SYSTEMATIC REVIEW OPEN ACCESS

Assessment of Matrix Metalloproteinases a Prognostic Indicator in Advanced Fibrotic Lung Disease: A Systematic Review

Mehvish Aqil[1], Saif Ur Rahman[1], Muhammad Zeeshan Aslam[2], Mostafa Ahmed Abdellah Ahmed[3], Ammar Ahmed[4], Sidra Javaid[5], Ehsan Ul Haq [6]

[1]Department of Pulmonology, Allied Hospital-II DHQ, Faisalabad Medical University, Faisalabad, Pakistan,[2]Department of Medicine, ABWA Medical College Faisalabad, Pakistan,[3] Department of General Surgery, Cairo University, Cairo, Egypt, [4] Department of Pulmonology, Niazi Medical and Dental College Sargodha, Pakistan,[5] Department of Internal Medicine, Services Hospital Lahore, Pakistan,[6]School of Biochemistry, Free University of Berlin, Germany.

ABSTRACT

Background: Fibrotic lung diseases were seen to have devastating effects among patients globally. Matrix metalloproteinases (MMP) including MMP-7, MMP-9, and MMP-1 have become promising biomarkers for idiopathic pulmonary fibrosis (IPF), and other fibrotic lung diseases. In this systematic review, the objective was to evaluate their roles in predicting disease severity, progression, and response to treatment to increase diagnostic and prognostic accuracy.

Methods: Following PRISMA guidelines, a systematic search of PubMed, Google Scholar, and Web of Science (January 2014 to December 2024) was conducted. Study screening was conducted using Covidence software and data extraction was performed using Microsoft Excel. Studies with MMP-7, MMP-9, or MMP-1 as potential biomarkers in IPF and fibrotic lung diseases with observed associations with disease outcomes met inclusion criteria. Studies not intended to be original, in focus, or with information that was insufficient in methodology were excluded as exclusion criteria. Qualitative synthesis was conducted based on fifteen studies (n=3,965 participants) that met eligibility criteria, mostly due to methodological heterogeneity. ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool was used to assess the risk of biasness for each study.

Results: This systematic review selected 15 studies out of an initial pool of 112 articles. The sample size ranged from 12 to 2,312 participants, with a total of 3,965 participants combined. The MMP-7 was consistently elevated in 73.3% (n=11) of the studies and correlated with disease severity, lung function decline, and progression. In 46.7% (7) of studies, MMP-9 was associated with imaging severity and functional impairments, and in 26.7% (4) of studies, MMP-7 was found as the strongest biomarker, and the correlation coefficient calculated was from (r = 0.65 to 0.80), for MMP-9 it was (r = 0.4 to 0.6) and for MMP-1 (r = 0.3 to 0.45). Direct comparisons were limited by methodological and population variability.

Discussion: MMP-7 seemed to be the most reliable biomarker of disease severity and progression, while MMP-9 and MMP-1 added insights for research into disease mechanisms. Limitations were seen in the small sample size, single-center design, and lack of longitudinal data. Validation of these findings and development of clinical applications would depend on the conduct of larger, multicentre studies.

Keywords: Matrix Metalloproteinase-7, Matrix Metalloproteinase-9, Matrix Metalloproteinase-1, Biomarkers, Pulmonary Fibrosis.

Corresponding Author:
Dr. Ehsan Ul Haq,
School of Biochemistry,
Free University of Berlin, Germany.
Email; Ehsanulhaqkhan33@gmail.com
ORCID: https://orcid.org/0009-0005-2392-2360
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INTRODUCTION

In respiratory medicine, fibrotic lung diseases, especially idiopathic pulmonary fibrosis (IPF), were seen to be major problems because of relentless progression, lack of effective treatment, and high mortality[1]. The most common form of idiopathic interstitial pneumonia known till today is IPF, in which excessive deposition of extracellular matrix (ECM) proteins leads to irreversible lung scarring and then impaired function[2]. With a median survival of three to five years after diagnosis, there was an immediate need for reliable biomarkers that could aid in early diagnosis, monitoring disease severity, predicting disease progression, and assessing therapeutic efficacy[3].

