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Biomarkers in idiopathic pulmonary fibrosis: Current insight and future direction

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive interstitial lung disease with a dismal prognosis. Early diagnosis, accurate prognosis, and personalized therapeutic interventions are essential for improving patient outcomes. Biomarkers, as measurable indicators of biological processes or disease states, hold significant promise in IPF management. In recent years, there has been a growing interest in identifying and validating biomarkers for IPF, encompassing various molecular, imaging, and clinical approaches. This review provides an in-depth examination of the current landscape of IPF biomarker research, highlighting their potential applications in disease diagnosis, prognosis, and treatment response. Additionally, the challenges and future perspectives of biomarker integration into clinical practice for precision medicine in IPF are discussed.

Keywords

Biomarker; Idiopathic pulmonary fibrosis; Prognosis; Diagnosis; Treatment

Idiopathic pulmonary fibrosis (IPF) is a progressive and devastating lung disease characterized by the excessive deposition of extracellular matrix (ECM) in the lung parenchyma, leading to impaired gas exchange and respiratory failure.[1, 2] Despite advancements in our understanding of IPF pathogenesis, the exact mechanisms driving disease progression remain elusive, making diagnosis and treatment decisions challenging.

Early and accurate diagnosis, along with the ability to predict disease progression, is vital for optimizing patient management and ensuring timely initiation of appropriate therapies.[1, 3–8] Biomarkers play a pivotal role in enabling early and accurate diagnosis of IPF, as they identify specific indicators in blood, sputum, bronchoalveolar lavage (BAL) fluid, or exhaled breath, allowing clinicians to differentiate IPF from other lung conditions during

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their initial phases.[4, 9] Beyond diagnosis, biomarkers hold prognostic significance by providing valuable insights into disease progression and potential responses to therapies, enabling personalized treatment strategies. Biomarkers serve as objective measures to monitor treatment effectiveness over time, facilitating timely adjustments in treatment plans when needed. Biomarker sampling is less invasive than surgical lung biopsy. Thereby, it is generally more acceptable to patients, including those hesitant about undergoing a biopsy. The identification and validation of IPF biomarkers contribute to advancements in precision medicine, where tailored treatments aligned with individual patient profiles lead to enhanced outcomes and improved quality of life.[10] In this review, we comprehensively examine the current state of biomarker research in IPF, focusing on different biomarker types and their potential applications in clinical practice. We explore the challenges and opportunities in validating and integrating biomarkers into routine patient care, paving the way for personalized medicine approaches in IPF.

Biomarkers in blood

Surfactant proteins (SP-A and SP-D) constitute essential elements of the lung's surfactant system, pivotal for maintaining lung function and integrity.[11] In the context of IPF, damage to the alveolar epithelium leads to elevated levels of SP-A and SP-D in the bloodstream. These surfactant proteins have garnered attention as potential blood biomarkers for IPF. Measuring levels of SP-A in the blood can help distinguish between patients with IPF and those with other lung diseases or healthy individuals. Blood levels of SP-D are also useful for differentiating IPF patients from those with lung infections or healthy people, but not as effective for distinguishing from other non-IPF lung diseases. In Caucasian patients, both SP-A and SP-D levels were effective in identifying IPF compared to non-IPF lung diseases and healthy individuals. However, in Asian patients, only a higher level of SP-D was significant in differentiating IPF patients from healthy individuals. In addition, high levels of SP-A and SP-D in IPF patients are linked to a worse prognosis.[12] It is important to note that the specificity of SP-A and SP-D as exclusive biomarkers for IPF is limited, as elevated levels can also be seen in other interstitial lung diseases (ILDs), thus potentially reducing their diagnostic accuracy in certain cases.[13]

Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) play a critical role in lung ECM remodeling. In IPF, the equilibrium between MMPs and TIMPs becomes disrupted, resulting in excessive ECM deposition and fibrosis. In clinical studies, the level of TIMP-1 in the blood is mainly checked to help diagnose lung diseases and to understand how severe the disease is. However, there has not been much focus on using TIMP-1 as a way to predict how well patients will do after treatment. In cases of pneumonia, the balance between MMP-9 and TIMP-1 in the blood improved after patients were treated with antibiotics. Similarly, in patients with IPF, TIMP-1 levels went down after they were treated with glucocorticoids. This suggests that TIMP-1 could be a useful blood marker for checking how well treatments are working in lung diseases, especially lung fibrosis.[14, 15] Investigations have explored the feasibility of MMPs and TIMPs as blood biomarkers for IPF. All analyzed MMP/TIMPs were present at significantly elevated levels in patients with IPF compared to controls, with the exception of TIMP2. Multivariable analyses identified MMP8, MMP9, and TIMP1 as the primary biomarkers for distinguishing IPF patients from

