Serum Matrix Metalloproteinase-7, Respiratory Symptoms, and Mortality in Community-Dwelling Adults

MESA (Multi-Ethnic Study of Atherosclerosis)

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Abstract

Rationale: Matrix metalloproteinase-7 (MMP-7) has been implicated in interstitial lung disease pathobiology and proposed as a diagnostic and prognostic biomarker of idiopathic pulmonary fibrosis.

Objectives: To test associations between serum MMP-7 and lung function, respiratory symptoms, interstitial lung abnormalities (ILA), and all-cause mortality in community-dwelling adults sampled without regard to respiratory symptoms or disease.

Methods: We measured serum MMP-7 in 1,227 participants in MESA (Multi-Ethnic Study of Atherosclerosis) at baseline. The 5-year outcome data were available for spirometry (n = 697), cough (n = 722), and dyspnea (n = 1,050). The 10-year outcome data were available for ILA (n = 561) and mortality (n = 1,227). We used linear, logistic, and Cox regression to control for potential confounders.

Measurements and Main Results: The mean ($\pm$ SD) serum MMP-7 level was 4.3 ($\pm$ 2.5) ng/ml (range, 1.2–24.1 ng/ml). In adjusted models, each natural log unit increment in serum MMP-7 was associated with a 3.7% absolute decrement in FVC% (95% confidence interval [CI] = 0.9–6.6%), a 1.6-fold increased odds of exertional dyspnea (95% CI = 1.3–1.9), a 1.5-fold increased odds of ILAs (95% CI = 1.1–2.1), and a 2.2-fold increased all-cause mortality rate (95% CI = 1.9–2.5). The associations with ILA and mortality tended to be stronger among never-smokers (*P* values for interaction 0.06 and 0.01, respectively).

Conclusions: Serum MMP-7 levels may be a quantitative biomarker of subclinical extracellular matrix remodeling in the lungs of community-dwelling adults, which may facilitate investigation of subclinical interstitial lung disease.

Keywords: matrix metalloproteinase-7; subclinical lung disease; dyspnea; interstitial lung disease

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At a Glance Commentary

Scientific Knowledge on the

Subject: Serum matrix metalloproteinase (MMP)-7 levels are elevated in adults with idiopathic pulmonary fibrosis (IPF) and have been linked to disease severity and a higher mortality rate in IPF.

What This Study Adds to the

Field: Among community-dwelling adults, higher serum MMP-7 levels are associated with reduced FVC and a higher prevalence of exertional dyspnea at 5-year follow-up, and with both interstitial lung abnormalities on computed tomography and an increased mortality rate at 10-year follow-up. Serum MMP-7 may be a biomarker of extracellular matrix remodeling of the lung in the general population.

The fibrotic interstitial lung diseases (ILDs), and idiopathic pulmonary fibrosis (IPF) in particular, are characterized by aberrant extracellular matrix (ECM) remodeling and

fibrosis in the alveolar wall (1). Clinically evident ILD, characterized by progressive dyspnea and functional decline, manifests itself only after significant scarring of the lung parenchyma has occurred, typically years after the initial injury. Until recently, a major barrier to identifying the causes of IPF and other fibrotic ILDs has been the inability to detect early stages of ILD. Subclinical ILD, defined by evidence of lung remodeling, inflammation, and fibrosis in asymptomatic adults on computed tomography (CT), is being increasingly recognized using both automated measurements of increased lung attenuation (high-attenuation areas) and visual identification of early interstitial changes (interstitial lung abnormalities [ILAs]) on chest CT (2–6). Studies of subclinical ILD may lead to a better understanding of the early steps in the pathogenesis of lung fibrosis.

Matrix metalloproteinase (MMP)-7 has been strongly implicated in the development of lung fibrosis in animal models (7), and shows strong construct validity as a diagnostic and prognostic serum protein biomarker in IPF (2, 8–16). We have previously shown an association between increased lung attenuation on

chest CT and MMP-7 in a cross-sectional analysis, suggesting the possibility that serum MMP-7 might be a noninvasive quantitative biomarker of subclinical ECM remodeling of the lung—potentially aiding in the identification of those at risk for incident ILD.

In the current study, we examined whether serum MMP-7 levels exhibit features expected of a quantitative biomarker of ECM remodeling in the lung. Specifically, we hypothesized that higher levels of serum MMP-7 would be associated with lower FVC, symptoms of exertional dyspnea and cough, ILA, and an increased mortality rate in community-dwelling adults.