IPF till recently was diagnosed and monitored by clinical evaluation, pulmonary function tests (PFTs), imaging, and occasionally with invasive procedures like surgical lung biopsy. These tools were quite helpful, but did not predict disease trajectory well or in other words are unable to separate IPF from other interstitial lung diseases (ILDs)[4]. Despite the advancements in antifibrotic therapies including pirfenidone and nintedanib, which had made disease management better by slowing progression, the ability to accurately identify patients who were at high risk of rapid decline remained limited. The biomarkers which were capable of reflecting disease activity and prognosis in real time, were thus critically needed to augment clinical decision-making and enhance patient outcomes[5].

Matrix metalloproteinases (MMPs) have been examined as potential approaches to this need. ECM degradation and remodeling processes which were considered crucial to the pathogenesis of fibrotic lung diseases were mediated by a family of zinc-dependent proteases called MMPs. Of these, MMP-7, MMP-9, and MMP-1 had shown the greatest promise[6]. Elevated levels of MMP-7 had been reported consistently in IPF and were associated with disease progression; both MMP-7 including its specific polymorphisms, along with MMP-12, contributed to epithelial injury and fibroblast activation[7]. MMP-9 had been linked with worse lung function and severe imaging patterns as it found its role in ECM degradation and modulation of fibrotic pathways. Although less extensively studied, MMP-1 has shown potential as a marker of ECM remodeling and early fibrotic changes. Taken together, these MMPs provided a mechanistic connection to the pathological processes that caused IPF. This makes them an attractive target for the development of biomarkers[8].

The roles of MMPs which were studied against fibrotic lung diseases were of diagnostic and prognostic biomarkers. Although serum assays and other minimally invasive techniques that measure MMP levels had given clues to disease severity, progression, and response to therapy, they were not yet broadly integrated into clinical practice[9]. Moreover, variability in study design, population characteristics, and measurement techniques hindered the establishment of the clinical utility of these biomarkers[10]. Therefore, a comprehensive review was required for a clear understanding of the potential role of these biomarkers and the limitations of current studies. So that they could be addressed properly.

This study aimed to systematically review the evidence present for MMP-7, MMP-9, and MMP-1 as prognostic biomarkers in IPF and other advanced fibrotic lung diseases. The aim was to assess the consistency, reliability, and clinical relevance of these MMPs across studies in different settings, to identify gaps in the literature, and to propose future research directions. All of this was underlined by the overarching aim of advancing our understanding and management of these chaotic conditions, thereby improving patient care and outcomes. The objective of this study was to identify the diagnostic and prognostic role of MMP-7, MMP-9, and MMP-1 against fibrotic lung diseases to improve treatment

outcomes in patients.

METHODS

This systematic review followed the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for transparency and rigour. Studies conducted between January 2014 and December 2024 were reviewed that corresponded to the advancements in biomarker research in fibrotic lung diseases. PubMed, Google Scholar, and Web of Science Databases were searched comprehensively. Search terms and Medical Subject Headings (MeSH) terms included "MMP-7," MMP-9," MMP-1," "matrix metalloproteinases," "idiopathic pulmonary fibrosis," "fibrotic lung disease," "prognostic biomarkers," and "pulmonary fibrosis." The references from the studies identified were also screened which included additional relevant studies.

This study focussed on idiopathic pulmonary fibrosis (IPF) and other fibrotic lung diseases by investigating MMP-7, MMP-9, or MMP-1 as prognostic biomarkers. Original research articles with full text available in English were included if they reported associations with disease severity, progression, or treatment responses and were eligible studies. Studies not relating to fibrotic lung diseases, not dealing with the selected MMPs, reviews, editorials, or commentaries, and those with insufficient methodological details or lack of original data were excluded.

Initially, 112 studies were identified. The remaining were 96 unique studies after the removal of duplicates. Articles from the list were screened for relevance, reducing the pool to 55. This was further reduced to 40 full-text articles that met the eligibility criteria, of which only 15 were included in the systematic review. The 15 studies that were included, showed diversity in methodology, sample size, and geographical context and offered valuable information about the prognostic capacity of the selected MMPs.