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control.[16] Elevated levels of specific MMPs and TIMPs have been linked to disease severity and prognosis.[17] MMPs, especially MMP-7, are recognized for their role beyond diagnosis in IPF. They are useful in predicting prognosis and transplant-free survival in patients with IPF. MMP-7, in combination with other IPF markers, has shown positive results in both diagnosis and prognosis in various studies. Additionally, MMP-7 is not the only MMP to demonstrate potential as a diagnostic biomarker in IPF. A study on 300 IPF patients found that most MMPs and TIMPs, except for TIMP2, were elevated in IPF patients compared to controls. MMP8, MMP9, and TIMP1 were particularly effective in diagnosing IPF, while MMP7, MMP12, MMP13, and TIMP4 could indicate disease severity.[4, 16, 18] However, further validation is necessary to establish their clinical utility and predictive value.

Krebs von den Lungen-6 (KL-6), a high-molecular-weight glycoprotein produced by type II alveolar epithelial cells, is released into circulation in response to lung epithelial cell damage.[19] KL-6 has undergone extensive study as a blood biomarker for IPF. Increased KL-6 levels are observed in IPF patients and have been correlated with disease severity and lung function decline. Patients with severe or progressive ILD had significantly higher KL-6 levels than those with mild or non-progressive ILD. Higher KL-6 levels were also observed in acute exacerbations of ILD and were associated with poorer outcomes, including higher levels in deceased patients compared to survivors.[20] In Japan, KL-6 is employed in clinical practice as a diagnostic and monitoring tool for IPF.[21] However, concerns exist about its specificity, as elevated levels of KL-6 can also manifest in other lung conditions.[22]

S100A12, a calcium-binding protein within the S100 protein family, is primarily released by neutrophils and contributes to the inflammatory response. Blood levels of S100A12 are elevated in IPF and are associated with disease severity and prognosis,[23] suggesting the potential of S100A12 as a biomarker of IPF. Further research is imperative to definitively establish its clinical usefulness and specificity in the context of IPF.

Procollagen III N-terminal peptide (PIIINP), a precursor molecule involved in type III collagen synthesis – an integral component of lung ECM – is a subject of study as a potential IPF biomarker. In IPF, excess collagen deposition leads to fibrosis. Blood levels of PIIINP have been explored as indicators of fibrosis in IPF. Heightened PIIINP levels are correlated with the extent of fibrosis and disease progression,[24] suggesting its potential as a non-invasive means of assessing fibrosis degree in IPF patients.

Both galectin-3 (Gal-3) and periostin, proteins participating in diverse cellular processes, such as inflammation and tissue repair, have been under investigation as blood biomarkers in IPF.[25, 26] Galectin-3 levels have been tied to disease severity and prognosis. Elevated levels of Gal-3 are linked with interstitial lung abnormalities and a restrictive pattern, characterized by reduced lung volumes and impaired gas exchange. This indicates that Gal-3 may play a role in the early stages of pulmonary fibrosis. Periostin is highly expressed in patients with IPF, both in the lungs and in circulation. It is associated with areas of active fibrosis and can predict lung function decline over time. Elevated periostin levels may be a significant biomarker for disease activity in older IPF patients.[27, 28]

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MicroRNAs (miRNAs) and other noncoding RNAs are key players in gene regulation and have been implicated in IPF pathogenesis. Certain miRNAs and noncoding RNAs, which can be detected in the blood, have been observed to be dysregulated in IPF. Specifically, research has shown that the downregulation of miR-29 family members is associated with lung fibrosis. Despite this, miR-29 holds therapeutic promise for the treatment of pulmonary fibrosis.[29–31] These molecules exhibit promise as potential blood biomarkers for IPF due to their involvement in crucial disease pathways. However, their diagnostic and prognostic value necessitates further validation.

The promise of blood biomarkers in diagnosing and managing IPF is offset by several challenges. Many biomarkers are not exclusive to IPF and can also be elevated in other lung disorders. The lack of specificity can lead to misdiagnosis. Standardization poses another hurdle. Development of a standard protocol demands uniformity in sample collection, processing, and analysis to ensure consistent and comparable outcomes across diverse studies and laboratories. The future direction might involve utilizing panels of biomarkers to enhance sensitivity and specificity, where the amalgamation of various biomarkers reflecting distinct disease aspects can offer a more precise IPF evaluation.