Methods

Participants and Study Design

MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter, prospective cohort study sponsored by the NHLBI with the purpose of investigating the progression of subclinical cardiovascular disease. Participant selection criteria have previously been described (17). Briefly, between 2000 and 2002, the study enrolled

Table 1. Baseline Characteristics

Characteristics	Serum MMP-7 Quartile				P for Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
MMP-7 ng/ml, range	1.2–2.9	2.9–3.7	3.7–4.8	4.8–24.1	
Participants, n	305	308	308	306	
Age, yr, mean $\pm$ SD	58.6 $\pm$ 9.0	61.6 $\pm$ 9.5	65.9 $\pm$ 9.5	68.7 $\pm$ 9.1	<0.001
Male, n (%)	153 (50)	133 (43)	136 (44)	119 (39)	0.07
Race/ethnicity, n (%)					<0.001
White	156 (51)	115 (37)	89 (29)	66 (22)	
Chinese	23 (8)	47 (15)	60 (20)	38 (12)	
Black	66 (22)	76 (25)	75 (24)	122 (40)	
Hispanic	60 (20)	70 (23)	84 (27)	80 (26)	
BMI, kg/m ² , mean $\pm$ SD	28.4 $\pm$ 5.2	28.2 $\pm$ 5.5	28.0 $\pm$ 5.1	29.6 $\pm$ 5.8	0.97
Height, cm	169 $\pm$ 10	165 $\pm$ 10	164 $\pm$ 10	163 $\pm$ 10	<0.001
Weight, kg	81 $\pm$ 17	77 $\pm$ 17	76 $\pm$ 17	79 $\pm$ 18	0.02
Waist circumference, cm	99 $\pm$ 14	97 $\pm$ 14	98 $\pm$ 13	102 $\pm$ 14	0.10
Hip circumference, cm	107 $\pm$ 12	105 $\pm$ 11	104 $\pm$ 10	107 $\pm$ 13	0.43
Education, n (%)					
High school or less	93 (31)	113 (37)	145 (47)	152 (50)	
At least some college or technical school	143 (47)	129 (42)	124 (40)	124 (41)	
Graduate or professional school	68 (22)	66 (21)	39 (13)	28 (9)	
Smoking					
Never-smokers, n (%)	151 (50)	152 (49)	148 (48)	133 (44)	
Former smokers, n (%)	126 (41)	121 (39)	123 (40)	134 (44)	
Current smokers, n (%)	28 (9)	35 (11)	37 (12)	39 (13)	
Cigarette pack-years, median (IQR)*	10 (2–25)	13 (1–27)	14 (4–30)	14 (1–35)	0.11

Definition of abbreviations: BMI = body mass index; IQR = interquartile range; MMP-7 = matrix metalloproteinase-7.

Note: This table does not account for the sampling strategy used.

*Among ever-smokers.

6,814 adults aged 45–84 years, from six communities in the United States who were free of clinical cardiovascular disease. There were no selection criteria based on lung disease, respiratory symptoms, or smoking history. MESA participants were followed longitudinally and attended serial follow-up visits, with the most recent visit between 2010 and 2012 (exam 5).

Serum MMP-7 was previously measured at baseline in 1,228 adults sampled from the MESA parent cohort (2), as described in the online supplement. In the current analysis, we excluded one participant with an MMP-7 value of 39.9 ng/ml, which highly skewed the distribution of MMP-7 levels. This left 1,227 participants for analysis, all of whom had complete follow-up data for mortality events. Spirometry was not performed at baseline. Of the 1,227 participants, 697 had spirometry performed at 5-year follow-up (see Table E1 in the online supplement), 1,050 completed questionnaires on dyspnea (Table E2), and 722 completed questionnaires on cough (Table E3) at 5-year follow-up; the difference in sample size is due to the number of participants enrolled in ancillary studies (2, 18). A total of 561 underwent full-lung CT imaging read for ILA at 10-year follow-up (Table E4; Figure E1). There were modest differences in MMP-7 values and the distribution of race and ethnicity between those with and those missing outcome data (Table E7). MESA and all ancillary studies were approved by institutional review boards at all collaborating centers, and all participants provided informed consent.

Biomarker Measurements

MMP-7 was previously measured in banked baseline serum samples from MESA participants using quantitative sandwich ELISA (R&D Systems, Minneapolis, MN) at the MESA Core Laboratory at the University of Vermont's Laboratory for Clinical Biochemistry Research (Burlington, VT), as previously described (2).