Two reviewers independently conducted data extraction to collect the study design, sample size, MMP measurement methods, key findings, and limitations. Discrepancies were resolved with the help of consensus. Study selection, removal of duplicates, and data tabulation were done through Covidence software, and Microsoft Excel was used to organize and analyse the data that were extracted. Due to the review objective and inclusion criteria, studies were systematically screened and refined, with eligibility being determined by relevance to the review's objective. ROBINS-I (Risk of Bias in Non-Randomized Studies of Interventions) tool was used to assess the risk of biasness for each study.

Data was sought based on participant characteristics (age, gender, disease stage, etc), intervention details, and funding sources. Assumptions were made for all missing data variables. Biomarker's measurement methods were inferred concerning context if unspecified. Primary outcomes included progression of disease, mortality, and acute exacerbations whereas secondary outcomes included MMP changes linked with treatment and quality of life. All results that aligned with outcome domains were included but preference was given to clinically relevant metrics. Where possible, missing data were addressed by contacting study authors. Where data could not be retrieved, missing values were either excluded from the synthesis or estimated according to reported medians and interquartile ranges (IQRs) when applicable. This strategy helped to keep the review transparent and minimized the effect of imperfect information on the review's conclusions. A qualitative synthesis was performed due to the heterogeneity of the study designs, populations, and methodologies. The work focused on delineating the consistent trends in MMP levels, associations with disease severity and progression, as well as the areas where current knowledge gaps existed. GRADE assessment was used for certainty of evidence.

Using this systematic and refined approach, the work made an exhaustive evaluation of the role of MMP-7, MMP-9, and MMP-1 as prognostic biomarkers in fibrotic lung diseases.

RESULTS

This systematic review selected 15 studies out of an initial pool of 112 articles identified through searches in PubMed, Google Scholar, and Web of Science. PubMed accounted for 41.1% (n=6), Google Scholar 33.9% (n=5), and Web of Science 25% (n=4) of studies, the flowchart of selection of studies is shown in **Figure 1**.

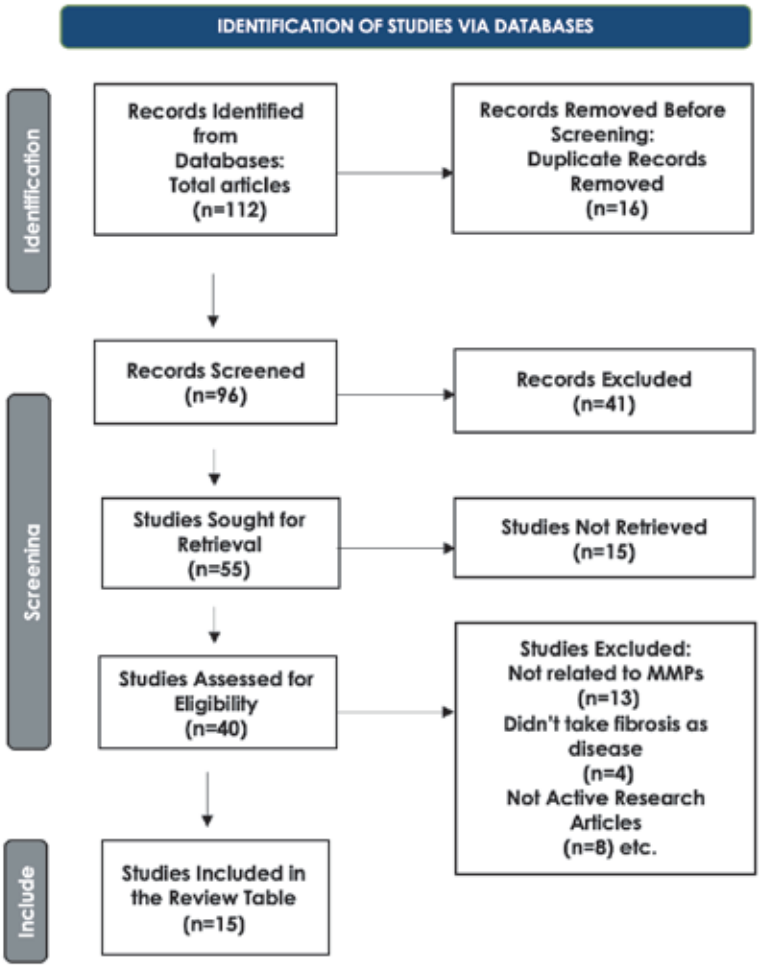

Figure 1: Flowchart showing of selection of studies based on inclusion and exclusion criteria as determined by PRISMA

