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Unveiling the role of circulating periostin in patients with idiopathic pulmonary fibrosis: A prognostic meta-analysis

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Abstract. *Background:* Periostin measurement has been suggested as a noninvasive biomarker for assessing the likelihood of IPF progression and predicting patient outcomes, but these results aren't entirely consistent. Therefore, we conducted a meta-analysis to study the relation between serum periostin and IPF. *Methods:* We conducted a comprehensive search in major electronic biomedical databases of (PubMed, Scopus, Cochrane Library, EMBASE and Web of Science) spanning from inception to September 2024. Meta-analysis of included studies was done, and quantitative data were pooled as standardized mean difference (SMD), odd rations (ORs) and coefficient (r) values, with corresponding 95% confidence intervals (CIs). *Results:* Eleven articles were included in final meta-analysis. Our results showed that there was no significant difference in periostin levels between IPF patients and healthy controls (SMD: 2.59, 95% CI: -0.59 to 5.77, p= 0.11). Moreover, it was shown that IPF patients with a progressive disease have higher periostin levels compared to those who remain stable (SMD: 0.52, 95% CI: 0.29 to 0.75, p>0.0001). In addition to, higher serum periostin levels were significantly associated with shortened overall survival among IPF patients (RR: 3.70, 95% CI: 1.84 to 7.43, p>0.0001). Finally, there was a significant negative correlation between periostin levels and relative decline in DLCO and VC over the follow-up period (COR: -0.36, 95% CI, -0.58 to -0.10), (COR: -0.49, 95% CI, -0.63 to -0.34) respectively. *Conclusions:* This study concludes that periostin may be a valuable biomarker for predicting prognosis in IPF patients.

Key words: IPF, periostin, meta-analysis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrosing interstitial lung disease (ILD) of unclear cause (1). Distinguishing IPF from other types of ILDs is quite important because patients with IPF typically have poor prognosis and high morbidity and mortality rates. The diagnosis of IPF in modern clinical practise is made by high-resolution computed tomography (HRCT) scan of the lung which usually shows a pattern of usual interstitial pneumonia (UIP) that is characterized by a reticular pattern with honeycombing, that may be associated with traction bronchiectasis, predominantly subpleural and basal in distribution, these abnormalities might be enough to diagnose IPF in patients with a recently discovered ILD of unclear etiology, without the necessity for performing invasive procedures (2). The majority of patients with IPF show a progressive disease course of IPF and patients exhibit different patterns of progression that can range from slowly progressive pattern to rapid decline in pulmonary function and death, so stratifying patients who are at risk of disease progression and death is necessary to direct physicians toward the appropriate treatment regimens. This need has shifted clinical

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investigations toward incorporating blood-derived biomarkers (eg, periostin, matrix metalloproteinase-7 (MMP7), surfactant protein-A (SP-A), surfactant protein-D (SP-D)) to use as potential prognostic markers in IPF that can reflect disease severity and progression, although none have been adapted in current clinical practise (3-5). POSTN (Periostin), historically named osteoblast specific factor 2, is an extracellular matrix protein that plays a significant role in stiffening the extracellular matrix of the lungs through inducing production and cross-linking of collagen fibers, indicating its valuability in the evolution and progression of lung fibrosis (6-8). Previous studies suggested that IPF patients showed elevated serum periostin levels, suggesting the value of periostin as a key prognostic biomarker in IPF (9,10). We aimed to assess the clinical utility of Perisotin in evaluating prognosis in IPF patients by conducting a meta-analysis of published studies.

Methods

Data sources and search strategy

The present meta-analysis was strictly conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered in the international prospective register of systematic reviews (PROSPERO) with registration number of (CRD42024513724). We conducted a comprehensive search in major electronic biomedical databases of (PubMed, Scopus, Cochrane Library, EMBASE and Web of Science) spanning from 1989 to September 2024, to identify all relevant studies. The following search terms were used: ((“periostin” OR "POSTN Protein" OR "OSF-2 protein" OR "osteoblast-specific factor 2") AND ("idiopathic pulmonary fibrosis" OR "IPF" OR "interstitial lung disease" OR "Usual Interstitial Pneumonia" OR "UIP")).

Inclusion and exclusion criteria

Studies eligible for the this study had to meet the following criteria: (1) adult patients (18 years or older) diagnosed with idiopathic pulmonary fibrosis based on standard diagnostic criteria; (2) studies that measured serum levels of periostin and compared them with healthy controls (3) studies that measured serum levels of periostin in the progressive phase of the disease and compared them with the non-progressive phase; (4) studies that reported the correlation between perisotin level and pulmonary function test (PFT) parameters, including: baseline forced vital capacity (FVC), baseline diffusing capacity for carbon monoxide (DLCO), short term change in DLCO and short term change in vital capacity (VC); (5) studies that investigated the correlation between perisotin level and fibrosis score measured on high-resolution computed tomography (HRCT); (6) studies that investigated the association between perisotin level and overall survival; (7) Observational studies including prospective and retrospective cohort studies, as well as case-control studies. On the other hand, studies of the following characteristics were considered ineligible: (1) case reports, conference abstracts and narrative reviews; (2) studies that did not specifically assess periostin levels as a biomarker for IPF or that included different interstitial lung diseases without clear segregation of IPF patients; (3) non-English studies; (4) studies with insufficient quantitative data for the meta-analysis.

Screening

First, two independent reviewers assessed titles and abstracts identified from the initial search to determine eligibility based on the eligibility criteria. Any study that appeared relevant or ambiguous was moved to the full-text screening stage. Second, the full-text articles were retrieved and assessed in detail. Each full-text article was evaluated independently by two reviewers to confirm eligibility. Conflicts between reviewers regarding inclusion were resolved by discussion. A PRISMA flow diagram was created to visually represent the studies’ identification and selection process.

Data extraction

Two reviewers independently extracted data from included studies using a standardized sheet. The following data were extracted from each study: (1) study characteristics: first author, year of publication, country and study period; (2) patient characteristics: definition of included patients, sample size, age, gender, smoking status and follow-up duration; (3) study outcomes: which were previously mentioned above.

Quality assessment

To ensure the reliability and validity of included studies, two independent reviewers evaluated the

quality and risk of bias of each study, and conflicts were resolved with a third reviewer's opinion. The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) (11). Studies with a NOS score of ≥ 7 stars were considered high quality, and the studies with a NOS score of < 7 stars were considered low quality.

Statistical analysis

The data were synthesized and analyzed using the RStudio version 3.4.3 with package meta. Standardized mean difference (SMD) with 95% CIs was used to measure the effect size in order to mitigate the impact of absolute value and measurement unit differences between studies. Studies that provided periostin data in the form of median and interquartile range were mathematically converted to mean and standard deviation (12,13). We also pooled odd ratios (ORs) with their corresponding 95% CIs to estimate the association between perisotin and overall survival. Summary correlation coefficient (r) values between perisotin and PFT paramters and fibrois score were also extracted. To obtain variance-stabilized correlation coefficients, Pearson's correlation coefficients were transformed into Fisher's Z scores before the pooled estimate. Then, the random effects model was used to calculate the pooled correlation coefficient. The level of heterogeneity across studies was assessed using the I^2 statistic. An I^2 value of 25% represented low heterogeneity, 50% moderate heterogeneity, and 75% or higher indicated substantial heterogeneity. If heterogeneity was detected, we used random-effects models to pool the results, as it accounts for variability across studies. We performed sensitivity analysis by removing each study at a time from the meta-analysis, in order to assess its effect on the pooled results. For outcomes with low heterogeneity, a fixed-effects model was used. Furthermore, meta-regression was done in cases of high heterogeneity with reporting bubble plots. Publication bias was assessed using Egger's test and funnel plots. P <0.05 indicated that the difference was statistically significant.

