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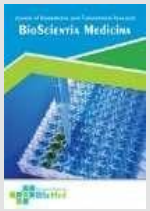

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Predictive Value of Circulating Pro-Fibrotic Cytokines for Progression in Idiopathic Pulmonary Fibrosis and Progressive Pulmonary Fibrosis (PPF): A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: The clinical trajectory of patients with idiopathic pulmonary fibrosis (IPF) and the broader phenotype of progressive pulmonary fibrosis (PPF) is highly variable. Current prognostic models lack precision, highlighting an urgent need for reliable biomarkers. Circulating pro-fibrotic cytokines are implicated in fibrogenesis, but their individual predictive utility for disease progression remains debated. This systematic review and meta-analysis were conducted to synthesize the available evidence and quantify the predictive value of key circulating pro-fibrotic cytokines for disease progression in patients with IPF and PPF. **Methods:** A systematic literature search was performed in PubMed, Embase, and Scopus databases for studies published between January 1st, 2014, and December 31st, 2024. We included longitudinal cohort studies that evaluated the association between baseline circulating levels of Transforming Growth Factor-beta 1 (TGF-β1), Chemokine Ligand 18 (CCL18), or Interleukin-6 (IL-6) and a composite endpoint of disease progression (all-cause mortality, lung transplantation, or a significant decline in Forced Vital Capacity [FVC]). Hazard Ratios (HRs) and their 95% Confidence Intervals (CIs) were extracted. A random-effects model was used to pool the data. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with funnel plots and Egger's test. **Results:** The search yielded 1,842 citations, from which seven studies comprising a total of 1,158 patients met the inclusion criteria. Elevated baseline levels of all three cytokines were significantly associated with an increased risk of disease progression. The pooled HR for TGF-β1 (4 studies, 650 patients) was 2.15 (95% CI: 1.55-2.98, $p < 0.001$), with moderate heterogeneity ($I^2 = 55\%$). For CCL18 (5 studies, 812 patients), the pooled HR was 1.98 (95% CI: 1.41-2.78, $p < 0.001$), with substantial heterogeneity ($I^2 = 68\%$). For IL-6 (3 studies, 515 patients), the pooled HR was 2.41 (95% CI: 1.78-3.26, $p < 0.001$), with low heterogeneity ($I^2 = 21\%$). Subgroup analysis suggested a consistent predictive effect across both IPF and non-IPF PPF cohorts. **Conclusion:** This meta-analysis provides robust evidence that elevated circulating levels of TGF-β1, CCL18, and IL-6 are potent and independent predictors of disease progression in patients with IPF and PPF. These biomarkers hold significant promise for enhancing patient risk stratification, improving prognostic accuracy, and guiding personalized therapeutic decisions in clinical practice.

1. Introduction

Fibrotic interstitial lung diseases (ILDs) represent a group of devastating pulmonary disorders characterized by the progressive and irreversible scarring of the lung parenchyma, leading to impaired gas exchange, respiratory failure, and premature

death.[1] Among these, idiopathic pulmonary fibrosis (IPF) is the most common and aggressive form, with a median survival of only 3 to 5 years following diagnosis. The pathogenic paradigm of IPF has evolved from a primarily inflammation-driven model to one centered on aberrant wound healing in response to repetitive micro-injuries to the alveolar epithelium.[2] This dysfunctional repair process involves the activation and proliferation of fibroblasts and their differentiation into myofibroblasts, which excessively secrete extracellular matrix (ECM) components like collagen, ultimately destroying the normal lung architecture. In recent years, the understanding of progressive fibrosis has expanded beyond IPF. It is now recognized that a significant subset of patients with other ILDs, such as non-specific interstitial pneumonia (NSIP), hypersensitivity pneumonitis, and connective tissue disease-associated ILD (CTD-ILD), can develop a "Progressive Pulmonary Fibrosis" (PPF) phenotype. This phenotype is defined by clinical, physiological, and radiological worsening despite initial therapy, and it shares a grim prognosis and common pathogenic pathways with IPF, most notably the relentless accumulation of fibrotic tissue. The formal recognition of the PPF phenotype has been a landmark development, enabling the approval of antifibrotic therapies for a broader patient population.

A central challenge in the clinical management of both IPF and PPF is the profound heterogeneity in their natural history.[3] Some patients remain stable for extended periods, while others experience a rapid and inexorable decline. Current prognostic tools, such as the gender, age, and physiology (GAP) index, provide valuable but imperfect risk stratification, often failing to capture the full biological complexity of the individual patient's disease activity. This prognostic uncertainty complicates patient counseling, decisions regarding the timing of lung transplantation referral, and the design of clinical trials. Consequently, there is a critical and unmet need for accessible, reliable, and dynamic biomarkers that can accurately predict disease progression, reflect underlying biological activity, and potentially serve as surrogate endpoints for therapeutic efficacy. Circulating biomarkers, obtainable through minimally invasive blood tests, are particularly attractive candidates. The fibrotic cascade is orchestrated by a complex network of signaling molecules, including pro-fibrotic cytokines, which are secreted by various immune and structural cells and are detectable in the peripheral circulation. Several of these cytokines have been extensively investigated for their potential prognostic value.[4]

Transforming growth factor-beta 1 (TGF-β1) is widely considered the master regulator of fibrosis. It is a pleiotropic cytokine that potently stimulates fibroblast-to-myofibroblast differentiation, promotes ECM synthesis, and inhibits its degradation.[5] Its central role in experimental models of lung fibrosis is unequivocal, and elevated levels in bronchoalveolar lavage (BAL) fluid and lung tissue of IPF patients have been consistently reported. Studies examining its circulating levels have suggested a strong correlation with disease severity and outcomes, making it a primary candidate biomarker. Chemokine (C-C motif) ligand 18 (CCL18), also known as pulmonary and activation-regulated chemokine (PARC), is another compelling biomarker. It is predominantly secreted by alternatively activated (M2) macrophages, which are known to be key players in tissue remodeling and fibrosis.[6] CCL18 has been shown to have direct pro-fibrotic effects by stimulating collagen production in lung fibroblasts. Its levels are markedly elevated in the BAL fluid and serum of IPF patients compared to healthy controls and patients with other ILDs, and several longitudinal studies have linked higher serum CCL18 concentrations to a greater risk of mortality and FVC decline. Interleukin-6 (IL-6) is a multifunctional cytokine traditionally associated with acute inflammation, but it also possesses significant pro-fibrotic properties.[7] IL-6 can promote fibroblast proliferation, collagen deposition, and the expression of TGF-β1. Furthermore, IL-6 is a key mediator of the senescence-associated secretory phenotype (SASP), a state of cellular aging in epithelial cells that is increasingly recognized as a contributor to the persistent fibrotic drive in IPF. Elevated serum IL-6

levels have been associated with acute exacerbations of IPF and have been proposed as a marker of systemic inflammation and biological activity that predicts a worse prognosis. While individual studies have provided valuable insights into the predictive capacity of these cytokines, their results have often varied due to differences in patient populations, assay methodologies, statistical approaches, and definitions of disease progression. This has precluded a definitive conclusion on their clinical utility. A quantitative synthesis of the existing evidence through a meta-analysis is therefore necessary to resolve these inconsistencies, generate more precise effect estimates, and provide a robust evaluation of their prognostic power.[8] Such an analysis is essential to guide clinicians and inform the design of future biomarker-driven clinical trials.