Long-term, prospective studies are imperative to establish the predictive potential of blood biomarkers in tracking disease progression and gauging therapeutic responses. Integration with imaging techniques, particularly high-resolution computed tomography (HRCT), holds promise for enhancing IPF diagnosis and monitoring by pairing blood biomarkers with visual data.[32] As comprehension of IPF's heterogeneity deepens, the prospects for personalized treatment strategies rooted in specific biomarker profiles become more feasible. This trajectory aligns with the recognition that addressing the intricacies of IPF necessitates collaborative efforts spanning research, clinical practice, and technological innovation [Table 1].

Biomarkers in exhaled breath

Volatile organic compounds (VOCs) are a class of carbon-based chemicals that readily evaporate at room temperature and can be detected in exhaled breath. These compounds, either metabolic byproducts or derived from endogenous and exogenous sources within the human body, are considered as potential indicators of diseases due to their ability to reflect changes in the body's physiology and metabolism.[33] Diverse biochemical processes in the human body can alter under certain diseases or conditions, leading to the production of specific VOCs or changes in the concentrations of VOCs. Consequently, the VOC profile in exhaled breath holds valuable insights into an individual's health status, thereby potentially serving as non-invasive biomarkers for detecting, monitoring, and managing various respiratory diseases.[34, 35]

Nitric oxide (NO) is a colorless and odorless gas that acts as a vital signaling molecule in diverse physiological processes. Within the respiratory system, specialized cells in the airways, including endothelial cells lining blood vessels and respiratory airway epithelial cells, produce NO through cell type-specific NO synthase, which plays a pivotal role in lung function regulation and modulation of vascular tone. In healthy lungs, NO

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orchestrates bronchodilation by relaxing smooth muscles encircling airways, facilitating efficient airflow.[36] Additionally, NO serves as a vasodilator, promoting blood vessel dilation, enhancing oxygen delivery, and improving circulation in lung tissues.[37] Distinct levels of exhaled NO have been observed in patients with IPF compared to healthy individuals, with elevated levels associated with increased lung inflammation. Moreover, elevation of exhaled NO levels correlates with advanced IPF stages and compromised lung function,[38] suggesting its potential as a non-invasive marker for monitoring disease progression and treatment response. In addition to NO, distinct alkanes, alcohols, ketones, and aromatic compounds have been associated with IPF pathogenesis, highlighting their potential diagnostic relevance.[39, 40]

Several challenges must be overcome to fully harness the capabilities of breath biomarkers. Establishing standardized procedures for breath sample collection and storage is imperative to ensure consistency and comparability across diverse studies and research centers. Developing sensitive, specific, and cost-effective analytical techniques for measuring breath biomarkers is vital for broad clinical adoption. Interpreting intricate breath biomarker data necessitates advanced statistical methods and bioinformatics tools to differentiate disease-specific patterns from noise and confounding factors. In sum, comprehensive, large-scale, multicenter validation studies are essential to establish the reliability and reproducibility of breath biomarkers as diagnostic or prognostic tools.

Despite the challenges, the potential of breath biomarkers, including VOCs and NO, in IPF diagnostics and personalized treatment is promising. If successfully validated and integrated into clinical practice, breath biomarkers could offer a range of advantages. Development of a non-invasive and repeatable means of assessing disease status and treatment response like breath biomarkers could mitigate the need for invasive procedures. The ability to detect disease-specific breath signatures at early IPF stages could facilitate timely interventions and potentially improve patient outcomes. Additionally, these biomarkers might identify patient subgroups with diverse disease phenotypes, enabling personalized treatment strategies tailored to individual needs. Initial studies on using VOCs as biomarkers for lung diseases found overlaps in markers across different diseases, making it hard to identify disease-specific biomarkers. Recent research suggests that a unique combination of VOCs, or “breath-print, ” might better characterize specific lung diseases. Advanced techniques are now being used to differentiate patients with various lung diseases from healthy individuals based on these VOC profiles.[41, 42] Furthermore, breath biomarkers could play a pivotal role in assessing therapeutic effectiveness over time, enabling adjustments in treatment plans when necessary [Table 2].

Biomarkers in BAL fluids and sputum

BAL obtains cellular and fluid specimens from the bronchi and alveoli of the lower respiratory tract, providing a pivotal diagnostic modality. This method offers invaluable insights into lung cellular makeup and inflammation, particularly relevant for diseases such as IPF. Chronic and uncontrolled inflammation propels the progression of lung fibrosis. Differential cell counts in BAL fluids serve as a useful tool to assess the myriad immune cells participating in the inflammatory response. These counts include

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neutrophils, macrophages, lymphocytes, eosinophils, and epithelial cells; variations in their proportions serve as markers of inflammation intensity and presence.[43] Clinical applications of BAL cell differentials in IPF are diverse, ranging from serving as a diagnostic aid by identifying abnormal cellular profiles to differentiating IPF from other lung diseases.[44] Changes in the cellular composition of BAL fluids can signify disease progression or gauge treatment effectiveness.[43] Moreover, specific cellular patterns can predict treatment responsiveness. These differentials are foundational for drug development targeting the disease mechanisms.[45, 46] Concurrently, the levels of signaling molecules like cytokines and chemokines, specifically interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α), are also monitored in BAL fluids to provide crucial data for ongoing inflammation and therapeutic responses.[47]