The included studies encompassed diverse designs, such as, cross-sectional (5), longitudinal (3), prospective cohort (2), experimental (2), and bioinformatics or comparative analyses (3). The sample size ranged from 12 to 2,312 participants, with a total of 3,965 participants combined. The studies were geographically from Europe (6), Asia (5), North America (3), and Latin America (1). These studies (11_25) nearly met all the inclusion criteria and were included in the systematic review table. As shown in **Table 1.**

Elevations of MMP-7 were observed in 11 studies (73.3%), along with associations with disease severity, lung function decline, and progression. It was also responsive to antifibrotic therapy in longitudinal studies. Elevations in MMP-9 were observed across 7 studies (46.7%) which correlated with imaging severity, impaired lung function, and downstream effect on fibrotic pathways. Less frequently researched (4 studies, 26.7%) MMP-1 was a marker of early ECM remodeling. It was seen to be localized to fibroblast foci in the IPF lung tissue.

Due to heterogeneity among studies, a narrative synthesis was performed and descriptive trends and correlations were focused on instead of meta-analytic estimates. MMP-7 was found as the strongest biomarker, and the correlation coefficient calculated was from (r = 0.65 to 0.80), for MMP-9 it was (r = 0.4 to 0.6), and for MMP-1 (r = 0.3 to 0.45). The results were tabulated for ease of reading and the findings were standardized to units of measurement to allow for comparison between studies.

The risk of bias across studies was assessed using the ROBINS-I tool, and moderate risks were found due to small numerical samples, single-center designs, and methodological variance. GRADE assessment for certainty of evidence revealed moderate confidence for MMP-7 and low to moderate for MMP-9 and MMP-1 because of study heterogeneity and lack of replication in larger cohorts.

Funnel plot analyses were not conducted due to the lack of formal assessment of publication bias, however, given the predominance of positive findings for MMP-7, a potential reporting bias is suggested.

No sensitivity or subgroup analyses were conducted, given that the primary interest was descriptive, rather than meta-analytic. These findings were recommended for future meta-analyses to refine and validate them.

The samples were small, design employed was single-centred, and the methods and outcomes varied, limiting generalizability to the restrictive review. Nevertheless, the findings indicated that MMPs might be useful as prognostic indicators for fibrotic lung diseases and should be further investigated in larger, well controlled studies.

Table 1: Summary of Studies Highlighting the Prognostic Capabilities of MMP-7, MMP-9, and MMP-1 in Fibrotic Lung Diseases

Author, Year, Region	Study Design	Sample Size	MMPs Studied and Methodology	Key Findings (with respect to MMPs)	Limitations
Baydar Toprak et al., 2022, Turkey[11]	Cross-sectional study	22	MMP-7, MMP-9; ELISA	No significant correlation between MMP-7 and MMP-9 levels with IPF severity; supports further research in larger cohorts.	Small sample size, pandemic impact, single-center study.
Balci et al., 2023, Turkey[12]	Comparative analysis	90	MMP-1, MMP-7; ELISA	MMP-1 and MMP-7 elevated in IPF compared to controls; associated with diagnostic and prognostic value.	Retrospective design; lack of generalizability due to population selection.
Luedders et al., 2024, USA[13]	Prospective cohort study	2,312	MMP-1, MMP-7, MMP-9; ELISA	Higher MMP-7 and MMP-9 levels associated with increased risk of RA-ILD, highlighting risk stratification potential.	Focused on the RA population; other factors influencing MMP levels are not fully addressed.
Liu et al., 2022, China[14]	Cross-sectional study	36 (31 IPAF, 5 IPF)	MMP-1, MMP-7, MMP-9; U-PLEX Biomarker Multiplex Assays	MMP-7 and MMP-9 linked to IPF but lacked statistical power for strong conclusions due to the small IPF cohort size.	Small IPF cohort, lack of longitudinal follow-up, variability in diagnostic algorithms.
Becerril et al., 2021, Mexico[15]	In vitro cell culture	Fibroblast cell lines	MMP-1; RT-qPCR and gelatin zymography	MMP-1 plays a role in ECM remodeling and fibroblast-to-epithelial transition relevant to lung fibrosis.	Requires further in vivo validation to confirm biological relevance.
Biomarker Study, 2022, Australia, UK[16]	Prospective cohorts	189 (AIPFR), 205 (TLF), 122 (PROFILE)	MMP-7; ELISA and proteomics	Elevated MMP-7 levels are associated with progression and poor prognosis in IPF patients.	Variability in proteomics results across cohorts, insufficient longitudinal data.
Lv et al., 2022, China[17]	Cross-sectional observational	64 (33 CTD-ILD, 31 CTD-NILD)	MMP-9; ELISA	Serum MMP-9 significantly elevated in ILD, including IPF; correlated with reduced FVC and UIP severity.	Small sample size, single-center study, limited to specific connective tissue diseases.
Espindola et al., 2021, USA[18]	Experimental (in vitro, in vivo)	Cell-based and humanized mouse models	MMP-9; Proteomic and genomic analysis, ELISA	MMP-9 upregulation in IPF lungs; antifibrotic effects of MMP-9 inhibition linked to TGF-β1 pathway and IFN levels.	Patient variability (responders vs. nonresponders to MMP-9 inhibition) is not fully explained.