Results

Literature search

A total of 601 articles were retrieved from our search: 116 from PubMed, 94 from Scopus, 9 from Cochrane, 293 from WOS and 89 from Embase. After removing 170 duplicates, 341 of the articles were included in the title and abstract screening. Of the 341 articles, only 81 articles were eligible for full-text screening. 70 articles were excluded during full-text screening, leaving 11 studies to be included in our analysis. The PRISMA flowchart illustrating the search, screening, and exclusion reasons is displayed in (Figure 1). Studies were conducted between 1992 and 2023 and included 3254 participants. The baseline characteristics of included studies are shown in (Table S1). While using New Castle Ottawa's, we found that three of our included studies demonstrated low quality and eight studies revealed high quality, as shown in (Table S2).

Outcomes

Meta-analysis of periostin levels in comparison of IPF patients and healthy controls

Five studies measured periostin levels in IPF patients compared to healthy controls. There was no significant difference in periostin levels between IPF patients and healthy controls (SMD: 2.59, 95% CI: -0.59 to 5.77, p= 0.11) (Figure 2). A high level of heterogeneity was detected with I^2 = 97.7%. Regression meta-analysis based on age was done, and there was no significant correlation (p=0.6838) (Figure 3). The Egger's test for funnel plot asymmetry showed a significant publication bias (z = 3.8025, p = 0.0001). The limit estimate was -3.3402 (CI: -6.6885, 0.0081), indicating that smaller studies may report more extreme effects than larger studies, suggesting potential publication bias in the included studies (Figure S1).

Meta-analysis of periostin levels in comparison of patients with progressive IPF and non-progressive IPF

Four studies assessed serum periostin levels in patients with progressive IPF compared to non-progrssive IPF. The progression of the disease was assessed over 48 weeks. It was shown that there was no significant difference in periostin level between patients with progressive IPF and non-progrssive IPF (SMD: -0.21, 95% CI: -1.55 to 1.14, p=0.7649) (Figure 4). There was a high level of heterogeneity in this analysis I^2= 91.6%. A sensitivity analysis was done by excluding Kayikci et al, heterogeneity was resolved with I^2= 0%, heterogeneity was resolved

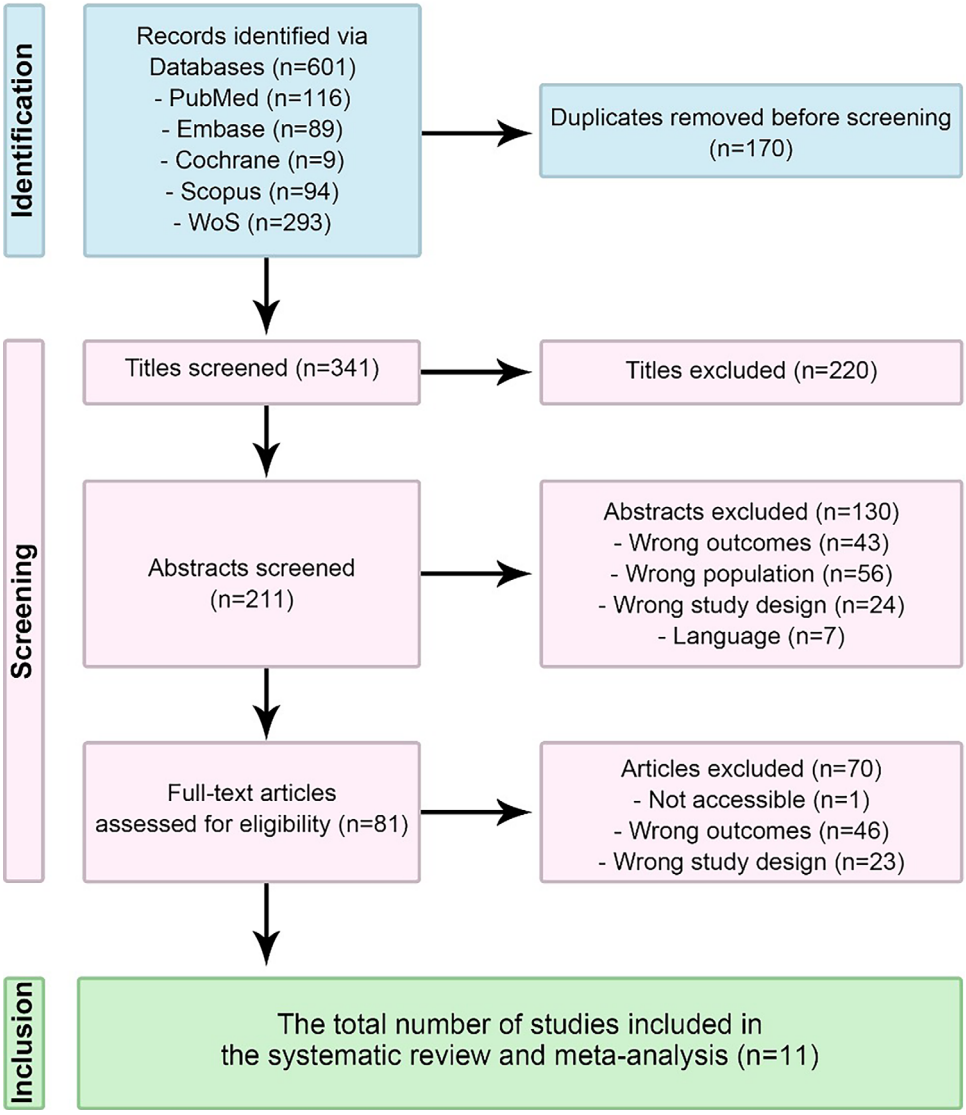

Figure 1. Flow diagram of included studies.

with I^2 = 0% and results showed that periostin levels among patients with progressive disease were significantly higher compared to patients with non-progressive disease (SMD: 0.52, 95% CI: 0.29 to 0.75, p>0.0001) (Figure 5). The Egger's test for funnel plot asymmetry showed a significant publication bias (p = 0.00447) (Figure S2).

Association between periostin levels and overall survival

Three studies studied the association between periostin levels and overall survival among IPF patients. Our analysis showed that higher blood periostin levels were significantly associated with shorter overall survival (RR: 3.70, 95% CI: 1.84 to 7.43, p>0.0001) with no heterogeneity among included studies I^2= 0% (Figure 6). The Egger's test for publication bias showed no potential bias with funnel symmetry (p = 0.7771) (Figure S3).

Correlation between periostin levels and baseline FVC

Four studies reported the correlation between periostin levels and baseline FVC. Our analysis showed no significant correlation between periostin levels and baseline FVC (COR: -0.25, 95% CI, -0.63 to 0.23)

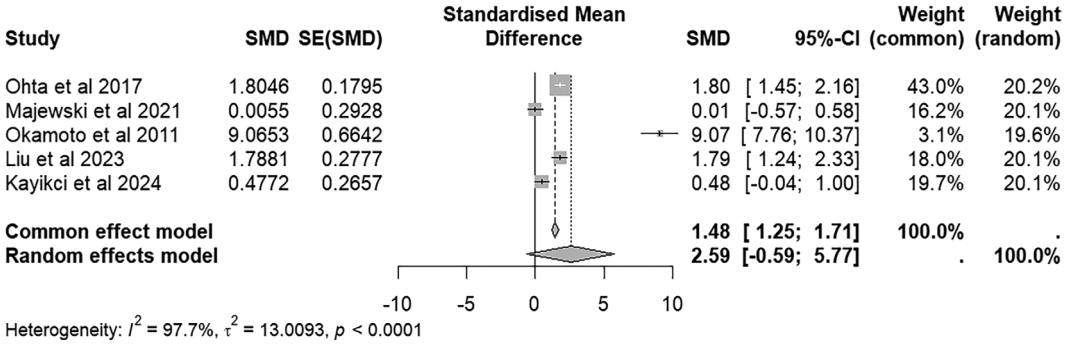

Figure 2. Serum periostin levels comparisons between IPF and healthy controls.