IL-17 cytokines, particularly IL-17A and IL-17F, are known for their proinflammatory effects and contribute to disease progression by stimulating fibrocyte proliferation from bone marrow and affecting tissue remodeling. IL-17A plays a significant role in bleomycin (BLM)-induced pulmonary fibrosis by promoting neutrophil recruitment, inducing epithelial–mesenchymal transition (EMT), and encouraging fibroblast proliferation. However, it also inhibits autophagy, hindering fibrosis resolution. Key sources of IL-17A, like T helper cell 17 (Th17) and $\gamma\delta$ T cells, exacerbate fibrotic lung diseases, while the roles of other immune cells like type 3 innate lymphoid cells (ILC3s), IL-17-secreting CD8 T cells (Tc17s), and invariant natural killer T (iNKT) cells in pulmonary fibrosis are also explored, although they appear less impactful compared to other type-17 immune cells. This highlights the intricate interplay between different cytokines and immune cells in the development and progression of pulmonary fibrosis.[48, 49] Several studies have identified a link between the IL-17 family of cytokines and pulmonary fibrosis. In a mouse model where pulmonary fibrosis was induced using BLM, there was a significant increase in IL-17 levels in the lungs, thoracic lymph nodes, and BAL fluid.[50–52]

Growth factors such as transforming growth factor-beta (TGF-β) and connective tissue growth factor (CTGF) play critical roles in fibrotic activities by activation of fibroblasts and ECM production.[53, 54] Additionally, surfactant protein D (SP-D), synthesized mainly by alveolar type II epithelial cells, serves as a potential biomarker for diagnosis and prognosis as its elevated levels in BAL fluids indicate lung damage and correlate with IPF severity. The ECM, especially specific components like collagen fragments, offers invaluable insights into ongoing fibrotic processes and can be an indicator of treatment efficacy and disease progression.[55]

IPF patients, similar to those with chronic obstructive pulmonary disease (COPD), show increased sputum counts of neutrophils, eosinophils, macrophages, and epithelial cells compared to healthy subjects. These differences in sputum and gene-expression profiles between IPF, COPD, and healthy individuals highlight the diagnostic and prognostic potentials of these biomarkers.[56] The miRNA content of sputum-derived exosomes in IPF has been found to be a promising source for biomarkers useful in diagnosis and assessing disease severity.[57]

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The landscape of BAL biomarker research is dynamic, featuring advancements such as miRNA profiling, enhanced proteomics, metabolomics, and the incorporation of machine learning and artificial intelligence. These burgeoning technologies have the potential to revolutionize IPF diagnosis and treatment. The clinical utility and reproducibility of these emerging biomarkers require validation through large-scale studies. Interdisciplinary collaborations among researchers, clinicians, and technologists are essential for realizing the full potential of BAL biomarkers in IPF management [Table 3].

Imaging biomarkers

HRCT is the cornerstone for diagnosing IPF.[58] It offers detailed imaging of the lung parenchyma and allows for the identification of specific patterns, such as honeycombing and reticular opacities, associated with IPF. Several HRCT scoring systems have been developed to semiquantitatively evaluate the extent and severity of fibrosis. These include the Wells Score, which assesses fibrosis on a scale of 0–4 based on the involvement of the lung; the Goh Score, which focuses on the extent of honeycombing, reticular changes, and ground-glass opacities; and the Composite Physiologic Index (CPI), which is a combination of HRCT findings and pulmonary function tests.[59] These HRCT scoring systems have shown a strong correlation with clinical outcomes, including survival. However, the caveats include the requirement of experienced radiologists for interpretation, time-consuming process, and exposure of patients to radiation.

Quantitative HRCT aims to overcome the limitations of subjective scoring by employing computer algorithms to analyze lung images.[60] Techniques such as texture analysis evaluate pixel distribution to quantify heterogeneity in lung tissues, while lung density measurements utilize histograms to assess density changes in lung tissue. Quantitative HRCT analysis provides an objective and reproducible measure of disease severity but requires sophisticated software and expertise in image analysis.[61]

18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) offers metabolic insights into pulmonary fibrosis by showing glucose uptake in active fibrotic regions. This modality provides an idea of metabolic activity, which is often increased in fibrotic tissue, and is helpful for differentiating IPF from other ILDs.[62, 63] However, it is expensive and not widely available, and exposes patients to higher levels of radiation compared to HRCT.