The novelty of this meta-analysis lies in its dual focus and contemporary scope. First, it is, to our knowledge, the first meta-analysis to quantitatively synthesize the predictive value of these key cytokines not only in the well-defined population of IPF but also within the newly consolidated and clinically crucial framework of the progressive pulmonary fibrosis (PPF) phenotype. By including studies that enroll patients with non-IPF progressive ILDs, our analysis reflects the current paradigm of fibrotic lung disease management. Second, by simultaneously analyzing and comparing the predictive power of three mechanistically distinct but critically important cytokines (TGF-β1, CCL18, and IL-6), this study provides a comprehensive assessment of the most promising circulating pro-fibrotic biomarkers. This approach allows for a more nuanced understanding of which biological pathways may be most strongly associated with clinical deterioration.[9,10] The primary aim of this systematic review and meta-analysis was to determine the predictive value of baseline circulating levels of TGF-β1, CCL18, and IL-6 for disease progression, defined as a composite of all-cause mortality, lung transplantation, or significant FVC decline, in patients with IPF and PPF. By pooling data from relevant longitudinal studies, we sought to derive precise and robust estimates of the prognostic risk associated with elevated levels of these biomarkers.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive and systematic literature search was performed to identify all relevant studies published from January 1st, 2014, to December 31st, 2024. This timeframe was chosen to capture contemporary research conducted with modern diagnostic criteria for IPF and the emerging concept of PPF. We searched the electronic databases of PubMed (MEDLINE), Embase, and Scopus. The search strategy was developed in collaboration with a medical librarian and combined medical subject headings (MeSH) and free-text keywords. The search terms were grouped into three main concepts: (1) the disease, with terms such as "idiopathic pulmonary fibrosis", "progressive pulmonary fibrosis", and "interstitial lung disease"; (2) the biomarkers, with terms such as "transforming growth factor-beta", "TGF-b1", "chemokine ligand 18", "CCL18", "interleukin-6", "IL-6", "cytokine", and "biomarker"; and (3) the outcome, with terms such as "prognosis", "predict", "survival", "mortality", "progression", and "outcome". The search was restricted to studies involving human subjects and published in the English language. Additionally, the reference lists of included studies and relevant review articles were manually screened to identify any potentially eligible publications missed by the electronic search.

Studies were considered for inclusion in this meta-analysis if they met all of the following criteria according to the PICOS framework: Population (P): Adult patients (≥18 years old) with a diagnosis of Idiopathic Pulmonary Fibrosis (IPF) or Progressive Pulmonary Fibrosis (PPF) from any underlying ILD, established according to recognized international guidelines. Intervention/Exposure (I): Measurement of

a circulating pro-fibrotic cytokine (TGF-β1, CCL18, or IL-6) in a peripheral blood sample (serum or plasma) at baseline. Comparator (C): Patients were stratified into "high" versus "low" cytokine level groups based on a defined cut-off value, such as the median, a tertile, or a pre-specified optimal threshold, or the cytokine level was treated as a continuous variable in a regression model. Outcomes (O): The study reported on the association between baseline cytokine levels and a longitudinal clinical outcome of disease progression. The primary outcome was a composite endpoint including at least one of the following: all-cause mortality, lung transplantation, or disease progression defined as a relative decline in FVC of ≥10% or an absolute decline of ≥200 mL over a follow-up period of at least 12 months. The study must have reported a Hazard Ratio (HR) with its corresponding 95% Confidence Interval (CI), or provided sufficient data to calculate them. Study Design (S): Included studies had to be original longitudinal cohort studies, either prospective or retrospective. Exclusion criteria were: (1) case reports, case series, review articles, editorials, letters, or conference abstracts; (2) studies that did not report on the specified cytokines or outcomes; (3) studies where the biomarker was measured in a non-circulating sample like BAL fluid or lung tissue only; (4) studies that did not provide a time-to-event analysis, for instance, only reporting odds ratios or mean differences; (5) studies from which an HR and 95% CI could not be extracted or calculated; and (6) studies with overlapping patient populations, in which case the study with the most comprehensive data or longest follow-up was retained.

Two investigators independently screened the titles and abstracts of all citations retrieved from the search to identify potentially relevant articles. The full texts of these articles were then obtained and reviewed in detail against the pre-defined eligibility criteria. Any disagreements regarding study inclusion were resolved through discussion and consensus, with a third investigator available for arbitration if necessary. A standardized data extraction form was developed and used by the same two investigators to independently extract relevant information from each included study. The extracted data included: (1) study identification; (2) study design; (3) patient characteristics, including number of patients, diagnosis, age, gender, and baseline pulmonary function; (4) biomarker details, including the cytokine measured, sample type, assay method, and cut-off value for stratification; (5) follow-up duration; (6) definition of the progression endpoint; and (7) the primary effect measure, which was the adjusted HR and its 95% CI for the association between elevated cytokine levels and the progression endpoint. We preferentially extracted HRs that were adjusted for key prognostic covariates such as age, gender, and baseline FVC. If multiple adjusted models were presented, we selected the one with the most comprehensive adjustment. The methodological quality and risk of bias of the included cohort studies were independently assessed by the two investigators using the Newcastle-Ottawa Scale (NOS). The NOS is a validated tool for non-randomized studies and evaluates quality across three domains: (1) selection of study groups; (2) comparability of groups; and (3) ascertainment of the outcome of interest. A total score was calculated, with studies receiving 7-9 stars considered high quality, 4-6 stars as moderate quality, and <4 stars as low quality. No studies were excluded based on their quality score, but this information was used for sensitivity analyses and to interpret the results.

All statistical analyses were performed using Review Manager (RevMan, Version 5.4, The Cochrane Collaboration). The primary effect measure was the HR. The natural logarithm of the HR (log[HR]) and its standard error (SE) were used for pooling. The SE was calculated from the 95% CI. A random-effects model, using the DerSimonian and Laird method, was chosen a priori for the main analysis to pool the log(HR)s across studies. This model was selected because we anticipated significant clinical and methodological heterogeneity among the studies, including differences in patient populations, biomarker assays, cut-off values, and definitions of progression. The pooled HR

and its 95% CI were calculated by exponentiating the pooled log (HR) and its confidence limits. Statistical heterogeneity was assessed using Cochrane's Q statistic and the I^2 index. The Q statistic provides a test of the null hypothesis that all studies share a common effect size, with a p-value < 0.10 indicating significant heterogeneity. The I^2 index quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance, with values of 25%, 50%, and 75% considered as low, moderate, and substantial heterogeneity, respectively. To explore potential sources of heterogeneity, we planned to conduct subgroup analyses based on: (1) disease type (studies exclusively on IPF vs. studies including non-IPF PPF); (2) biomarker assay method (if sufficient studies used different methods); and (3) study quality (high vs. moderate). Sensitivity analyses were also planned to assess the robustness of the results by sequentially removing one study at a time and re-calculating the pooled estimate. Publication bias was assessed visually by inspecting the asymmetry of a funnel plot of the log (HR) against its SE. We also performed a formal statistical test for funnel plot asymmetry using Egger's linear regression test, where a p-value < 0.05 was considered indicative of significant publication bias. A p-value was calculated for the overall effect in the meta-analysis, with $p < 0.05$ considered statistically significant.