Li et al., 2023, China[19]	Transcriptomic and integrative genomic analysis	Large dataset (431 IPF, 296 healthy)	MMP-1, MMP-7; RNA-seq	MMP-1 and MMP-7 were identified as diagnostic indicators in IPF; linked to alveolar density and lung function decline.	The observational nature of transcriptomic data limits causality; and lack of experimental validation.
Wang et al., 2022, China[20]	Retrospective bioinformatics study	176 IPF patients, 20 controls	MMP-7, MMP-9; gene expression profiling in bronchoalveolar lavage cells	MMP-7 and MMP-9 linked to prognosis; immune cell infiltration (mast and NK cells) correlated with risk.	Limited to gene expression data; needs experimental validation in diverse populations.
Cabrera Cesar et al., 2021, Spain[21]	Observational, cross-sectional	29 IPF, 14 CTD-ILD, 30 controls	MMP-7; ELISA	MMP-7 levels were significantly elevated in IPF vs. controls; not effective at distinguishing IPF from CTD-ILD.	Single-center study; small sample size; cross-sectional design limits causal inference.
Majewski et al., 2021, Poland[22]	Exploratory longitudinal	28 IPF patients, 20 controls	MMP-7; ELISA	MMP-7 elevated in IPF vs. controls; correlated with lung function changes during antifibrotic therapy.	Small cohort; limited to IPF patients receiving antifibrotic therapy; lack of diverse representation.
Kreus et al., 2021, Finland[23]	Experimental (in vitro)	12 (4 ADC, 4 IPF, 4 controls)	MMP-1; qRT-PCR, immunohistochemistry	MMP-1 upregulated in IPF fibroblast foci; localized in stromal cells in lung tissue.	Small sample size; no statistical significance achieved for qRT-PCR results.
Kass et al., 2020, USA[24]	Observational (comparative)	86 RA-ILD, 17 RA, 22 controls	MMP-7; ELISA	MMP-7 elevated in RA-ILD; potential biomarker for distinguishing RA-ILD from RA without ILD.	Limited focus on other MMPs; potential confounding from unmeasured variables.
Todd et al., 2020, USA[25]	Observational (multicentre)	IPF (300), Controls (100)	MMP-1, MMP-7, MMP-9; Multiplex ELISA	MMP-7 and MMP-9 elevated in IPF; higher MMP-7 levels linked to worse disease severity (lower DLCO, higher CPI).	Lack of longitudinal data for progression analysis; potential biases in cohort selection.