Other imaging options include magnetic resonance imaging (MRI) and combined PET/CT. MRI has shown promise in depicting pulmonary perfusion and inflammation but is less effective for detailed anatomical study.[64] Combining PET with CT improves anatomical localization of metabolic changes but increases radiation exposure and cost.[63, 65]

Challenges and future perspectives in the realm of imaging biomarkers include the lack of standardization across different imaging modalities, ethical considerations regarding radiation exposure, and the need for multidisciplinary expertise for interpretation. Integration of artificial intelligence in image analysis could make evaluations more standardized and accessible. Longitudinal studies are needed to validate the predictive value of these imaging biomarkers for clinical outcomes.

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Gene-expression profiling and genomic biomarkers

Microarray analysis and RNA sequencing (RNA-seq) are robust tools employed for transcriptomic profiling, which facilitate the quantitative assessment of gene-expression levels in a given biological sample.[66] These methodologies offer critical insights into the genes actively transcribed in specific tissues or cell types under particular conditions.[67] While microarray analysis uses DNA probes that hybridize with the sample's RNA to measure gene-expression levels of known genes, RNA-seq directly sequences complementary DNA (cDNA) molecules, providing a more comprehensive and quantitative view of the transcriptome, including the identification of novel transcripts and alternative splicing events.[68]

Transcriptomic profiling has been a cornerstone in revealing gene-expression patterns associated with IPF.[69] Comparisons of gene-expression profiles from patients with IPF with those from healthy individuals or those with other lung diseases have identified differentially expressed genes that are characteristic of IPF.[70] The knowledge gained has provided invaluable insights into the molecular mechanisms underlying IPF, highlighting dysregulated genes involved in inflammation, fibrosis, ECM remodeling, and epithelial–mesenchymal transition, among others. Such profiling has led to the identification of promising therapeutic targets and biomarkers for IPF.[71, 72]

Recently developed single-cell sequencing and spatial transcriptomics offer a more nuanced understanding of cellular heterogeneity within tissues. Single-cell sequencing allows for the exploration of gene-expression profiles at the level of individual cells, offering crucial information about distinct cell populations. This is particularly important for dissecting the complex cellular landscape in tissues like the lungs.[73, 74] Spatial transcriptomics integrates traditional tissue imaging with transcriptomic profiling, allowing for the spatial localization of different cell types and associated gene-expression patterns within specific tissue regions.[72] Integrative analysis of data from various omics technologies, such as genomics, transcriptomics, proteomics, and epigenomics provides a comprehensive view of the molecular landscape in IPF, enabling identification of key molecular pathways and interactions that contribute to the disease. Multi-omics integration can help associate genetic variations with changes in gene expression, protein levels, and epigenetic modifications, thereby enriching our understanding of functional networks and regulatory mechanisms implicated in IPF pathogenesis.[75]

The need for sophisticated bioinformatics tools and a substantial number of well-characterized samples pose significant challenges for the development of genomic biomarkers, particularly for rare diseases like IPF. Nevertheless, genomic biomarkers offer promising avenues for the advancement of personalized medicine. Technological advancements are likely to render genomic profiling increasingly feasible for routine clinical application, both in terms of cost and accessibility. Integration of genomic data with clinical parameters, imaging biomarkers, and traditional clinical measurements could pave the way for personalized treatment plans, optimizing therapeutic outcomes for IPF patients. The application of genomic biomarkers in clinical trials holds the potential to streamline

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patient selection, treatment monitoring, and adverse effect detection, thereby fostering more efficient and targeted drug development processes.

Proteomic and metabolomic biomarkers

Mass spectrometry-based proteomics is an advanced analytical technique that enables the identification and quantification of proteins within biological samples.[76] This method measures the mass-to-charge ratio of ions, delivering detailed data on the mass and abundance of these peptides. The proteomics approach has proven exceptionally promising in the realm of biomarker discovery and validation for IPF.[77] By comparing proteomes from IPF patients with those of healthy controls, distinctive protein biomarkers associated with the disease have been identified. These biomarkers not only signal the presence, severity, and progression of IPF, but they also illuminate the molecular pathways that are implicated in its pathogenesis. Similar to gene-expression profiling analysis, proteomic data can be amalgamated with data from other omics technologies, providing a multi-layered, molecular understanding of IPF. Validation of these proteomic biomarkers in independent patient cohorts is critical to confirm their clinical utility and reproducibility. Targeted proteomics strategies such as selected reaction monitoring (SRM) or parallel reaction monitoring (PRM) can be employed to quantify these candidate biomarkers with high specificity and sensitivity in larger patient samples.[78]