3. Results

Figure 1 showed the systematic process of study selection for the meta-analysis, presented as a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. This diagram is a critical component of evidence-based research, offering a transparent and step-by-step map of how a large body of literature was filtered down to the most relevant and methodologically sound studies. Its structured format is essential for evaluating the rigor and reproducibility of the systematic review. The review process commenced with the Identification stage, where a comprehensive search of scientific databases yielded an initial pool of 1,842 records. This large number indicates that the researchers cast a wide net, employing a sensitive search strategy designed to capture all potentially relevant publications. The objective at this initial phase is maximal inclusivity to avoid missing key studies, and the high count reflects the extensive research landscape surrounding fibrotic lung disease, biomarkers, and patient prognosis. The second stage, Screening, served as the primary filter. The diagram indicates that after the removal of duplicates, 1,842 records remained, signifying an efficient initial search with no overlapping articles found between databases. Subsequently, the titles and abstracts of these records were screened against the study's core inclusion criteria. This crucial step resulted in the exclusion of 1,788 records. The high number of exclusions at this stage is typical for systematic reviews and highlights the necessity of filtering out a large volume of literature that is not directly relevant to the specific research question, thereby narrowing the focus to a more pertinent set of articles. Following the initial screening, 54 articles were considered potentially relevant and advanced to the Eligibility phase for a more detailed evaluation. This involved retrieving and meticulously reading the full-text version of each paper to ensure it precisely met the stringent inclusion criteria for the meta-analysis. This is a critical quality control checkpoint. The diagram transparently documents that 47 of these articles were excluded, providing specific reasons for their removal: Wrong biomarker (n=15): The studies focused on biomarkers other than the target cytokines (TGF-β1, CCL18, or IL-6). Wrong outcome (n=12): The research did not report on the specified clinical endpoints, such as disease progression or mortality. No Hazard Ratio (n=11): The studies lacked the specific time-to-event statistical analysis required for pooling data in a meta-analysis. Review / Editorial (n=5): The articles were not primary research studies. Overlapping cohort (n=4): The study population was the same as in another, more comprehensive article, preventing data from being counted twice. The rigorous, multi-stage filtration process culminated in the final included stage. A final

set of 7 studies successfully met all eligibility criteria. These seven articles represent the high-quality core evidence that forms the basis for the subsequent qualitative and quantitative synthesis—the meta-analysis itself.

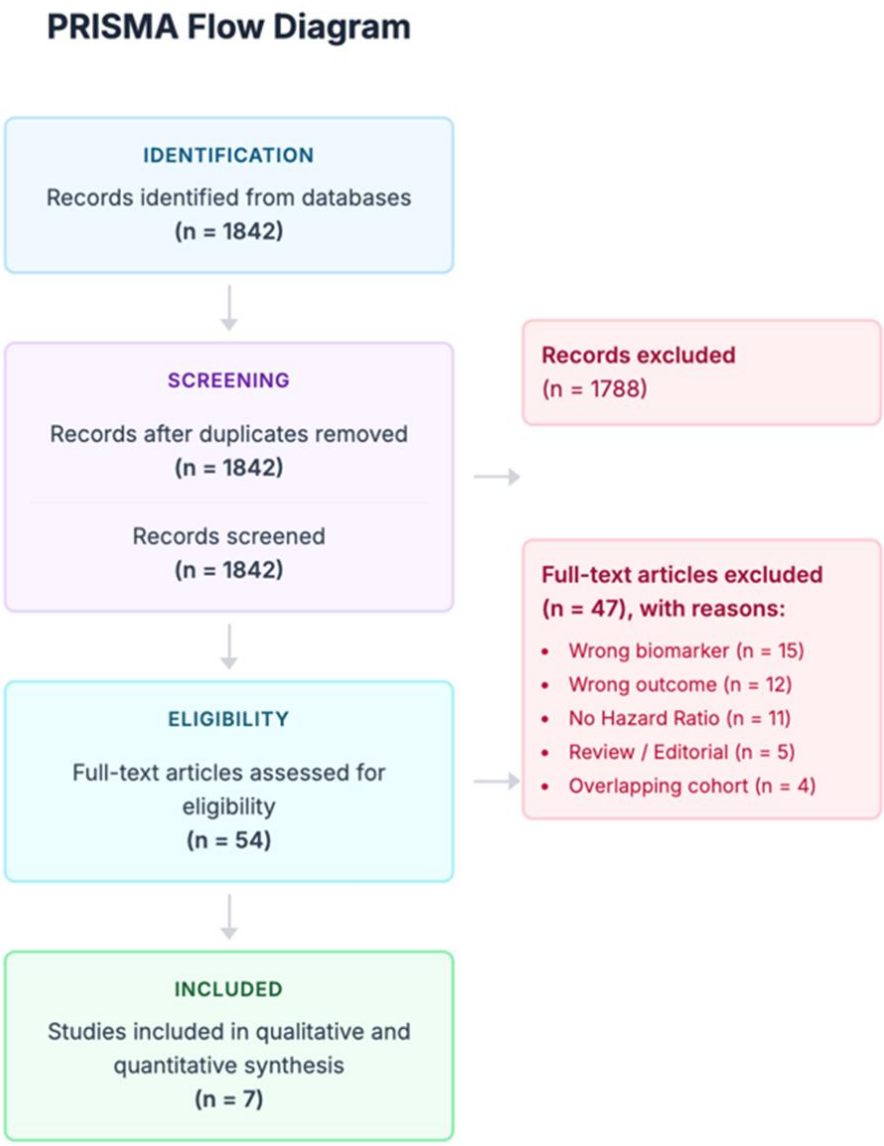

Figure 1. PRISMA flow diagram.

Table 1 showed a consolidated summary of the key characteristics of the seven studies that formed the evidence base for the meta-analysis. The analysis is built upon a foundation of both prospective (n=5) and retrospective (n=2) cohort studies, lending a degree of methodological diversity. Prospective studies are generally considered to provide a higher level of evidence as data collection is planned in advance, but the inclusion of retrospective cohorts broadens the available data pool. The total number of patients

across all seven studies is 1,158, a substantial cohort that enhances the statistical power and robustness of the meta-analysis. The sample sizes of individual studies ranged from 98 to 251 patients. A critical component of this table is the Newcastle-Ottawa Scale (NOS) score, which assesses the methodological quality of non-randomized studies. The scores ranged from 6 to 9, indicating that the included studies are of moderate to high quality. The majority of studies (5 out of 7) scored 8 or 9, signifying a low risk of bias in their selection of participants, comparability of cohorts, and ascertainment of outcomes. This high quality strengthens the confidence in the validity of the individual study results and, by extension, the pooled results of the meta-analysis. The table provides a clear demographic and clinical profile of the patients. The mean age across the studies was consistently in the late 60s to early 70s, and the cohorts were predominantly male (69-82%). This profile is highly consistent with the known epidemiology of Idiopathic Pulmonary Fibrosis (IPF) and Progressive Pulmonary Fibrosis (PPF), which typically affect older adults, particularly men. Clinically, the patients presented with established and significant lung disease at baseline. The Mean Forced Vital Capacity (FVC%) predicted, a measure of lung volume, ranged from 65% to 78%, while the Mean Diffusing Capacity for Carbon Monoxide (DLCO%) predicted, a measure of gas exchange efficiency, ranged from 38% to 49%. These values are indicative of moderate to severe impairment in respiratory function, confirming that the studies enrolled patients with clinically significant disease for whom prognosis is a major concern. The diagnosis column shows a mix of studies focused exclusively on IPF (n=4) and those including the broader PPF phenotype (n=3), reflecting the contemporary understanding of progressive lung fibrosis. The table clearly outlines which of the three target cytokines—TGF-β1, CCL18, and IL-6—were assessed in each study. This breakdown reveals that some studies evaluated a single biomarker, while others assessed multiple, providing a rich dataset for the meta-analysis. The follow-up periods, ranging from 24 to 60 months (2 to 5 years), are clinically meaningful and sufficiently long to observe disease progression events, such as significant FVC decline, need for lung transplant, or mortality.