Table 2: Risk of Bias Table of Individual Studies using ROBINS-I Tool

Reference	Study Type	Bias due to confounding	Bias in the selection of participants	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported results
Baydar Toprak et al., 2022	Cross-sectional study	Moderate	Moderate	Low	Low	Low	Moderate	Low
Balci et al., 2023	Comparative analysis	Moderate	Moderate	Low	Low	Low	Moderate	Low
Luedders et al., 2024	Prospective cohort study	Low	Low	Low	Low	Low	Low	Low
Liu et al., 2022	Cross-sectional study	Moderate	Moderate	Low	Low	Moderate	Moderate	Low

Becerril et al., 2021	In vitro cell culture	High	High	Low	Low	Low	Moderate	High
Biomarker Study, 2022	Prospective cohorts	Moderate	Low	Low	Low	Moderate	Low	Low
Lv et al., 2022	Cross-sectional study	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
Espindola et al., 2021	Experimental (in vitro, in vivo)	High	High	Low	Low	Low	Moderate	Moderate
Li et al., 2023	Transcriptomic analysis	Moderate	Low	Low	Low	Low	Moderate	Moderate
Wang et al., 2022	Retrospective bioinformatics study	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
Cabrera Cesar et al., 2021	Observational, cross-sectional	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
Majewski et al., 2021	Exploratory longitudinal	Moderate	Moderate	Low	Low	Moderate	Moderate	Low
Kreus et al., 2021	Experimental (in vitro)	High	High	Low	Low	Low	Moderate	High
Kass et al., 2020	Observational comparative	Moderate	Moderate	Low	Low	Low	Moderate	Low
Todd et al., 2020	Observational (multicenter)	Moderate	Low	Low	Low	Moderate	Moderate	Low

DISCUSSION

Matrix metalloproteinases (MMPs), especially MMP-7, MMP-9, and MMP-1, were identified as critical factors for the pathophysiology of idiopathic pulmonary fibrosis (IPF) and other advanced condition of the lungs related to fibrosis26. These enzymes played a central role in remodeling the extracellular matrix (ECM) which was a defining feature of fibrosis. The dysregulated activity has been continuously implicated in the progression of the disease. The findings of this systematic review the importance of MMPs in diagnosis and prognosis of disease which underscored their potential for utility in clinical practice and their role in mechanisms of disease.

MMP-7 was seen as the most studied MMP in the context of IPF. In IPF patients, its level was elevated consistently compared to healthy controls and was strongly associated with disease severity and progression[27]. The reliability of MMP-7 as a biomarker for tracking diseased states was validated by the correlation between MMP-7 levels and critical clinical parameters such as forced vital capacity (FVC) and diffusion capacity (DLCO)[28]. Longitudinal studies also showed that MMP7 levels were associated with treatment responses against fibrosis, suggesting the dynamic use of MMP7 as a marker for monitoring treatment efficacy. Nevertheless, inconsistency was found in the ability of MMP-7 to distinguish IPF from other interstitial lung diseases (ILDs)[29]. This led to a question of whether its specificity could be extended to more clinical use, emphasizing the need for further research to determine its differential diagnostic value.

Similarly, MMP-9 was also shown to be a promising biomarker in fibrotic lung diseases, including IPF. The patterns of elevated MMP-9 correlated with more severe imaging patterns, increased functional impairments, and progression. Studies on the mechanism have demonstrated a role for MMP-9 in ECM degradation and fibrosis modulation through pathways involving TGF-β and interferon signaling[30]. This underscored its functional importance in supporting the fibrotic process. However, variability in patient's response to MMP-9 modulation and heterogeneity in the populations studied suggested that its utility might be influenced by underlying disease characteristics or comorbidities. This variability showed that MMP-9 has strong mechanistic relevance, but might need to be

carefully contextualized when applied as a prognostic tool[31].

Although not extensively studied, the emerging potential of MMP-1 as a diagnostic and prognostic marker of IPF was also seen. IPF patients frequently showed elevation in MMP-1 as it was associated with structural changes in the lung including reduced alveolar density and ECM remodeling[32]. Studies showed the localized expression of MMP-1 to fibroblast foci in IPF lung tissue which suggested its role in disease pathogenesis. Even though the statistical power of studies on MMP-1 was often limited by small sample sizes, these findings consistently indicated that it was relevant in disease processes[33]. MMP-1's link to early fibrotic changes suggested that it may contribute to novel information regarding the early stages of the disease, complementing its role with that of MMP-7 and MMP-9.