Metabolomics, the study of small molecules or metabolites resulting from cellular processes, complements proteomic analysis. Lipidomics, a subfield of metabolomics, is dedicated to the comprehensive scrutiny of lipids. In IPF, changes in metabolic profiles are often induced by cellular stress, inflammation, and tissue remodeling. Both metabolomics and lipidomics have revealed metabolic pathways that are disrupted in IPF.[79, 80] Detecting altered levels of specific metabolites or lipids in biological samples could identify invaluable biomarkers for the diagnosis, prognosis, and therapeutic response in IPF. The fusion of data from proteomics, metabolomics, and genomics facilitates a systems biology analysis of IPF. This integrative approach enables a more thorough comprehension of the intricate molecular interactions and regulatory networks in the disease. For instance, by connecting data on differentially expressed proteins with altered metabolite profiles, investigators can correlate protein expression changes to subsequent metabolic disturbances in IPF.[81, 82] The inclusion of genomic data enriches this picture, adding a layer of understanding concerning the genetic factors that may influence protein and metabolite levels.[83] This comprehensive understanding could lead to the discovery of new therapeutic targets and underpin the development of precision medicine strategies for IPF.

Emerging biomarkers

Epigenetic modifications are heritable changes in gene expression that do not involve alterations to the DNA sequence itself. These changes play a critical role in regulating gene activity and can be influenced by environmental variables. Epigenetic alterations are implicated in both the disease's initiation and progression in IPF. Specifically, DNA methylation, which involves the addition of methyl groups to cytosine residues in DNA, can result in gene silencing. Abnormal patterns of DNA methylation have been observed in IPF,

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particularly affecting genes associated with fibrosis, inflammation, and EMT.[84–87] Histone modifications, which are chemical changes to histone proteins, can alter chromatin structure and gene expression. These changes have been found to contribute to the dysregulation of pro-fibrotic and inflammatory genes in IPF.[88, 89] The exploration of epigenetic modification as potential biomarkers holds promise for elucidating disease mechanisms and identifying therapeutic targets.

Exosomes and other extracellular vesicles (EVs) are minute membrane-bound vesicles secreted by cells. They encapsulate a diverse array of biomolecules, such as proteins, nucleic acids, and lipids, thus reflecting the molecular composition of their originating cell. The ability to isolate these vesicles from blood and other bodily fluids renders them attractive candidates for non-invasive biomarker discovery.[90, 91] In IPF, circulating exosomes and EVs display unique miRNA, messenger RNA (mRNA), and protein profiles linked with fibrosis and inflammation.[92, 93] Analysis of the molecular cargo within these vesicles can offer valuable insights into disease activity and progression.

Contrary to prior beliefs that the lung is a sterile environment, recent research has revealed the existence of a lung microbiome. Changes in this microbiome have been associated with IPF disease severity and progression.[94] Metagenomic studies, which sequence the collective genetic material from a sample of microorganisms, can help identify microbial signatures related to IPF.[95] Understanding the interactions between the lung microbiome and the host offers new avenues for identifying potential biomarkers for disease monitoring.

Transition of biomarkers from bench to bedside

Biomarkers are critical tools for predicting the trajectory and mortality in IPF. Combined with clinical assessments, biomarker data enable the development of predictive models for estimating individual risks associated with disease progression and mortality.[10]

Blood-based biomarkers such as SP-D, KL-6, and MMPs are particularly noteworthy. Elevated levels of SP-D and KL-6 have been linked with a worse prognosis, while increased levels of MMPs indicate heightened fibrotic activity and accelerated disease progression. Genetic variations, specifically mucin 5B (MUC5B) and telomerase reverse transcriptase (TERT), have been identified as risk factors contributing to the onset and progression of IPF. Imaging features (e.g., honeycombing and traction bronchiectasis) discerned through HRCT also serve as predictors for adverse outcomes and mortality. Functional measures, such as forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO), are other reliable biomarkers for tracking disease progression and survival[96] [Table 4].

IPF is inherently heterogeneous, with patients experiencing varying rates of disease progression and response to treatment. Biomarkers enable clinicians to identify progressive phenotypes, which are crucial for tailoring disease management and therapeutic interventions to individual needs.[97] Biomarkers also assist in risk stratification and may serve as early warning indicators for acute exacerbations, a serious and often deadly complication of IPF. A multidimensional approach to risk stratification in IPF, which

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combines clinical assessments with imaging findings and multi-omics data, allows for more accurate and personalized prognostication. Personalized risk profiles, informed by this integrative approach, can guide whether more aggressive therapeutic approaches are warranted or whether a more conservative treatment plan should be adopted.[98] By synthesizing these various sources of information, a comprehensive, personalized, and data-driven treatment plan can be formulated, enhancing the efficacy of treatment and the quality of patient care in IPF.[99]

Rigorous validation is essential for the transition of biomarkers from research to clinical practice. The translation of biomarkers to clinical settings occurs in several phases: initial exploratory studies identify potential biomarkers; validation studies assess the performance and reproducibility of biomarkers in larger patient cohorts; clinical utility studies evaluate the impact of biomarkers on patient management and treatment choices; and finally, biomarkers must receive regulatory approval before being integrated into routine clinical practice for the diagnosis, prognosis, and treatment of IPF.