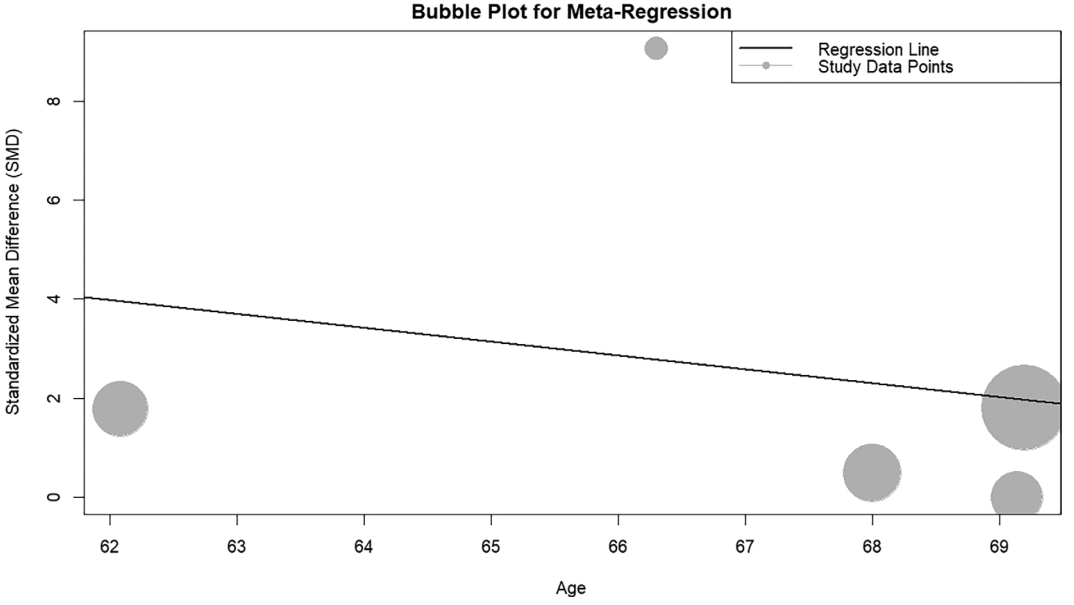

Figure 3. Bubble plot showing regression analysis of periostin levels based on age of participants.

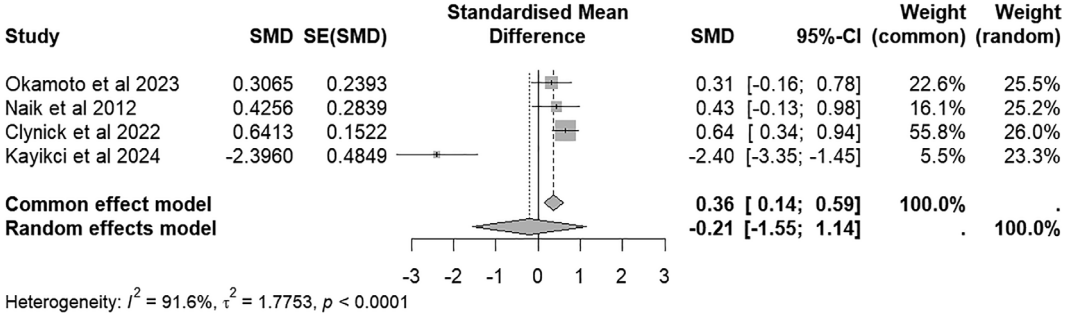

Figure 4. Serum periostin levels comparisons between progressive and non-progressive IPF.

(Figure S4). A significant level of heterogeneity with I^2= 68.7% was detected. Sensitivity analysis was done by excluding Shimizu et al., heterogeneity was resolved with no change in the results (COR: -0.11, 95% CI, -0.4 to 0.21) (Figure S5). Regarding Publication bias, there was no significant asymmetry in the funnel plot (0.8102), implying that there is no evidence of publication bias in the included studies. (Figure S6).

Correlation between periostin levels and baseline DLCO

Six studies reported the correlation between periostin levels and baseline DLCO. Our analysis showed significant correlation between periostin levels and baseline DLCO (COR: -0.17, 95% CI, -0.3 to -0.02) (Figure S7). There was a minimal degree of heterogeneity with I^2= 27.1%. Sensitivity analysis was done by excluding Shimizu et al., heterogeneity was resolved, and results showed no significant correlation between periostin levels and baseline DLCO (COR: -0.11, 95% CI, -0.24 to 0.03) (Figure S8). In terms of Publication bias, there was no significant asymmetry in the funnel plot (0.531), implying that there is no evidence of publication bias in the included studies (Figure S9).

Correlation between periostin levels and change in DLCO

Four studies reported the correlation between periostin levels and change in DLCO. Our analysis showed significant negative correlation between periostin levels and change in DLCO (COR: -0.36, 95% CI, -0.58 to -0.10) (Figure S10). A high level of heterogeneity was found with I^2= 78.3%. We performed a meta-regression by number of smokers analysis; there was a significant correlation between number of smokers and change in DLCO (P= 0.0003) (Figure S11). Regarding Publication bias, there was no significant asymmetry in the funnel plot (p=0.8556), implying that there is no evidence of publication bias in the included studies. (Figure S12).

Correlation between periostin levels and change in VC

Two studies reported the correlation between periostin levels and change in VC. Our analysis showed significant negative correlation between periostin levels and change in VC (COR: -0.49, 95% CI, -0.63 to -0.34) with no evidence of heterogeneity among studies (Figure S13).

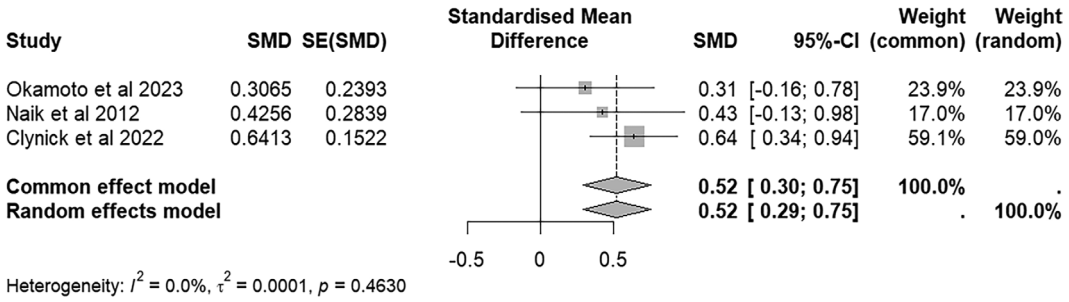

Figure 5. Sensitivity analysis of serum periostin levels comparisons between progressive and non-progressive IPF.

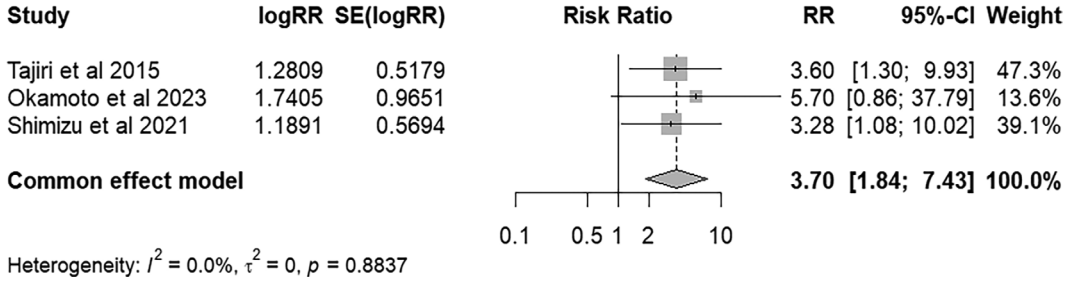

Figure 6. Association between periostin levels and overall survival.

Correlation between periostin levels and fibrosis score

Three studies reported the correlation between periostin levels and fibrosis score measured on HRCT. Our analysis showed no significant correlation between periostin levels and fibrosis score (COR: 0.63, 95% CI, -0.20 to 0.93). A high level of heterogeneity was found with I^2= 96.2% (Figure S14). Furthermore, meta-regression based on age was conducted, there was a no correlation between age and fibrosis score (P=0.4138) (Figure S15). The Egger's test for funnel plot asymmetry showed a significant publication bias (p<0.0001) (Figure S16).