Spirometry

Spirometry was conducted according to the American Thoracic Society/European Respiratory Society guidelines (19), as previously described (20).

Dyspnea and Cough

Dyspnea and cough were ascertained by trained interviewers. Dyspnea was defined as

an answer of “yes” to either of the following questions: “When walking on level ground, do you get more breathless than people your own age?” and/or “Do you ever have to stop walking due to breathlessness?” Cough was defined as an answer of “yes” to the question “Do you usually have a cough on most days for 3 or more months during the year?”

ILAs

A complete description defining ILA on exam 5 full-lung CT scans has previously been published (2). Briefly, ILA was defined as the presence of ground-glass, reticular abnormality, diffuse centrilobular nodularity, honeycombing, traction bronchiectasis, nonemphysematous cysts, or architectural distortion in at least 5% of nondependent portions of the lung (2, 4, 6, 21). Scans with a usual interstitial pneumonia pattern (bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a subpleural distribution) were also included in the definition of ILA. Scans with a solitary focus of ground-glass attenuation, reticulation, or multifocal ground-glass abnormality in less than 5% of the lung were read as equivocal for ILA and were excluded from further analysis, as previously described (2, 4, 6).

Mortality

MESA participants were followed prospectively. Every 9–12 months, interviewers contacted MESA participants or family members to determine vital status. To ensure complete follow-up of mortality, a review of the National Death Index through the most recent National Death Index update (March 13, 2015) was performed.

Analytical Approach

We first used generalized additive models to examine nonlinear associations between serum MMP-7 and our outcomes of interest. Since all associations appeared linear on the log scale, we used natural log-transformed MMP-7 in all models. We used inverse probability weighting in all models to account for the sampling strategy used to select study participants for biomarker measurements in MESA (see online supplement). We used linear regression to examine the association of MMP-7 with spirometry measurements, and logistic regression to examine the associations between MMP-7 and dyspnea, cough, and ILA. We adjusted for variables that we considered possible confounders or precision variables: age; sex; race/ethnicity; body mass index; smoking status; and cigarette pack-years. We used Cox models to examine the association between MMP-7

Table 2. Associations between Serum MMP-7 Level and FVC among 697 MESA Participants

	Decrement (95% CI) per Natural Log Unit Increment in MMP-7	P Value*
FVC		
Unadjusted, ml	−637.9 (−797.3 to −478.6)	<0.001
Unadjusted, % predicted	−3.4 (−6.2 to −0.5)	0.02
Adjusted, ml [†]	−197.1 (−310.1 to −84.2)	<0.001
Adjusted, % predicted [†]	−3.7 (−6.6 to −0.9)	0.01
FVC, ever-smokers		
Unadjusted, ml	−658.3 (−882.7 to −433.9)	<0.001
Unadjusted, % predicted	−5.0 (−8.8 to −1.3)	0.009
Adjusted, ml [†]	−263.4 (−426.4 to −100.4)	0.002
Adjusted, % predicted [†]	−6.3 (−10.0 to −2.7)	0.001
FVC, never-smokers		
Unadjusted, ml	−661.1 (−873.0 to −449.2)	<0.001
Unadjusted, % predicted	−0.9 (−5.2 to 3.4)	0.68
Adjusted, ml [†]	−168.6 (−309.4 to −27.8)	0.02
Adjusted, % predicted [†]	−0.7 (−5.1 to 3.6)	0.74

Definition of abbreviations: CI = confidence interval; MESA = Multi-Ethnic Study of Atherosclerosis; MMP-7 = matrix metalloproteinase-7.

Spirometry was measured at MESA exam 3 or 4.

*P values for the interaction between log MMP-7 and smoking status were 0.07 for FVC and 0.13 for FVC % predicted.