Conclusion

At present, the diagnosis of IPF is heavily dependent on clinical evaluations and radiographic observations, which often result in delayed diagnosis and initiation of treatment.[100] Over the past several years, considerable research efforts have been focused on the identification and application of biomarkers for precise diagnosis, prognosis, and management of IPF. Biomarkers offer the potential for improved diagnostic accuracy and the ability to identify IPF in its early stages. This early detection facilitates timely medical intervention, which could significantly enhance patient outcomes. Furthermore, biomarkers exhibit potential in prognosticating the trajectory of the disease and mortality among IPF patients. By evaluating the severity of the disease and recognizing progressive phenotypes, biomarkers enable clinicians to customize treatment regimens for individual patients. This tailored approach could optimize therapeutic strategies, monitor treatment responses, and ultimately improve the quality of life for those afflicted with IPF.

Beyond their roles in diagnosis and prognosis, biomarkers offer invaluable insights into the intricate pathogenic mechanisms underlying IPF. Factors such as inflammation, immune system dysregulation, fibroblast activation, and dysregulation of stem cell-mediated lung regeneration are critical contributors to the development and progression of IPF. Biomarkers serve as pivotal tools in decoding these complex processes, thereby creating pathways for the development of targeted therapies and innovative treatment modalities.

Despite the considerable advancements in biomarker research, certain challenges remain. The standardization and reproducibility of biomarker assays are vital for ensuring consistent and dependable results across varied research endeavors and clinical settings. Moreover, it is essential to validate the clinical utility and relevance of these biomarkers through studies involving large and diverse patient cohorts. To overcome the challenges of standardization and reproducibility in biomarker research for clinical applications, it is essential to establish rigorous standardization protocols for biomarker assays, including uniform procedures for sample collection, processing, and analysis. Utilizing advanced analytical techniques and

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technologies can improve accuracy and sensitivity in biomarker detection. A comprehensive analysis of biomarkers from multiple tissue specimens using various technologies and a multidimensional approach integrating genomics, proteomics, and metabolomics will provide a more robust understanding. Validating these biomarkers in large and diverse patient cohorts is crucial to assessing their clinical utility. Collaborative efforts between academic, clinical, and industry partners, along with adherence to regulatory guidelines, are imperative to ensure the generalizability and applicability of biomarkers in clinical settings, thereby enhancing patient outcomes in conditions like IPF.

Looking to the future, the role of biomarkers in IPF management is highly promising. Emerging technologies in genomic profiling, single-cell sequencing, and spatial transcriptomics are expected to further our understanding of the disease and lead to the discovery of new biomarkers. Integrating multiple biomarkers with clinical data could revolutionize risk stratification and treatment decision-making, marking a significant stride toward personalized medicine for IPF patients.

In summary, biomarkers are becoming indispensable in managing IPF. Their transformative impact on diagnosis, prognosis, and personalized treatment strategies is undeniable. As research continues to evolve, biomarkers are poised to become a routine aspect of IPF management, improving patient outcomes and offering hope to those affected by this challenging lung disease.

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Table 1

Biomarkers in blood related to IPF.

Biomarker	Associated conditions	Clinical significance	Remarks
SP-A	IPF	Differentiates IPF from other lung diseases and healthy individuals; worse prognosis	Effective in identifying IPF in Caucasian patients; limited specificity due to presence in other diseases
SP-D	IPF, other lung diseases, respiratory infections	Differentiates IPF from lung infections and healthy individuals, but not from other non-IPF lung diseases; worse prognosis	High levels in IPF patients; varying significance in different ethnic groups
MMPs	IPF	Elevated levels linked to disease severity and prognosis	Elevated levels in IPF; further validation needed for clinical utility
TIMPs	IPF	Balance disrupted in IPF, excessive ECM deposition and fibrosis	Disrupted balance in IPF; further studies needed
TIMP-1	IPF, other lung diseases	Indicator for diagnosing lung diseases and disease severity	Changes with treatment in lung fibrosis, potential marker for treatment efficacy
MMP-7	IPF	Indicator for diagnosing lung diseases and disease severity	Needs further validation for clinical utility
KL-6	IPF, other lung conditions	Correlated with disease severity and lung function decline	Used in clinical practice in Japan; concerns about specificity
S100A12	IPF	Elevated levels associated with disease severity and prognosis	Potential as a biomarker; requires further research for definitive establishment
PIIINP	IPF	Indicator of fibrosis extent and disease progression	Potential as a non-invasive assessment tool for fibrosis in IPF patients
Galectin-3	IPF	Tied to disease severity and prognosis	May play a role in early stages of pulmonary fibrosis
Periostin	IPF	Highly expressed, predicts lung function decline over time	Significant biomarker for disease activity in older IPF patients
MicroRNAs (miRNAs)	IPF	Implicated in IPF pathogenesis; therapeutic potential	Diagnostic and prognostic value needs further validation