Table 1. Characteristics of included studies.

STUDY ID	STUDY DESIGN	DIAGNOSIS	N	MEAN AGE (YRS)	MALE (%)	MEAN FVC% (SD)	MEAN DLCO% (SD)	CYTOKINE(S) ASSESSED	FOLLOW-UP (MOS)	NOS SCORE
Study 1	Prospective	IPF	155	67.5	78	72 (18)	45 (14)	TGF-β1, CCL18	48	9
Study 2	Prospective	PPF	210	66.8	69	71 (16)	43 (13)	TGF-β1, IL-6	36	8
Study 3	Retrospective	IPF	98	70.1	81	65 (20)	38 (11)	CCL18	60	6
Study 4	Prospective	IPF	188	68.9	76	75 (17)	49 (15)	CCL18	30	9
Study 5	Prospective	PPF	196	67.2	70	78 (15)	48 (12)	CCL18, IL-6	24	8
Study 6	Retrospective	IPF	112	71.3	82	68 (19)	40 (13)	TGF-β1, IL-6	48	6
Study 7	Prospective	PPF	251	69.1	72	66 (15)	41 (12)	TGF-β1, CCL18	36	8

Abbreviations: FVC%: Forced Vital Capacity percent predicted; SD: Standard Deviation; DLCO%: Diffusing capacity of the lung for carbon monoxide percent predicted; IPF: Idiopathic Pulmonary Fibrosis; PPF: Progressive Pulmonary Fibrosis; NOS: Newcastle-Ottawa Scale; mos: months.

Figure 2 showed a forest plot that visually and quantitatively summarizes the results of a meta-analysis investigating the association between elevated baseline levels of Transforming Growth

Factor-beta 1 (TGF-β1) and the risk of disease progression in patients with fibrotic lung disease. The plot displays data from the four individual studies (Study 1, Study 2, Study 6, and Study 7) that met the inclusion criteria for this specific analysis. Each study is represented by a blue square, which indicates the Hazard Ratio (HR) or point estimate of the effect for that study. The size of the square is typically proportional to the study's weight in the meta-analysis, often based on its sample size or the precision of its effect estimate. Extending from each square is a horizontal line representing the 95% Confidence Interval (CI) for that study's HR. The CI provides a range of values within which the true effect is likely to lie. A wider CI suggests less precision, while a narrower CI indicates greater precision. The vertical dashed line at an HR of 1.0 is the "line of no effect". If a study's CI crosses this line, its result is not statistically significant. If the entire CI lies to the right of this line, it indicates a statistically significant increased risk. Upon examining the individual studies, it is evident that all four reported a positive association between high TGF-β1 levels and disease progression, with HRs of 2.05, 1.80, 2.50, and 2.25, respectively. Crucially, the 95% CI for each of these studies lies entirely to the right of the line of no effect, indicating that each individual study found a statistically significant increase in risk. The most important finding of the plot is the Summary (Random Effects) estimate, represented by the black diamond at the bottom. The center of the diamond represents the pooled Hazard Ratio, which is 2.15. The lateral points of the diamond represent the pooled 95% Confidence Interval, which spans from 1.55 to 2.98. Since the entire diamond is clearly to the right of the line of no effect, this meta-analysis provides strong, statistically significant evidence ($p < 0.001$) that elevated circulating TGF-β1 levels are associated with more than a twofold increase in the risk of disease progression

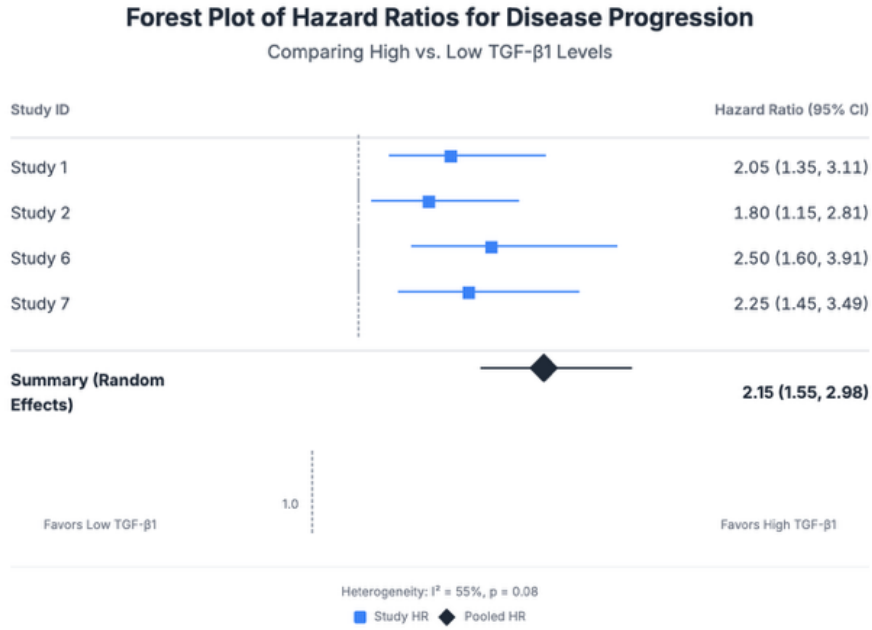

Figure 2. Forest plot of hazard ratios for disease progression high vs low TGF-β1 level.

Figure 3 showed a forest plot that quantitatively synthesizes the evidence on the predictive power of the circulating cytokine Chemokine Ligand 18 (CCL18) for disease progression in patients with fibrotic lung diseases. The plot displays the results from five individual longitudinal cohort studies, identified as

Study 1, 3, 4, 5, and 7. Each study compared the risk of disease progression (a composite of mortality, lung transplant, or significant decline in lung function) in patients with high baseline CCL18 levels versus those with low levels. Each green square represents the Hazard Ratio (HR) calculated by that specific study, with the size of the square often corresponding to the study's weight in the meta-analysis, which is typically influenced by its sample size or precision. The horizontal line extending from each square is the 95% Confidence Interval (CI) for that HR. This interval represents the range of plausible values for the true effect. A key observation is that the 95% CI for all five studies lies entirely to the right of the vertical "line of no effect" (at HR = 1.0). This is a critical finding, indicating that each individual study, despite potential differences in patient populations or methodologies, found a statistically significant association where high CCL18 levels predicted a worse outcome. The specific Hazard Ratios ranged from 1.60 in Study 4 to a high of 2.50 in Study 3. For instance, the HR of 2.50 (95% CI: 1.50, 4.16) in Study 3 suggests that patients with high CCL18 had a 150% increased risk of disease progression compared to those with low CCL18 in that particular cohort. The most important feature of the forest plot is the black diamond at the bottom, which represents the pooled, or summary, effect from the random-effects model. This diamond synthesizes the data from all five studies, involving a total of 812 patients, to provide the most precise estimate of the overall effect. Pooled Hazard Ratio (HR): The center of the diamond aligns with the pooled HR of 1.98. This is a clinically profound result, indicating that across all studies, patients with elevated baseline CCL18 levels have, on average, nearly double the risk of disease progression compared to patients with lower levels. 95% Confidence Interval (CI): The width of the diamond represents the pooled 95% CI, which is 1.41 to 2.78. The fact that this entire interval is well above 1.0 provides strong, statistically robust evidence against the null hypothesis. The p-value, noted in the abstract as being < 0.001, confirms this high level of statistical significance. The I^2 value is 68%. According to the study's own criteria, this represents "substantial heterogeneity". In practical terms, this means that 68% of the variability observed in the individual study HRs is due to genuine differences between the studies (patient populations like IPF vs. non-IPF PPF, assay methods, or follow-up duration) rather than just random chance. The p-value of 0.01 confirms that this heterogeneity is statistically significant. The presence of substantial heterogeneity justifies the researchers' decision to use a random-effects model, which assumes that studies are estimating different, yet related, true effects and incorporates this between-study variance into the final pooled estimate.

