-analysis, indicating that the SF levels in RP-ILD were notably higher than those in C-ILD (WMD = 484.99 ng/mL, 95% CI: 211.12-758.87, $p = 0.001$). Subgroup analysis based on the IIM subtypes showed that in DM-ILD patients the SF levels in RP-ILD were significantly higher than those in C-ILD (WMD= 509.75

ng/mL, 95% CI: 215.34-804.16, $p=0.001$) (Fig. 3).

The analysis between survival and death

There was no significant heterogeneity ($I^2 = 45.7\%$, $p=0.056$) between 312 survivals and 152 deaths in ten IIM-ILD studies. Inverse-Variance method was used for the meta-analysis and the result revealed that death patients had significantly higher SF levels compared to survivals (WMD= 722.16 ng/mL, 95% CI: 572.32-872.00, $p < 0.001$). Subgroup analysis based on the IIM subtypes showed that death patients with DM-ILD had significantly higher SF levels than survivals (WMD= 735.62 ng/mL, 95% CI: 574.92-896.32, $p < 0.001$) and death patients with PM/DM-ILD had significantly higher SF levels than survivals

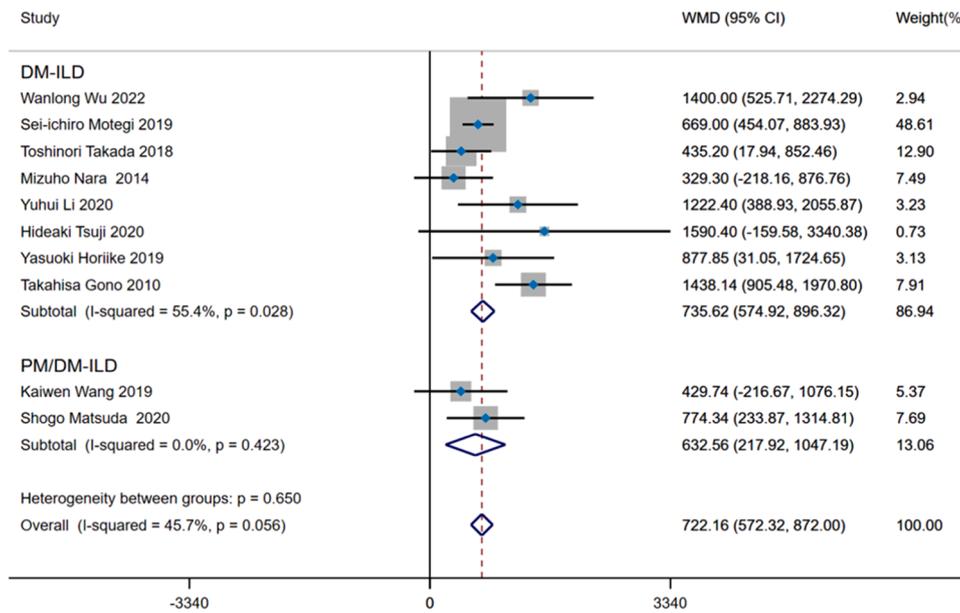


Fig. 4. The forest plot pooled the WMD (95% CI) of serum ferritin level between survival and death.