Discussion

Biomarkers that can reliably predict clinical outcomes and prognosis in IPF have been widely advocated in the literature. Periostin has been suggested as one of the laboratory tests that could play this role. Multiple studies reported that higher serum levels of periostin is linked to decline in lung function and worse outcomes in IPF patients (14-16). Therefore, we conducted a meta-analysis to study the prognostic utility of periostin in IPF, focusing on its association with key pulmonary function parameters, disease progression, and overall survival. Our results showed that there was no significant difference in periostin levels between IPF patients and healthy controls. To explore potential sources of heterogeneity, we conducted a meta-regression using age as a covariate. Regression analysis showed no significant relationship between age and periostin effect size, suggesting that observed heterogeneity was not primarily caused by age differences among study populations. Moreover, the results showed that periostin levels were significantly associated with disease progression and overall survival, in which IPF patients with elevated periostin levels showed more disease progression and shortened overall survival. This finding aligns with previous studies that link periostin with key fibrotic pathways in IPF, including extracellular matrix deposition and remodeling (14,15). Considering the progressive and irreversible nature of IPF, this association reinforces periostin's potential utility as a biomarker for high-risk individuals, which may help in earlier intervention and closer monitoring of disease course. Regarding pulmonary function test, statistically significant negative correlations were found between periostin levels and changes in D_{LCO} and VC, with pooled correlation coefficients of (COR: -0.36, 95% CI, -0.58 to -0.10) and (COR: -0.49, 95% CI, -0.63 to -0.34), respectively. These findings indicate that increased periostin levels correspond with more severe declines in lung function over time, highlighting its potential as a marker of IPF progression. To explore potential sources of heterogeneity, we conducted a meta-regression using the number of smokers as a covariate. The analysis showed a statistically significant association between the number of smokers and change in D_{LCO}, this suggests that smoking status may influence the relationship between periostin and decline in DLCO, potentially through its effect on inflammatory and fibrotic pathways that modulate periostin production. However, baseline D_{LCO} and FVC values were not significantly associated with periostin, suggesting that periostin may reflect dynamic disease progression rather than initial severity of IPF. Fibrosis score analyses revealed a positive but non-significant association with periostin, suggesting periostin may be more reflective of ongoing fibrogenesis rather than established fibrosis (17). This finding highlights periostin's potential as a marker for active fibrotic changes, which may be particularly valuable in assessing response to antifibrotic therapies. To explore potential sources of heterogeneity, we conducted a meta-regression using age as a covariate. Regression analysis showed no significant relationship between age and fibrosis score. The significant heterogeneity and the lack of a clear variable (such as age) to explain the variability point to the need for more well-designed, larger studies to clarify this association. Periostin's utility in evaluating active fibrogenesis aligns with its role in fibrogenic pathways, further suggesting it could be effective for monitoring disease response in real-time (15). Clinically, these findings underscore periostin's potential to serve as a prognostic marker in IPF. Regular monitoring of periostin levels could provide early warnings of disease progression, aiding in risk stratification and personalized treatment planning. Periostin's correlation with progressive functional decline also supports its role in assessing therapeutic response, particularly for patients undergoing antifibrotic treatment, where periostin

might serve as an indicator of treatment efficacy. While periostin has demonstrated prognostic potential in IPF, it is important to acknowledge that elevated periostin levels have also been observed in other interstitial lung diseases (ILDs), including granulomatous conditions such as sarcoidosis. This overlap raises questions regarding periostin specificity for IPF. For instance, periostin expression has been found to be elevated in pulmonary sarcoidosis, where it may reflect ongoing fibrotic activity rather than a disease-specific process (18). Future studies should account for potential confounding from coexisting respiratory comorbidities when interpreting periostin levels (19). Given the periostin role in extracellular matrix remodeling and fibrogenesis, it is expected that its expression is not exclusive to IPF but may also extend to other fibrotic ILDs, such as chronic hypersensitivity pneumonitis and connective tissue disease-associated ILD (20,21). While this reduces its diagnostic specificity, it may still hold value as a prognostic indicator of fibrotic progression across the ILD spectrum. For IPF-specific trials, careful phenotyping and biomarker-driven stratification may be necessary to account for this broader expression. To enhance prognostic accuracy, periostin could be integrated into a multimarker panel alongside established biomarkers such as MMP-7, KL-6, or surfactant protein D (22,23). This composite approach may improve risk stratification and disease monitoring in IPF by compensating for the individual limitations of each biomarker. Future prospective studies are needed to validate such combinations and define their role in clinical practice. Our study had some limitations, including the substantial heterogeneity observed in the reported outcomes, which could potentially be attributed to the observational nature of the included studies, their relatively modest sample sizes, and the absence of pre-specified power calculations. Additionally, variability in IPF severity among patients may have contributed to the observed heterogeneity. Notably, the correlation with baseline FVC and fibrosis scores remains unclear, as evidenced by overlapping confidence intervals, which suggests unresolved heterogeneity. To address this, we performed regression analyses to explore the impact of different covariates on the overall findings. Future studies should aim to include well-defined IPF populations with larger sample sizes and pre-specified power calculations, which may help mitigate these sources of heterogeneity and clarify the relationships between periostin levels and clinical outcomes.

Conclusion

Periostin appears to be a promising biomarker for IPF prognosis, especially in tracking disease progression and treatment response. However, the observed heterogeneity and variation in outcomes across studies call for larger, longitudinal studies to validate periostin's prognostic utility. Future research should prioritize standardizing periostin measurement techniques and incorporate periostin alongside clinical, imaging, and pulmonary function metrics to better clarify its role in managing IPF.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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ANNEX

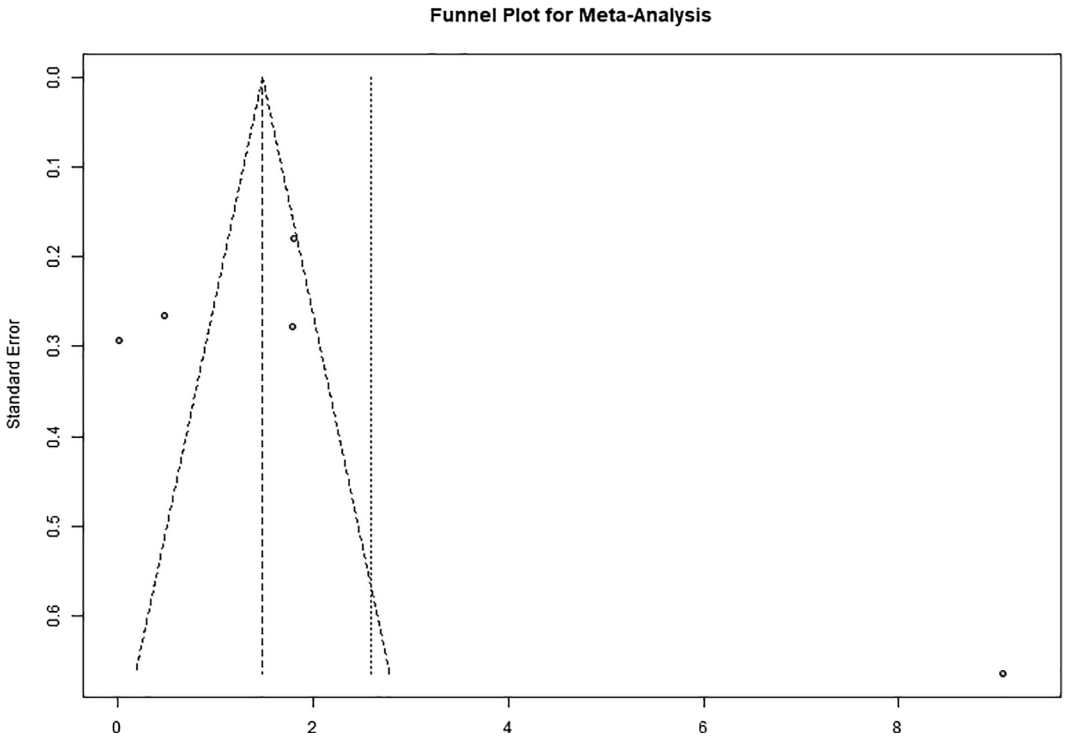

Figure S1. Funnel plot for publication bias in periostin levels outcome.