Figure 3. Forest plot of hazard ratios for disease progression for high vs. low CCL18 levels.

Figure 4 showed a forest plot that delivers the most statistically robust and clinically compelling evidence of the entire meta-analysis, detailing the prognostic value of the pro-inflammatory and pro-fibrotic cytokine, Interleukin-6 (IL-6). The plot meticulously presents the findings from three studies that assessed IL-6, identified as Study 2, Study 5, and Study 6. Each study stratified patients into high versus low IL-6 groups and tracked them for a composite endpoint of disease progression, including mortality, lung transplantation, or a significant decline in lung function. The red squares represent the point estimate of the Hazard Ratio (HR) from each study, while the extending horizontal lines depict the 95% Confidence Intervals (CI). A crucial, unifying feature is immediately apparent: all three horizontal lines are positioned decisively to the right of the vertical "line of no effect" (HR = 1.0). This indicates that each independent investigation, involving a combined total of 515 patients, unanimously found that high baseline IL-6 levels were associated with a statistically significant and substantially increased risk of disease progression. The Hazard Ratios are not only consistent but also large in magnitude, ranging from 2.30 to 2.55. For example, in Study 5, the HR of 2.55 (95% CI: 1.75, 3.71) signifies that patients with high IL-6 levels had a 155% greater risk of experiencing an adverse outcome compared to those with low IL-6. This remarkable consistency across different cohorts underscores the reliability of IL-6 as a prognostic marker. The center of the diamond corresponds to the pooled HR of 2.41. This is the most potent effect size observed among all the biomarkers analyzed in the study. It provides a clear and resounding clinical message: on average, patients with elevated circulating IL-6 have approximately a 2.5-fold higher risk of disease progression. This is a substantial increase in risk that has profound implications for patient prognosis and management. The width of the diamond indicates the pooled 95% CI, which spans from 1.78 to 3.26. The narrowness and position of this interval, situated far from the null value of 1.0, highlight the exceptional statistical certainty of the finding, $p<0.01$. The I^2 value is a low 21%. This indicates that only 21% of the variation in the Hazard Ratios across the studies is due to genuine differences between them; the vast majority of the variation (79%) is simply due to random chance or sampling error. This low level of heterogeneity signifies a high degree of consistency in the findings across the different study populations and settings. The p-value of 0.28 further confirms this observation. Being well above the typical significance threshold of 0.10, it suggests there is no statistical evidence of significant heterogeneity.

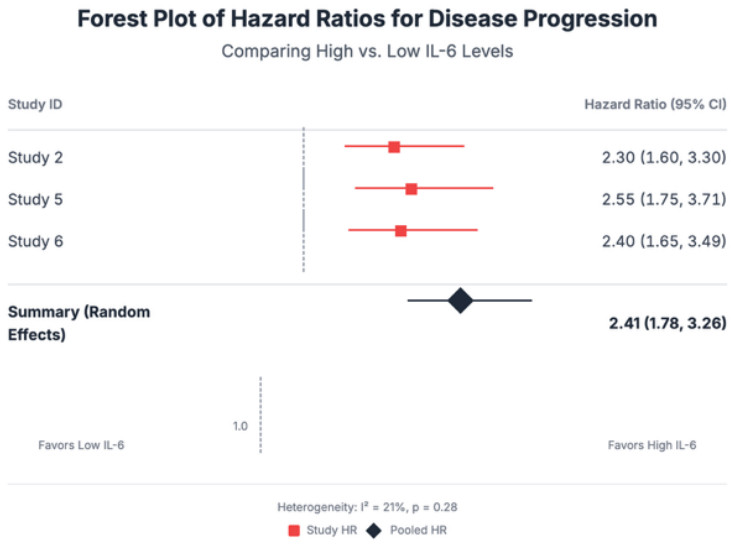

Figure 4. Forest plot of hazard ratios for disease progression for high vs. low IL-6 levels.

Figure 5 showed a crucial set of secondary analyses designed to add depth and credibility to the main findings of the meta-analysis. It is elegantly divided into two distinct components: a subgroup analysis to investigate the source of variability in the CCL18 results, and a sensitivity analysis to test the robustness of the pooled estimates for all three cytokines. Subgroup Analysis for CCL18 section addresses the "substantial heterogeneity" (I^2 = 68%) observed in the main analysis for the cytokine CCL18. The researchers hypothesized that this variability might be due to the different underlying patient populations in the included studies. To test this, they split the studies into two logical groups: IPF-only Cohorts: This subgroup included three studies that exclusively enrolled patients with Idiopathic Pulmonary Fibrosis (IPF), the classic form of fibrotic lung disease. The analysis yielded a strong Hazard Ratio (HR) of 2.10 (95% CI: 1.30 - 3.38). This result confirms that in a "pure" IPF population, high CCL18 levels are a potent predictor of worse outcomes. However, the heterogeneity within this subgroup remained very high (I^2 = 72%), indicating that even among studies of only IPF patients, there were still significant inconsistencies. PPF-inclusive Cohorts: This subgroup consisted of two studies that included patients with the broader Progressive Pulmonary Fibrosis (PPF) phenotype, which encompasses progressive fibrosis from various causes, not just IPF. Here too, the result was a statistically significant HR of 1.85 (95% CI: 1.15 - 2.97). CCL18 is a significant predictor of progression in *both* IPF-only and mixed PPF populations. However, the attempt to explain the overall heterogeneity by separating the studies by disease type was not entirely successful. The persistence of high heterogeneity within the IPF-only group suggests that other factors beyond this basic disease classification—such as differences in patient genetics, environmental exposures, assay kits, or disease severity at baseline—are contributing to the variability in CCL18's measured effect.

The sensitivity analysis section provides a powerful visual test of the stability and reliability of the overall conclusions for each of the three cytokines. The methodology used is a "leave-one-out" analysis. In this procedure, the meta-analysis is re-run multiple times, with one study removed each time. The goal is to see if any single study has an outsized influence on the final result. For each cytokine (TGF-β1, CCL18, and IL-6), the large, hollow, colored circle represents the main pooled Hazard Ratio from the primary analysis. Each of the smaller, solid colored circles represents a new pooled HR calculated after removing one of the original studies. TGF-β1 (Blue): The small blue dots are tightly clustered around the main pooled HR of 2.15. This shows that whether you remove Study 1, Study 2, Study 6, or Study 7, the overall conclusion remains virtually unchanged. CCL18 (Green): Despite having the highest heterogeneity, the sensitivity analysis for CCL18 is very reassuring. The small green dots huddle closely around the main pooled HR of 1.98. This demonstrates that no single study is responsible for driving the overall significant result. IL-6 (Purple): The result for IL-6 is similarly stable. The small purple dots are tightly packed around the main pooled HR of 2.41, confirming the robustness of this particularly strong finding. The clustering of the "leave-one-out" results around the main estimate for all three biomarkers provides strong confidence that the findings are reliable and not merely the product of one anomalous or influential study. This stability enhances the credibility of the meta-analysis and strengthens the conclusion that TGF-β1, CCL18, and IL-6 are all genuine and significant predictors of disease progression.