Several limitations in the current literature were identified despite the promising role of these MMPs. The robustness and generalizability of the findings were limited because of small sample sizes across studies, and due to the reason that study design and methodologies for MMP quantification were variable and were generating variable results. In addition, most of the studies relied on cross-sectional designs, thereby hindering the inference of causality or time-dependent changes in MMP levels concerning progression of disease. Additionally, the impact of demographic and genetic variability on MMP expression was poorly understood and needed to be explored using more diverse study populations and multicenter trials for further validation[34].

Beyond biomarker discovery, the relevance of these findings extended to the understanding of the underlying mechanisms responsible for driving fibrotic lung diseases. IPF and other advanced fibrotic conditions were characterized by excessive ECM deposition, progressive scarring, and irreversible loss of function[35]. While antifibrotic therapies were effective in slowing disease progression, these therapies could not reverse established fibrosis, thereby making the diagnosis of the disease at an early stage and effective monitoring of the after-effects of treatment crucial. MMP biomarkers (MMP-7 and MMP-9) offered not only prognostic measures but also possible therapeutic targets[36]. They provided insights into the biological processes which accelerated the disease. Further expansion on the potential utility of these biomarkers in identifying early fibrotic changes and guiding therapeutic interventions was provided by MMP-1 due to its association with structural remodeling[37].

To convert these findings into clinical practice, several limitations and barriers must be addressed. There was a need to standardize methodologies for the measurement of MMPs to assure consistency and comparability between studies[38]. Combining MMP data with the clinical, imaging, and other functional parameters might enhance the stratification of the disease and obtain a wider picture of the state of the disease. In addition, the therapeutic potential of MMP as a target could provide new paths towards treatment. Modulating MMP activity could influence fibrotic pathways, but clinical validation was still needed for confirmation of the safety and efficacy of such approaches[39].

In the end, fibrotic lung diseases were seen to be clinically challenging disorders as they were progressive and non-reversible[40]. This review revealed the possibility of MMP 7, MMP 9, and MMP 1 as biomarkers offering the opportunity to transform the diagnostic and prognostic landscape of these diseases. Nevertheless, further work was needed to resolve current limitations and take full advantage of their potential clinical utility. Longitudinal studies with larger cohorts and more diverse populations would be crucial in overcoming the current gaps and advancing the applicability of these biomarkers into routine clinical practice.

CONCLUSION

This systematic review showed that MMP-7, MMP-9, and MMP-1 were strong candidates for prognostic biomarkers of IPF and other advanced fibrotic lung diseases. Of these, MMP-7 was the most reliable indicator for disease severity and progression, and MMP-9 and MMP-1 appeared to provide additional insight into disease mechanisms and diagnosis. However, the weakness of current evidence, including small sample size, variability in methodology, and lack of longitudinal data, highlighted the need for further research. To fully exploit the beneficial potential of MMPs for the diagnosis, monitoring, and treatment of advanced fibrotic lung diseases, these gaps would have to be addressed.

LIST OF ABBREVIATIONS

AIPFR: Australian Idiopathic Pulmonary Fibrosis Registry
BAL: Bronchoalveolar Lavage
CPI: Composite Physiologic Index
CTD-ILD: Connective Tissue Disease-associated Interstitial Lung Disease
CTD-NILD: Connective Tissue Disease-associated Non-Interstitial Lung Disease
DLCO: Diffusing Capacity of the Lung for Carbon Monoxide
ECM: Extracellular Matrix
ELISA: Enzyme-linked Immunosorbent Assay
FVC: Forced Vital Capacity

ILD: Interstitial Lung Disease
IPAF: Interstitial Pneumonia with Autoimmune Features
IPF: Idiopathic Pulmonary Fibrosis
MMP: Matrix Metalloproteinase
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PFT: Pulmonary Function Test
RA: Rheumatoid Arthritis
RA-ILD: Rheumatoid Arthritis-associated Interstitial Lung Disease
RT-qPCR: Reverse Transcription Quantitative Polymerase Chain Reaction
TGF-β: Transforming Growth Factor Beta
VEGF: Vascular Endothelial Growth Factor

AUTHORS' CONTRIBUTIONS
All authors contributed equally as per ICMJE.

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