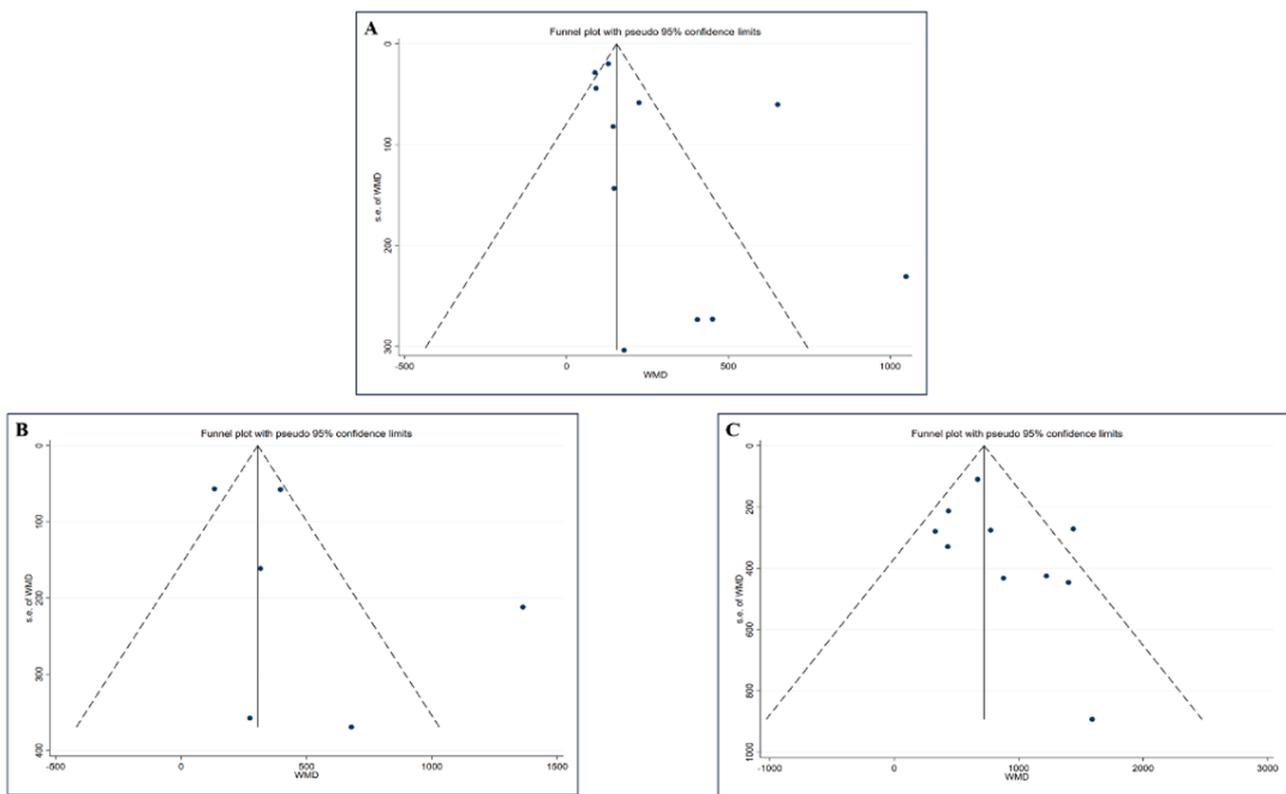


Fig. 5. (A-C) Funnel plots showing publication bias and heterogeneity for IIM vs IIM-ILD group (A), C-ILD vs RP-ILD group (B), and survival and death group (C).

Table 2
Egger's test for three groups meta-analysis studies.

Group	nStudy	t	p
IIM/IIM-ILD	8	1.58	0.149
C-ILD/RP-ILD	6	1.15	0.313
Survival/Death	10	1.32	0.225

(WMD= 632.56 ng/mL, 95% CI:217.92-1047.19, p=0.003) (Fig. 4).

Sensitivity analysis and publication bias

The sensitivity analysis demonstrated the stability of all meta-analysis results (Supplementary Fig. 1-3). Funnel plot analysis indicated the presence of heterogeneity in our study (Fig. 5 A-C). Furtherly, there was no publication bias detected by Egger's test for three groups meta-analysis (p > 0.05) (Table 2).

Discussion

Our study suggested that elevated SF level was clinically significant in IIM-ILD different stages and SF could serve as a potential biomarker for the occurrence and prognosis of IIM-ILD patients. To the best of our knowledge, this is the first systemic review and meta-analysis to focus on the role of SF in the occurrence, progression, and death of patients with IIM-ILD.

IIM-ILD refers to the non-infectious inflammation caused by IIM involvement in the lungs. In our results, the SF levels in patients with IIM-ILD were notably higher than those without IIM. It is well known that SF is considered an important protein reflecting the body's inflammatory state and is positively correlated with inflammatory signaling substances such as interleukin-6 (IL-6), tumor necrosis factor- α , and high-sensitivity C-reactive protein[31].

Inflammation can progress to pulmonary fibrosis through multiple pathways[32]. Ferritin is a crucial molecule in pathways related to oxidative damage and it was previously thought that increased ferritin levels could stabilize lysosomes within cells, protecting airway epithelial cells from oxidative damage[33]. However, recent studies have suggested that ferritin can also increase oxidative damage to lung epithelial cells through the autophagy pathway, thereby participating in the progression of pulmonary fibrosis[34]. In patients with systemic lupus erythematosus, SF is a clue to disease activity and renal involvement[35], suggesting that ferritin can be used to assess the CTD activity and organ involvement, including pulmonary involvement. For example, in systemic sclerosis-associated interstitial lung disease, SF levels are significantly higher than those without IIM[36]. Our subgroup analysis also confirmed that SF levels were higher in both DM-ILD patients and PM/DM-ILD patients compared to those without IIM, indicating the importance of ferritin in the development of IIM in IIM patients.