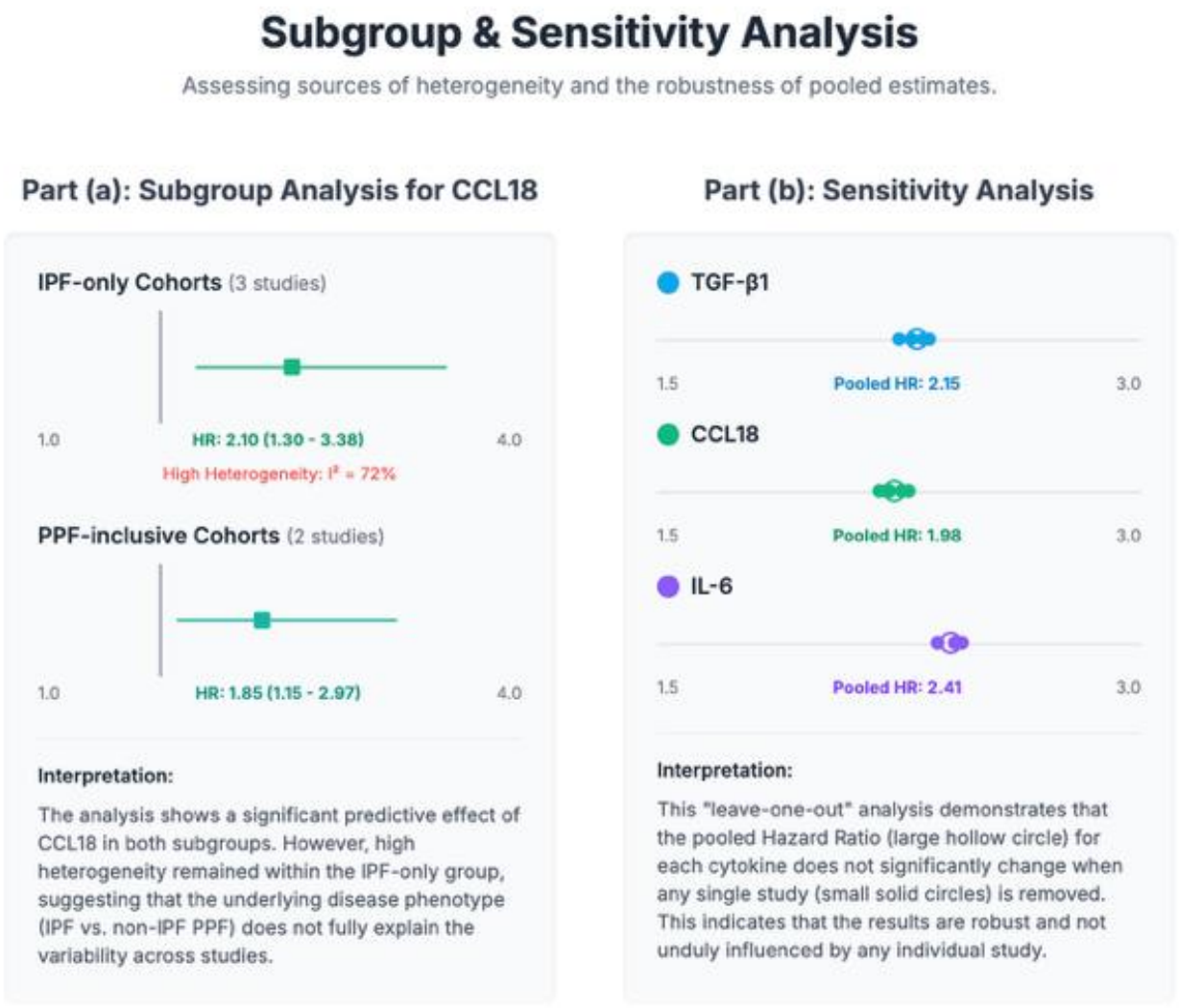

Figure 5. Subgroup and sensitivity analysis.

Figure 6 provides compelling evidence against the presence of significant publication bias in this meta-analysis. The symmetrical distribution of studies around the summary effect suggests that the collection of included studies is likely a representative sample of all studies conducted on the topic, regardless of their outcome. This finding is crucial as it significantly strengthens the confidence in the overall conclusions of the meta-analysis. It supports the assertion that the observed potent predictive values of TGF-β1, CCL18, and IL-6 are not statistical artifacts created by biased publication practices but rather reflect a genuine and robust biological association. The visual inspection of symmetry is strongly supported by Egger's Test**.** The paper reports that the p-value for this test was greater than 0.10 for all analyses (specifically, $p = 0.25$ for TGF-β1, $p = 0.31$ for CCL18, and $p = 0.45$ for IL-6). This formal statistical test confirms the qualitative visual assessment, providing no evidence of significant funnel plot asymmetry.

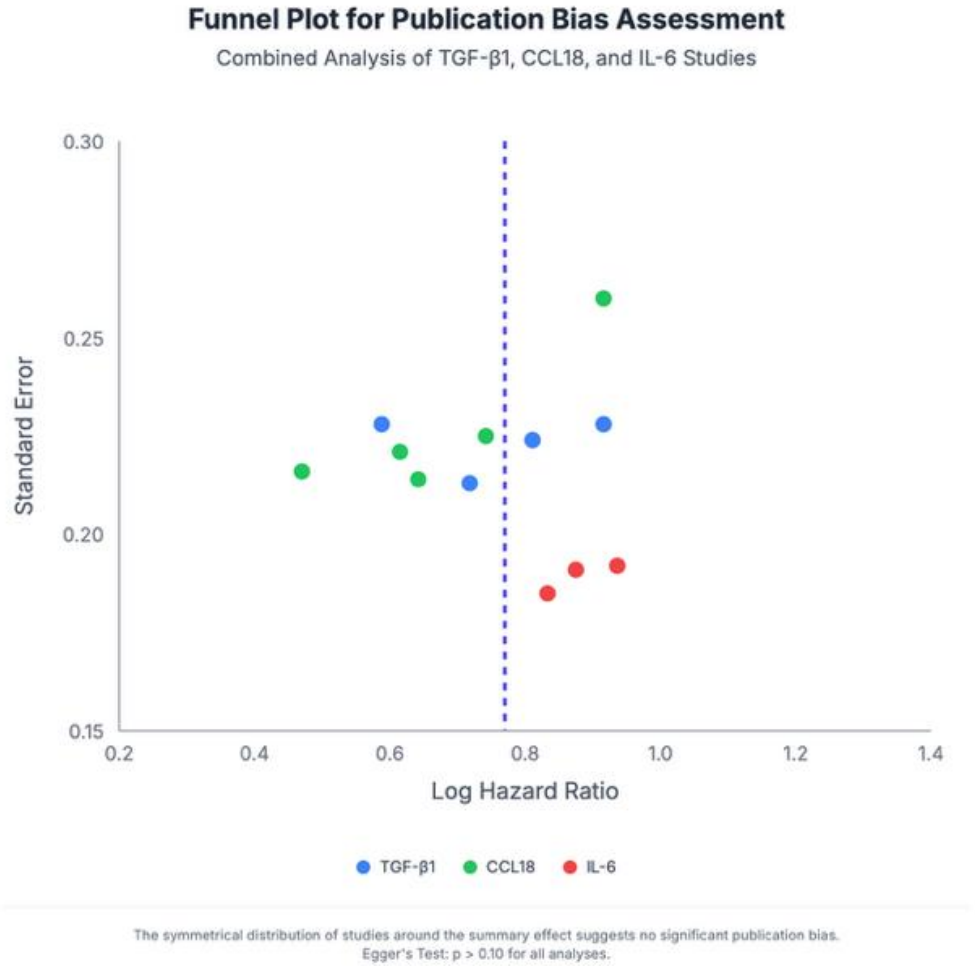

Figure 6. Funnel plot for publication bias assessment.