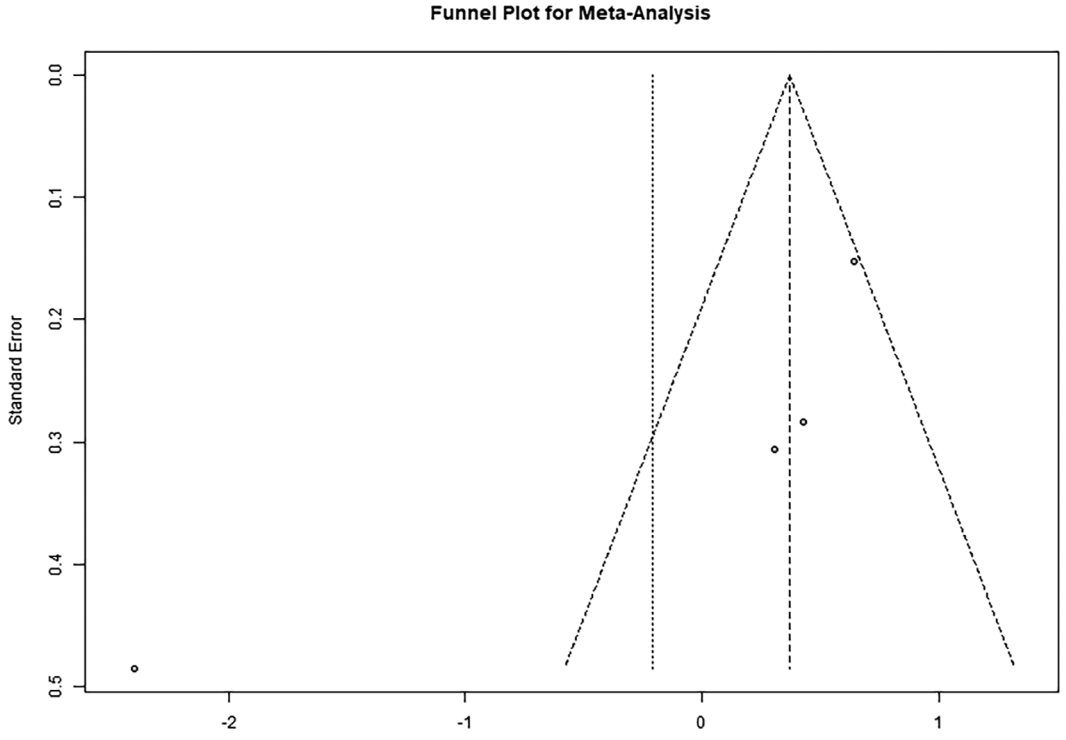

Figure S2. Funnel plot for publication bias in progression outcome.

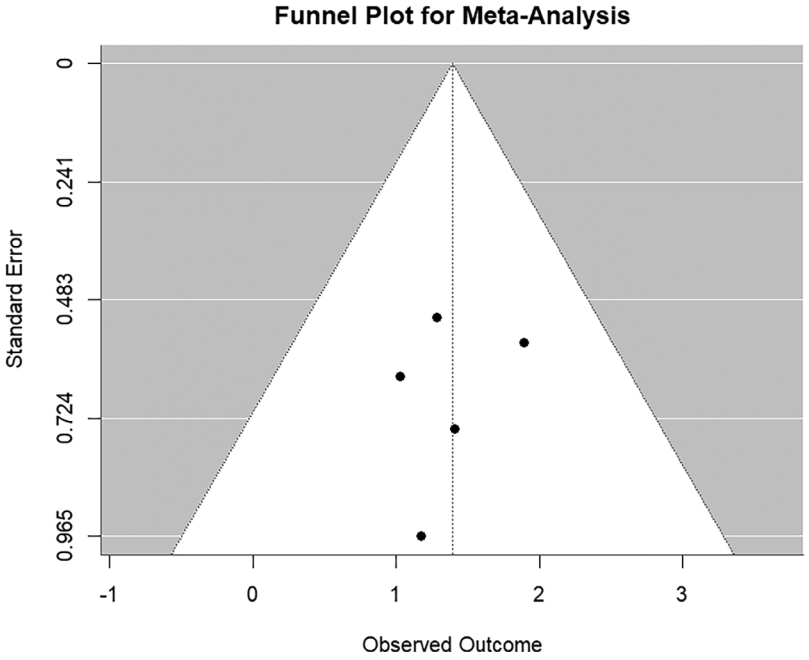

Figure S3. Funnel plot for publication bias in overall survival levels outcome.

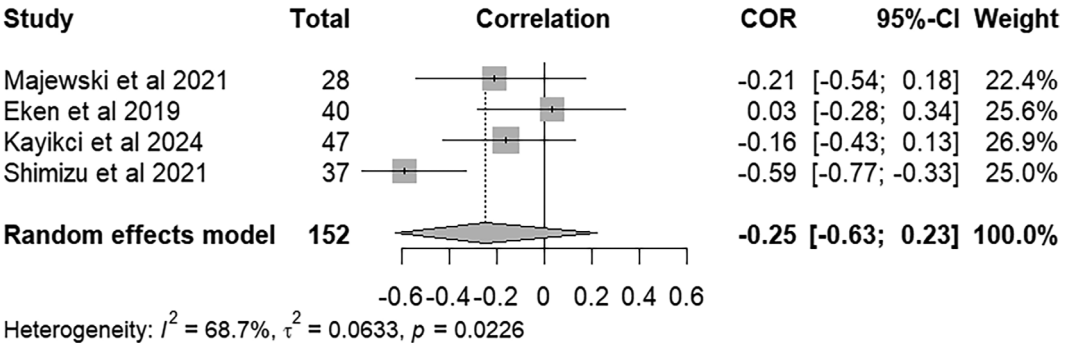

Figure S4. Forest plot of periostin and baseline FVC.

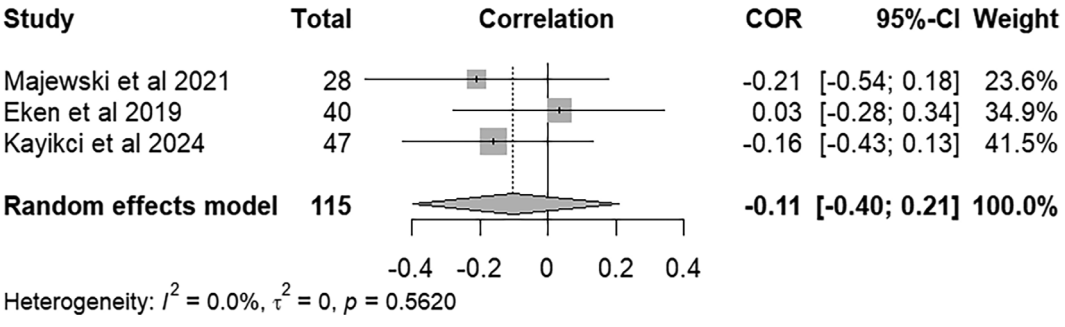

Figure S5. Sensitivity analysis of periostin and baseline FVC.

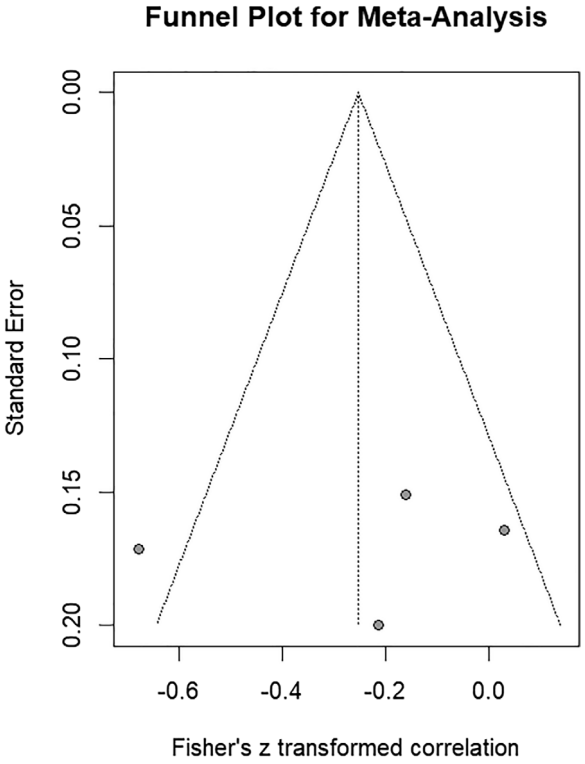

Figure S6. Funnel plot for publication bias in Correlation between periostin levels and baseline FVC outcome.