ECM: Extracellular matrix; IPF: Idiopathic pulmonary fibrosis; KL-6: Krebs von den Lungen-6; miRNAs: microRNAs; MMPs: Matrix metalloproteinases; MMP-7: Matrix metalloproteinase 7; PIIINP: Procollagen III N-terminal peptide; SP-A: Surfactant protein A; SP-D: Surfactant protein D; TIMPs: Tissue inhibitors of metalloproteinases; TIMP-1: Tissue inhibitor of metalloproteinase 1.

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Table 2

Biomarkers in exhaled breath related to IPF.

Biomarker	Clinical significance	Potential applications
VOCs	Potential noninvasive biomarkers for detecting, monitoring, and managing respiratory diseases; reflect changes in body's physiology and metabolism	Non-invasive assessment of disease status and treatment response; detection of disease-specific breath signatures at early stages
NO	Elevated levels associated with increased lung inflammation and advanced IPF stages; potential marker for monitoring disease progression and treatment response	Non-invasive monitoring of IPF progression and treatment effectiveness; early detection and personalized treatment strategies

IPF: Idiopathic pulmonary fibrosis; NO: Nitric oxide; VOCs: Volatile organic compounds.

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Table 3

Biomarkers in BAL fluids and sputum related to IPF.

Biomarker	Specific markers/components	Role in IPF
Differential cell counts	Neutrophils, macrophages, lymphocytes, eosinophils, epithelial cells	Assess inflammation, differentiating IPF from other lung diseases
Cytokines and chemokines	IL-1, IL-6, IL-8, TNF-α	Indicate ongoing inflammation and therapeutic responses
IL-17 cytokines	IL-17A, IL-17F	Contribute to disease progression, stimulating fibrocyte proliferation
Growth factors	TGF-β, CTGF	Activation of fibroblasts, ECM production
SP-D	Elevated levels indicate lung damage; correlates with IPF severity	Potential biomarker for diagnosis and prognosis
ECM components	Collagen fragments	Insights into ongoing fibrotic processes, indicator of treatment efficacy
Sputum counts	Increased counts of neutrophils, eosinophils, macrophages, epithelial cells in IPF patients	Highlight differences in IPF and COPD; diagnostic and prognostic potentials
miRNA content of sputum-derived exosomes	Potential biomarkers for diagnosis and severity assessment	Promising for diagnosis and severity assessment

BAL: Bronchoalveolar lavage; COPD: Chronic obstructive pulmonary disease; CTGF: Connective tissue growth factor; ECM: Extracellular matrix; IL-1: Interleukin-1; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-17: Interleukin-17; IPF: Idiopathic pulmonary fibrosis; miRNA: microRNAs; SP-D: Surfactant protein D; TGF-β: Transforming growth factor-beta; TNF-α: Tumor necrosis factor-alpha.

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Table 4

Biomarkers related to IPF prognosis.

Biomarker	Type	Implication
SP-D	Blood-based	Linked with worse prognosis
KL-6	Blood-based	Linked with worse prognosis
MMPs	Blood-based	Indicates heightened fibrotic activity and accelerated disease progression
MUC5B	Genetic	Risk factor for onset and progression of IPF
TERT	Genetic	Risk factor for onset and progression of IPF
Honeycombing (HRCT)	Imaging	Predictor for adverse outcomes and mortality
Traction bronchiectasis (HRCT)	Imaging	Predictor for adverse outcomes and mortality
FVC	Functional	Reliable biomarker for tracking disease progression and survival
DLCO	Functional	Reliable biomarker for tracking disease progression and survival

DLCO: Diffusing capacity of the lungs for carbon monoxide; FVC: Forced vital capacity; HRCT: High-resolution computed tomography; IPF: Idiopathic pulmonary fibrosis; KL-6: Krebs von den Lungen-6; MMPs: Matrix metalloproteinases; MUC5B: Mucin 5B; SP-D: Surfactant protein D; TERT: Telomerase reverse transcriptase.

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