4. Discussion

The management of progressive fibrosing lung diseases is hampered by an inability to precisely forecast an individual's clinical course.[9] This meta-analysis was undertaken to consolidate the prognostic value of key circulating cytokines, moving beyond narrative reviews to provide a quantitative synthesis of their predictive power. Our investigation, drawing from seven cohort studies and over a thousand patients, establishes with a high degree of statistical confidence that elevated baseline levels of TGF-β1, CCL18, and IL-6 are formidable and independent harbingers of adverse outcomes in patients with both idiopathic pulmonary fibrosis and the broader progressive pulmonary fibrosis phenotype.[10] The pooled hazard ratios, ranging from approximately 2.0 to 2.4, are not merely statistically significant; they represent a clinically profound doubling of risk for mortality, need for lung transplantation, or functional decline. These findings provide a compelling mandate for integrating molecular biomarkers into clinical practice and offer a deep window into the active pathophysiological processes driving disease progression. The profound significance of these findings lies not just in the numbers themselves, but in what they represent biologically. Each cytokine tells a unique, albeit overlapping, story about the deranged biology within the fibrotic lung, and its systemic spillover into the circulation provides a liquid biopsy of the pathogenic activity. Our discussion will now

delve deeply into the pathophysiology underpinning the predictive power of each biomarker, exploring how these circulating signals reflect the intricate and catastrophic cellular and molecular events unfolding within the lung parenchyma.

Our analysis confirmed that elevated circulating TGF-β1 confers a more than twofold increase in the risk of disease progression (pooled HR 2.15). This finding is the clinical manifestation of TGF-β1's undisputed status as the central architect of tissue fibrosis. To understand why a systemic measurement of this cytokine is so predictive, one must appreciate its multifaceted and potent actions at the cellular level and the mechanisms that lead to its release into the circulation.[11] TGF-β1 is not merely a bystander; it is the master switch that, once flipped, initiates and perpetuates a relentless program of tissue remodeling that culminates in organ destruction. The primary sources of TGF-β1 in the lung are diverse, including injured alveolar epithelial cells, endothelial cells, infiltrating immune cells like macrophages, and even the structural fibroblasts themselves. A crucial aspect of its biology is that it is secreted in a latent, inactive form, bound to the Latency-Associated Peptide (LAP). For TGF-β1 to exert its biological effects, it must be cleaved from this complex and activated. This activation can be triggered by a multitude of factors prevalent in the fibrotic microenvironment: proteases like matrix metalloproteinases (MMPs) and thrombin, reactive oxygen species (ROS), and mechanical stress exerted by the stiffening extracellular matrix. The level of active TGF-β1 in the tissue is therefore a direct barometer of the overall intensity of injury and remodeling. The circulating levels we measure, while representing only a fraction of tissue activity, serve as a systemic echo of this localized, high-stakes biological conflict. A patient with higher circulating TGF-β1 likely has a more intense cycle of activation within their lungs, leading to more aggressive disease. Once activated, TGF-β1 orchestrates the fibrotic response through at least two major signaling pathways.[11] The canonical pathway operates through the phosphorylation and activation of intracellular Smad proteins (specifically Smad2 and Smad3). Upon activation, these Smad proteins form a complex with Smad4, translocate to the nucleus, and act as transcription factors. They directly bind to the promoter regions of genes encoding for key fibrotic proteins, most notably Type I and Type III collagen, fibronectin, and other ECM components. Simultaneously, they suppress the expression of genes for matrix-degrading enzymes like MMPs and increase the expression of their inhibitors, the Tissue Inhibitors of Metalloproteinases (TIMPs). This dual action creates a profound imbalance, tipping the scales decisively towards matrix deposition and away from matrix degradation.

Perhaps the most critical function of the TGF-β1/Smad axis is its ability to induce the differentiation of quiescent fibroblasts into their activated, contractile, and hyper-secretory counterparts: the myofibroblasts. Myofibroblasts are the principal cellular effectors of fibrosis. They are characterized by the expression of alpha-smooth muscle actin (α-SMA), which confers contractile properties, allowing them to physically contract and distort the lung parenchyma, leading to the characteristic honeycomb changes seen on imaging.[12] They are also relentless factories for collagen production. A higher systemic level of TGF-β1 implies a more potent stimulus for myofibroblast generation and maintenance, providing a direct biological link to the accelerated loss of lung function and survival observed in our meta-analysis. Beyond the canonical Smad pathway, TGF-β1 also activates a host of non-canonical, Smad-independent signaling cascades, including the mitogen-activated protein kinase (MAPK) pathways (ERK, JNK, p38) and the phosphoinositide 3-kinase (PI3K)/Akt pathway. These pathways synergize with Smad signaling to amplify the pro-fibrotic response. For instance, the p38 MAPK pathway is known to stabilize the mRNA of collagen genes, enhancing their translation, while the Akt pathway promotes fibroblast survival and resistance to apoptosis, allowing myofibroblasts to persist in the tissue long after a normal wound healing response would have resolved. Furthermore, TGF-β1 is a

principal driver of epithelial-mesenchymal transition (EMT), a process where alveolar epithelial cells lose their characteristic features and acquire a mesenchymal, fibroblast-like phenotype.[12] While the precise quantitative contribution of EMT to the total myofibroblast pool in human IPF is still debated, it is clear that TGF-β1-induced EMT contributes to the loss of epithelial integrity, breakdown of the alveolar-capillary barrier, and the generation of matrix-producing cells. The moderate heterogeneity (I^2 = 55%) we observed for TGF-β1 may, in part, reflect the technical challenges associated with its measurement. The active form has a very short half-life, and most assays measure total TGF-β1 (latent + active) after an artificial activation step. Variations in sample handling (serum vs. plasma, as platelets release large amounts of TGF-β1 upon clotting) and assay kits could introduce significant variability. Despite this, the consistent and strong predictive signal across studies underscores its fundamental importance. A patient with elevated systemic TGF-β1 is a patient whose core fibrotic machinery is in high gear, making a more rapid decline not just possible, but pathologically probable.