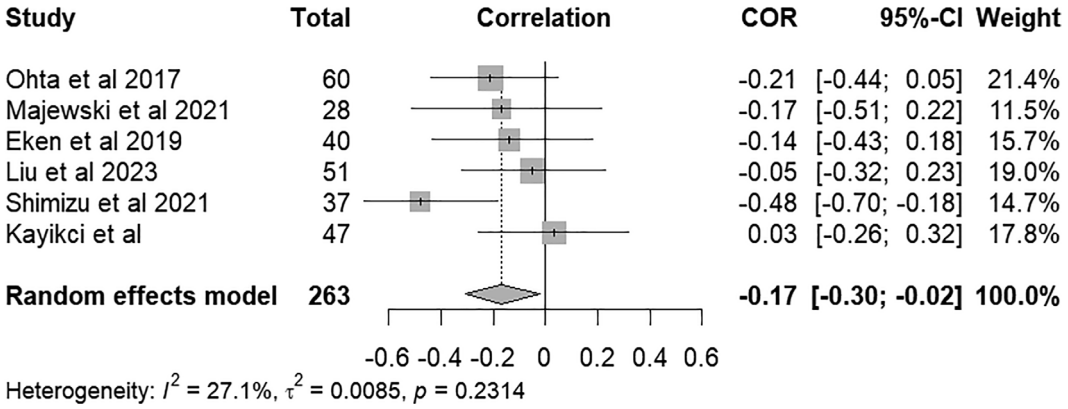

Figure S7. Forest plot of periostin and baseline DLCO.

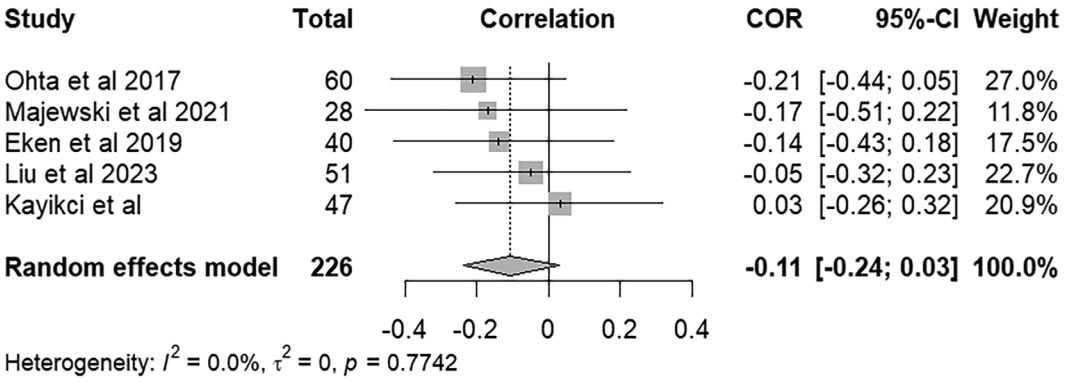

Figure S8. Sensitivity analysis of periostin and baseline DLCO.

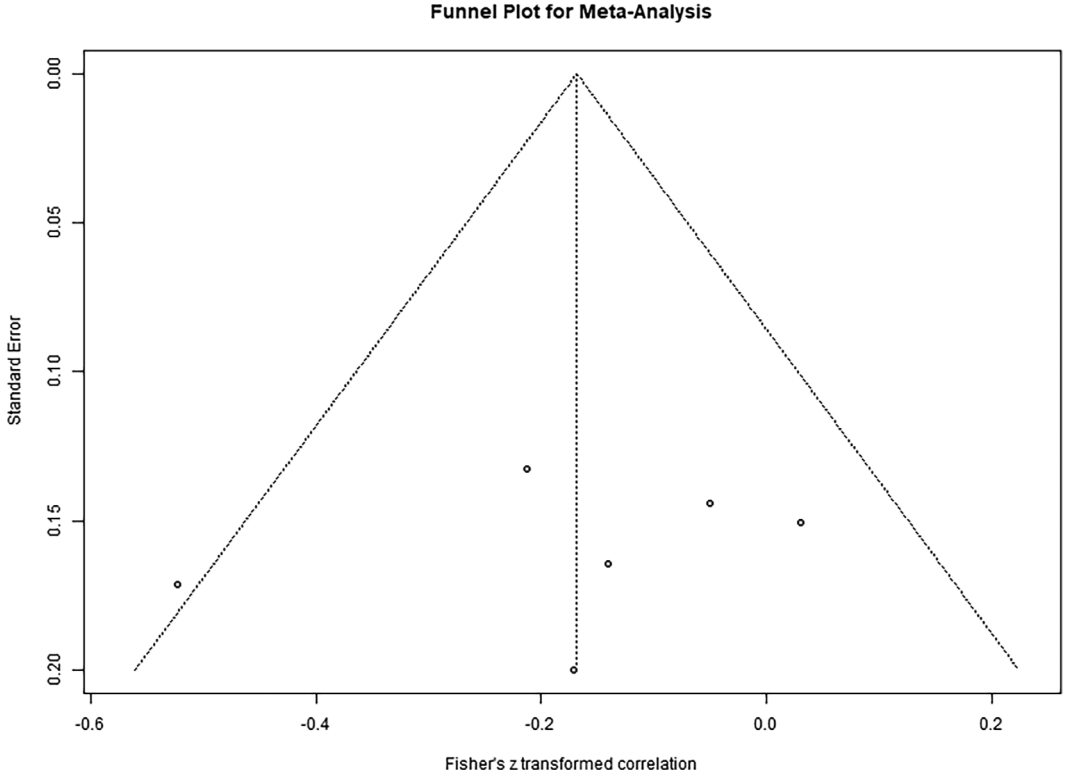

Figure S9. Funnel plot for publication bias in Correlation between periostin levels and baseline DLCO outcome.

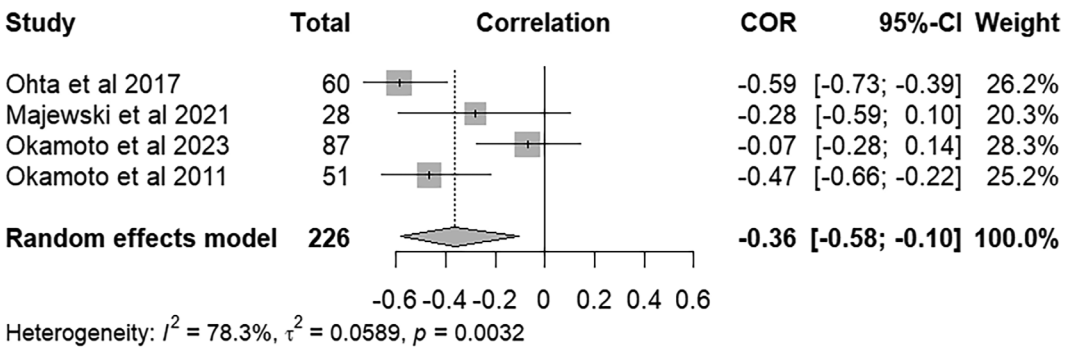

Figure S10. Forest plot of periostin and change in DLCO.