In our study, there was a higher level of SF in RP-ILD patients than in C-ILD patients, suggesting that SF levels reflect the rapid progression of IIM-ILD. Rapid disease progression is characterized by worsened clinical symptoms, a significant increase in imaging lesions, and the need for additional oxygen supplementation or tracheal intubation. Studies have pointed out that elevated SF can serve as a predictive signal for disease progression in patients with acute lung injury caused by COVID-19 infection, which is related to the inflammatory response induced by viral infection[37,38]. Inflammatory storm plays a vital role on the rapid progression of IIM. In PM/DM-related RP-ILD patients, there is not only a high level of SF[39], but also an increase of IL-6, interleukin-8 and interleukin-10, all of which are essential members of the inflammatory family and play their distinct roles in the process of acute lung injury[40, 41]. Additionally, ferritin can also aggravate acute lung injury by autophagy-mediated ferroptosis pathway[42], and it is worth mentioning that ferroptosis may also trigger inflammation leading to the acute lung injury[43]. Therefore, it is believed that SF may reflect disease progression by participating in the inflammatory response pathways involved in acute lung injury.

Furthermore, the prediction of death in patients with IIM-ILD was also an outcome indicator of concern in our study. Previous studies have identified SF as a risk factor for predicting death in IIM-ILD[44], but without quantitative analysis. Our results showed that the level of SF in the death group was significantly increased than that in the survival group, which may be related to the following factors. Firstly, SF is an indicator of rapid progression in IIM-ILD, signifying a rapid deterioration of the disease. Secondly, SF levels reflect systemic inflammatory status[45], and high SF level may indicate severe systemic inflammatory response. Finally, elevated SF levels are also associated with functional impairment of other important organs[46,47]. A study on COVID-19 patients revealed that increased SF levels not only indicated disease progression but also carried a higher risk of death[31], which was consistent with our results, suggesting that SF would be a reliable marker for predicting death in IIM-ILD.

There are some limitations in our study: (1) All included studies on

IIM-ILD were from Asian area and some studies did not mention the time of serum ferritin measurement, which may introduce selection and information bias. (2) IIM encompasses a large category of diseases, leading to inevitable heterogeneity in the included studies, but sensitivity analysis and Egger's test results support the stability and reliability of our results. (3) The effects of medications and comorbidities on disease progression and prognosis in patients with IIM-ILD could not be fully ruled out. (4) Anti-MDA5-associated DM-ILD is characterized by progressive development and high mortality risk. We attempted to explore the clinical significance of SF in patients with anti-MDA5 positive DM-ILD, however, the included studies did not report SF as a major observation indicator, thus preventing the extraction of relevant data. Moreover, due to the specificity of SF, combining multiple biomarkers is necessary to predict the occurrence, progression and prognosis of IIM-ILD. It is worth noting that we found less studied on SF in other CTD-ILD than IIM-ILD, and the potential clinical value of SF in other types of CTD-ILD remained unclear.

In conclusion, our findings demonstrate that elevated SF level served as a clinically biomarker for the occurrence, progression, and death of IIM-ILD and play a significant role to evaluate the condition and prognosis in IIM-ILD patients. However, there are still some issues needed to be further investigated, including exploring the molecular mechanisms associated with SF and its potential participation in other CTD-ILD.

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Data availability statement

The original data presented in the study are included in the article/ Supplementary Material, further inquiries can be directed to the corresponding author.

Author contribution

Conception and design: X He, J Ji, L Guo; database search and data extraction: X He, J Ji, X Chen; study evaluation: S Fang, Z Luo, X Chen; planned and conducted the statistical analysis: X He, X Chen, H Yan; drew all the figures and tables: X He; draft the manuscript: X He, J Ji, X Chen; corrected and validated the manuscript: X He, L Guo.

Declaration of Competing Interest

Authors have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.semarthrit.2023.152350](https://doi.org/10.1016/j.semarthrit.2023.152350).

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