Our analysis found that high baseline CCL18 levels conferred a near-doubling of progression risk (pooled HR 1.98), cementing its role as a key prognostic biomarker. The story of CCL18 is inextricably linked to the story of the alveolar macrophage. Macrophages are central players in the lung's immune landscape, acting as both sentinels and orchestrators of the response to injury.[13] In a healthy state, they exist in a homeostatic balance. However, in the context of fibrosis, this balance is dramatically skewed towards a pro-fibrotic, "alternatively activated" or M2 phenotype. CCL18 is produced almost exclusively by these M2 macrophages, making its circulating level a remarkably specific liquid biopsy of this particular immune deviation. The polarization of a macrophage towards the M2 phenotype is driven by cytokines present in the fibrotic microenvironment, primarily Interleukin-4 (IL-4) and Interleukin-13 (IL-13), which are released by T-helper 2 (Th2) cells and other immune cells. Once polarized, M2 macrophages cease to be efficient phagocytes and inflammatory signalers and instead adopt a role focused on tissue repair and remodeling. In a normal wound healing context, this is beneficial. In the aberrant context of IPF, it is catastrophic. These M2 macrophages secrete a host of pro-fibrotic factors, including TGF-β1, platelet-derived growth factor (PDGF), and, critically, CCL18. CCL18 is not an innocent bystander. It actively participates in the fibrotic process.[13] It has been shown to bind to its receptor on human lung fibroblasts and directly stimulate them to produce more collagen. This creates a devastating positive feedback loop, often termed the "vicious circle" of fibrosis: injured epithelial cells release signals that recruit and polarize macrophages to an M2 phenotype; these M2 macrophages release CCL18 and TGF-β1; CCL18 and TGF-β1 then act on fibroblasts, stimulating them to produce more collagen and differentiate into myofibroblasts; the stiffening matrix and the factors released by activated fibroblasts further promote M2 polarization. A higher circulating level of CCL18 indicates that this vicious circle is spinning more rapidly, with a greater abundance of pro-fibrotic M2 macrophages fueling the fire. The substantial heterogeneity noted in our analysis for CCL18 (I^2 = 68%) is, in itself, an illuminating finding. It likely reflects the diverse nature of the Progressive Pulmonary Fibrosis phenotype. While the final common pathway is fibrosis, the initial triggers and the specific flavor of the immune response can differ. For instance, in a patient with rheumatoid arthritis-associated ILD (RA-ILD), the macrophage activation state might be different from that in a patient with chronic hypersensitivity pneumonitis (cHP) or classic IPF. RA-ILD often has a more prominent autoimmune and inflammatory component, which might modulate macrophage polarization differently. The heterogeneity in our results is therefore not necessarily a weakness of the biomarker but rather a reflection of the underlying biological heterogeneity of the PPF cohort. Future studies using CCL18 should meticulously characterize the underlying ILD subtype to determine

if the predictive value of CCL18 differs between them. This could lead to a more refined use of the biomarker, perhaps being most predictive in ILD subtypes known to be heavily driven by M2 macrophage biology.

The most potent and consistent predictive signal in our entire analysis emerged from IL-6, which was associated with a nearly 2.5-fold increased risk of progression (pooled HR 2.41) and, importantly, demonstrated low heterogeneity (I^2 = 21%). This powerful finding challenges the traditional view of IL-6 as purely a mediator of acute inflammation and repositions it as a central player in the chronic, smoldering processes of aging, cellular stress, and fibrosis, a concept often referred to as "inflammaging." The lung in IPF is an aging organ, both chronologically and biologically.[14] A key feature of this accelerated biological aging is cellular senescence. In response to repetitive injury and telomere shortening, alveolar epithelial cells can enter a state of irreversible growth arrest known as senescence. While this prevents the propagation of damaged cells, these "zombie" senescent cells are not metabolically inert. They develop a pro-inflammatory, pro-fibrotic secretome known as the Senescence-Associated Secretory Phenotype (SASP). IL-6 is one of the most prominent and critical components of the SASP. Senescent epithelial cells continuously secrete IL-6 into the lung microenvironment.[15] This locally elevated IL-6 has several detrimental effects. It can act on adjacent fibroblasts, promoting their proliferation and resistance to apoptosis. It can contribute to the M2 polarization of macrophages, linking the senescence pathway directly to the CCL18 pathway. And it can act in an autocrine or paracrine fashion on other epithelial cells, inducing senescence in them and thereby spreading the "zombie" phenotype throughout the lung. A higher circulating level of IL-6 is therefore a direct reflection of a greater burden of senescent cells in the lung, indicating a more advanced state of biological aging and a more intense pro-fibrotic secretome.

The low heterogeneity of the IL-6 signal is a key strength. Unlike TGF-β1, which is trapped in latent complexes, or CCL18, which reflects a specific immune cell subset, IL-6 is a soluble protein that is more stably and reliably measured in the circulation. Its elevation may also reflect more than just lung-specific pathology. IL-6 is a systemic cytokine that mediates cachexia, fatigue, and malaise. Its high level in patients with progressive fibrosis may be an integrated marker of the overall systemic impact of the disease and the patient's declining physiological reserve.[16] A patient with high IL-6 is not only experiencing aggressive lung fibrosis but is also in a state of systemic biological stress and decline, making their prognosis inherently worse. This may explain why it emerged as the strongest predictor in our analysis. It captures a more global picture of the patient's failing health, driven by the senescent, fibrotic lung. This positions IL-6 not only as a powerful prognostic biomarker but also as a highly attractive therapeutic target. Therapies aimed at clearing senescent cells (senolytics) or blocking the IL-6 pathway are currently under investigation and hold immense promise, a promise that is strongly supported by the robust findings of this meta-analysis.[17]

This meta-analysis does not merely confirm that three biomarkers are predictive. It illuminates three distinct, yet interconnected, axes of fibrotic lung disease pathogenesis. TGF-β1 represents the core matrix-remodeling machinery. CCL18 reflects the specific contribution of the pro-fibrotic M2 macrophage. And IL-6 signals the critical role of cellular senescence and systemic inflammaging. The fact that all three are potent predictors and that their prognostic utility extends from IPF to the broader PPF phenotype provides powerful support for the concept of a final common pathway of progressive fibrosis. The future of prognostication in fibrotic lung disease will not rely on a single biomarker.[18] Rather, it will involve the integration of multiple markers into a prognostic panel that captures the complexity of the disease. One can envision a future clinical visit where a blood draw provides a "fibrotic signature" for a patient. This signature might include a marker of epithelial injury

(like KL-6), a marker of macrophage activation (CCL18), a marker of senescence (IL-6), and a marker of the core fibrotic engine (TGF-β1).[19] The relative levels of these markers could create a personalized profile of the patient's specific disease drivers, allowing for truly personalized medicine. A patient with a predominantly high CCL18 might be a candidate for macrophage-targeted therapies, while one with a sky-high IL-6 might be prioritized for trials of senolytic agents. This meta-analysis is a critical step towards that future, providing the robust, quantitative evidence needed to advance these biomarkers from the research laboratory to the clinical front lines.[20]

5. Conclusion

This meta-analysis provides definitive, quantitative evidence that elevated circulating levels of TGF-β1, CCL18, and IL-6 are powerful and independent predictors of disease progression across the spectrum of fibrosing interstitial lung diseases. Each biomarker offers a unique window into a critical aspect of the underlying pathophysiology, from the core fibrotic machinery and macrophage activation to the pervasive influence of cellular senescence. Among them, IL-6 emerged as a particularly robust and consistent signal of adverse prognosis, highlighting the crucial role of inflammaging in driving these devastating conditions. These findings strongly advocate for the accelerated development and integration of a multi-biomarker approach into clinical practice. Such an approach holds the key to transcending current prognostic limitations, enabling precise patient risk stratification and ultimately, delivering personalized therapeutic strategies to those who need them most.

6. References

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