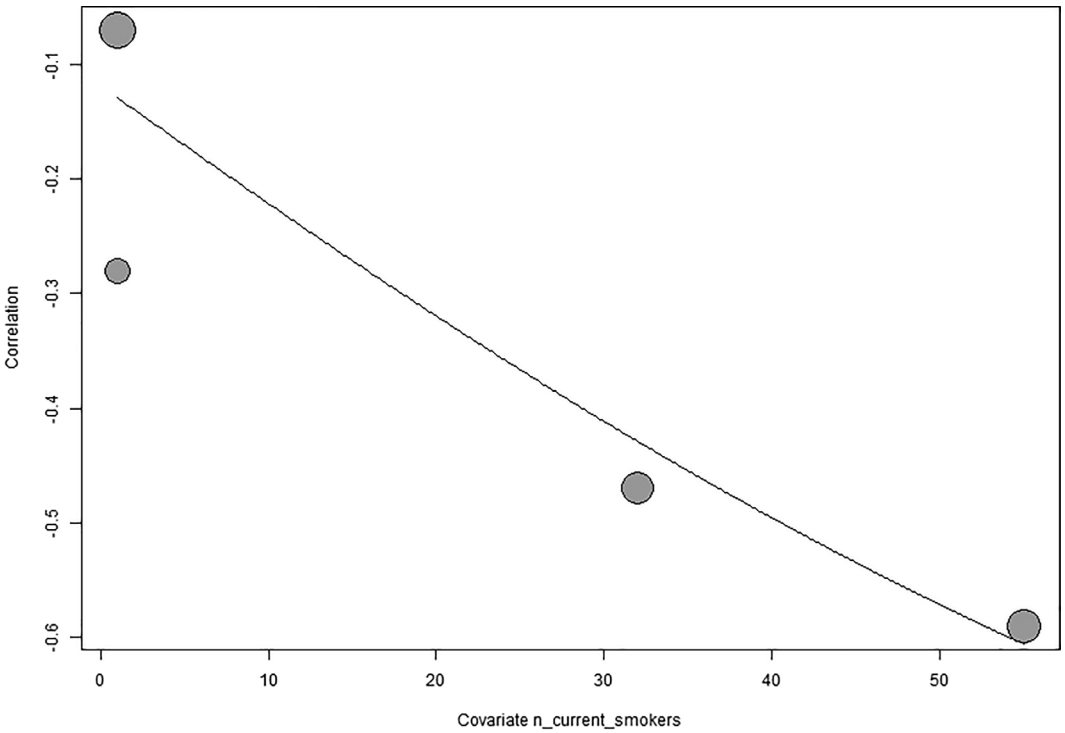

Figure S11. Bubble plot showing regression analysis of change in DLCO based on number of current smokers of participants.

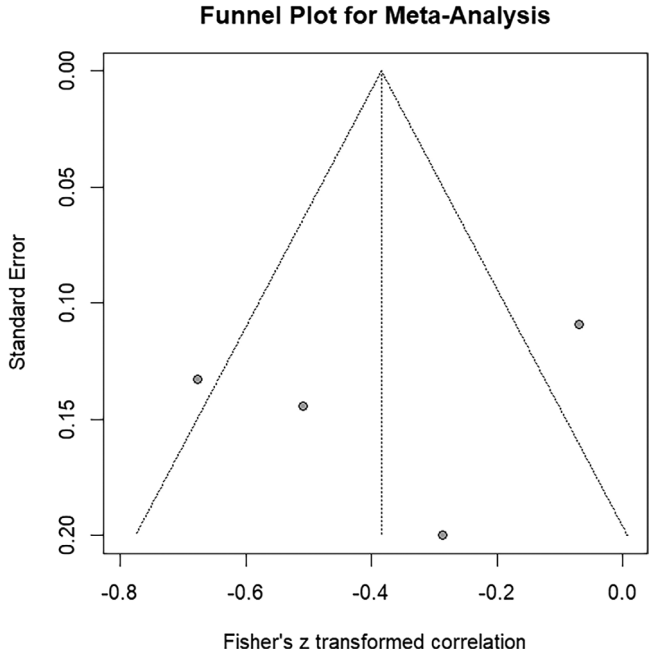

Figure S12. Funnel plot for publication bias in correlation between periostin levels and change in DLCO outcome.

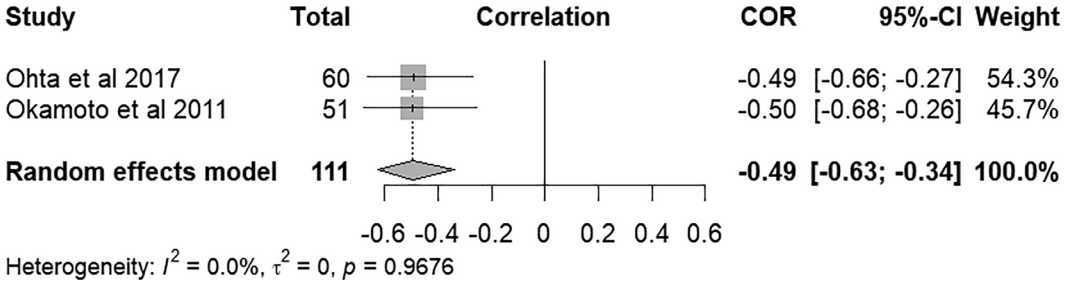

Figure S13. Forest plot of periostin and change in VC.

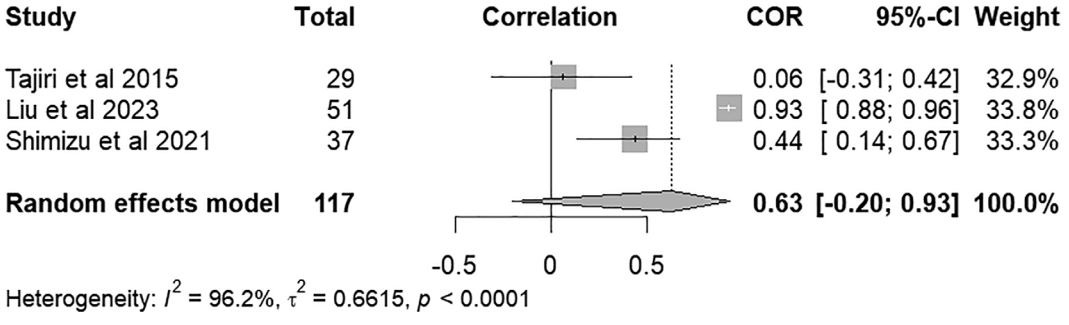

Figure S14. Forest plot of periostin and fibrosis score.

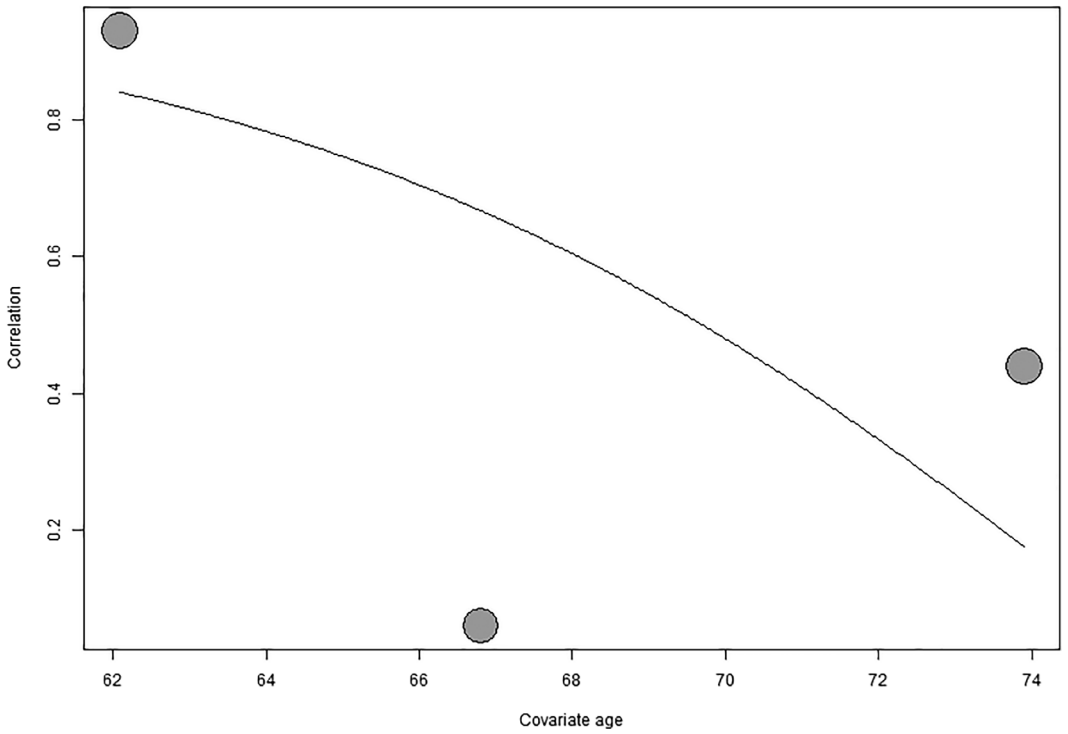

Figure S15. Bubble plot showing regression analysis of fibrosis score based on age of participants.

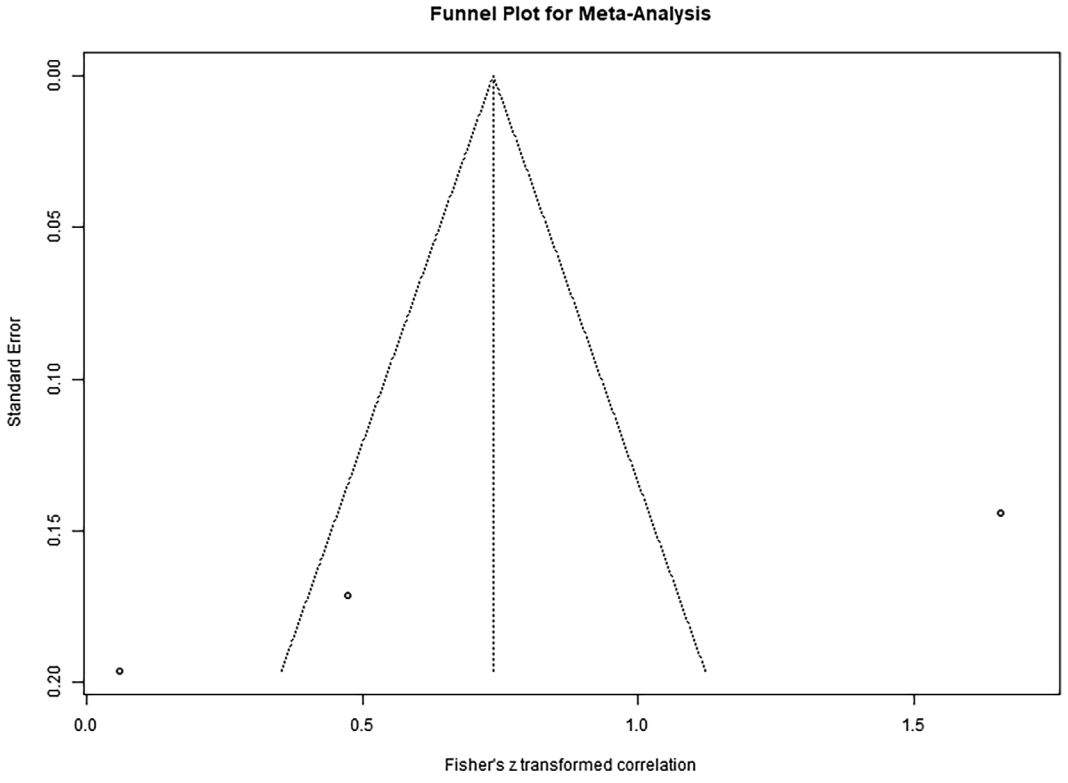

Figure S16. Funnel plot for publication bias in correlation between periostin levels and fibrosis score outcome.

Table S1. Characteristics of included studies

Study ID	Year	Study period	IPF patients				Non - IPF patients				Follow-up period
			Patients (n)	Age	Male/ Female (n)	Current smoking (n)	Patients (n)	Age	Male/Female (n)	Current smoking (n)	
Ohta et al (1)	2017	June 2011 to June 2014	60	69.2 ± 8.1	(55/5)	55	fNSIP: 7, HC: 137	fNSIP: 66.9 ± 7.1, HC: 41.1 ± 11.5	fNSIP: (1/6), HC: (91/46)	fNSIP: 2, HC: NA	12 months
Tajiri et al (2)	2015	2004 to 2014	29	66.8 ± 9.0	(27/2)	26	NA	NA	NA	NA	1035.2 days
Majewski et al (3)	2021	NA	28	69.14 ± 7.86	(17/11)	1	HC: 20	68.40 ±6.11	(10/10)	8	24 months
Eken et al (4)	2019	June 2016 to September 2016	40	65.05 ± 7.27	(31/9)	NA	NA	NA	NA	NA	28.5 months (median)
Okamoto et al (5)	2023	2015 to 2021	87	72.0 (68.0–76.0)	(78/9)	1	NA	NA	NA	NA	1174.0 (928.0–1537.0) days (median (interquartile range))
Okamoto et al (6)	2011	1994 to 2008	51	66.3 ± 1.2	(43/8)	32	fNSIP= 20, cNSIP= 7 COP= 14 HC=71	fNSIP: 56.0± 2.0, cNSIP: 64.6± 2.0, COP: 63.4±4.8, HC: 60.7 ± 2.1	fNSIP: (9/11), cNSIP: (3/4), COP: (8/6) HC:(40/26)	fNSIP: 9, cNSIP: 1, COP:6, HC:29	NA
Naik et al (7)	2012	NA	54	64.27 ± 8.19	(39/15)	NA	HC: 8	NA	(2/6)	NA	80 weeks (max)
Liu et al (8)	2023	January 2020 and May 2022	51	62.08 ± 9.29	(44/7)	NA	27	44.37± 15.77	(14/13)	NA	195.27 days (mean)

Table S1 (*Continued*)

Study ID	Year	Study period	IPF patients				Non - IPF patients				Follow-up period
			Patients (n)	Age	Male/ Female (n)	Current smoking (n)	Patients (n)	Age	Male/Female (n)	Current smoking (n)	
Clynick et al (9)	2021	NA	189	69.1±7.8	(136/53)	NA	NA	NA	NA	NA	12 months
			205	73.2±8.7	(152/53)	NA	NA	NA	NA	NA	12 months
			122	70.6±8.0	(96/26)	NA	NA	NA	NA	NA	12 months
Shimizu et al (10)	2021	January 2013 to March 2017	48	NA	NA	NA	HC = 5	NA	NA	NA	3 months
Kayikci et al (11)	2024	NA	47	68±7	(39/8)	11	non-IPF ILD = 27, HC= 21	non-IPF ILD = 65±8, HC= 66±6	non-IPF ILD = (14/13), HC= (11/10)	non-IPF ILD = 4, HC= 0	NA

Abbreviations: IPF: idiopathic pulmonary fibrosis; fNSIP: fibrotic Non-specific interstitial pneumonia; cNSIP: cellular Non-specific interstitial pneumonia ILD: interstitial lung disease; COP: cryptogenic organizing pneumonia; HC: healthy controls; NA: Not Available.

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Table S2. Quality assessment of the included studies.

Author (Year)	Selection				Comparability		Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	The outcome of interest was not present at the start of the study	Comparability of cohorts		Assessment of outcome	Sufficient follow-up time	Adequacy of follow-up	
					Age/Sex	Other factors				
Kayikci (2024)	★	★	★	★	-	-	★	-	★	6
Okamoto (2023)	★	-	★	★	★	★	★	★	★	8
Liu (2023)	★	★	★	★	-	-	★	★	★	7
Clynick (2022)	★	-	★	★	★	★	★	★	★	8
Shimizu (2021)	★	★	★	★	★	★	★	★	★	9
Majewski (2021)	★	★	★	★	★	★	★	★	★	9
Eken (2019)	★	-	★	★	-	-	★	★	★	6
Ohta (2017)	★	★	★	★	★	★	★	★	★	9
Tajiri (2015)	★	-	★	★	★	★	★	★	★	8
Naik (2012)	★	★	★	★	★	★	★	★	★	9
Okamoto (2011)	★	★	★	★	-	-	★	-	★	6

★: One point