[†]Adjusted for age, sex, race, body mass index, smoking status, cigarette pack-years (adjustment for smoking and cigarette pack-years not included in stratified models). Models for FVC % predicted exclude adjustment for age and sex.

and the time from biomarker measurement to death, with adjustment for age, sex, race/ethnicity, body mass index, smoking status, cigarette pack-years, and study site. We examined models stratified on smoking status, age group, race/ethnicity, sex, and obesity. Log-likelihood tests were used to test for interactions between MMP-7 and potential effect modifiers in fully adjusted models. We tested the proportional hazards assumption using time interactions. None were significant. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline characteristics of the 1,227 study participants are shown in Table 1. The mean ($\pm$ SD) age was 64 ($\pm$ 10) years, 44% were male, 35% were white, 28% were black, 24% were Hispanic, and 14% were Asian. A total of 52% were former or current smokers, with a median cigarette pack-years of 12.6. The mean ($\pm$ SD) serum MMP-7 level was 4.3 ($\pm$ 2.5) ng/ml with a range of 1.2–24.1 ng/ml. Those with higher serum MMP-7 levels tended to be older and have lower educational attainment, and were more frequently current smokers. There was a larger proportion of blacks and women in the highest quartile of MMP-7. Boxplots showing the distribution of serum MMP-7 level by age group, sex, race/ethnicity, smoking status, and obesity are shown in Figure E2.

Spirometry

Greater serum MMP-7 levels at baseline were associated with lower FVC and FVC % predicted (FVC%; Table 2) measured 5 years later. In unadjusted models, each natural log unit increment in serum MMP-7 was associated with a 637.9-ml decrement in FVC (95% confidence interval [CI] = 478.6–797.3 ml; $P < 0.001$) and an absolute decrement of 3.4% in FVC% (95% CI = 0.5–6.2%; $P = 0.02$). In fully adjusted models, each natural log unit increment in serum MMP-7 was associated with a 197.1-ml decrement in FVC (95% CI = 84.2–310.1 ml; $P < 0.001$) and an absolute decrement of 3.7% in FVC% (95% CI = 0.9–6.6%; $P = 0.01$). Findings were similar for forced expiratory volume in 1 second (FEV₁), but there was no association between serum MMP-7 and the FEV₁/FVC ratio (Table E5).

There was weak evidence that smoking status modified the association between serum MMP-7 and FVC% (P for interaction, 0.13), with a stronger association among ever-smokers than among never-smokers (Table 2). There was moderate evidence of effect modification by age (P for interaction, 0.15), with older participants having larger decrements in FVC per natural log unit increment in MMP-7 than younger individuals. There was moderate evidence of effect modification by race (P for interaction, 0.07), with Asians having the largest decrement in FVC per natural log unit increment in MMP-7 (Table E6). In addition, there was evidence of effect modification by obesity (P for interaction, 0.02) with nonobese individuals having larger decrements in

FVC per natural log unit increment in MMP-7 than obese participants (Table E6).

Dyspnea and Cough

A total of 16% of study participants reported exertional dyspnea. In a fully adjusted model, each natural log increment in serum MMP-7 was associated with a 1.6-fold increased odds of exertional dyspnea (95% CI = 1.3–1.9; $P < 0.001$; Table 3) 5 years after enrollment. Smoking status did not modify the association between serum MMP-7 and self-reported exertional dyspnea (P for interaction, 0.34). A total of 11% of the cohort report cough; there was no significant association between serum MMP-7 and self-reported cough in adjusted models (Table 3).

Table 3. Associations between Serum MMP-7 Level and Exertional Dyspnea, Cough, and Interstitial Lung Abnormalities in MESA

	Odds Ratio (95% CI) per Natural Log Unit Increment MMP-7	P Value
Dyspnea		
Overall		
Unadjusted	1.8 (1.5–2.1)	<0.001
Adjusted	1.6 (1.3–1.9)	<0.001
Ever-smokers		
Unadjusted	1.6 (1.3–1.9)	<0.001
Adjusted	1.5 (1.2–1.9)	<0.001
Never-smokers		
Unadjusted	2.1 (1.6–2.7)	<0.001
Adjusted	2.2 (1.6–2.9)	<0.001
Cough		
Overall		
Unadjusted	1.2 (0.9–1.5)	0.21
Adjusted	0.9 (0.7–1.2)	0.45
Ever-smokers		
Unadjusted	1.0 (0.7–1.3)	0.89
Adjusted	1.0 (0.7–1.4)	0.86
Never-smokers		
Unadjusted	1.6 (1.0–2.4)	0.04
Adjusted	1.3 (0.8–2.2)	0.28
ILAs		
Overall		
Unadjusted	2.0 (1.5–2.7)	<0.001
Adjusted	1.5 (1.1–2.1)	0.01
Ever-smokers		
Unadjusted	1.8 (1.2–2.5)	0.003
Adjusted	1.1 (0.8–1.7)	0.55
Never-smokers		
Unadjusted	2.4 (1.6–3.8)	<0.001
Adjusted	2.3 (1.4–3.9)	0.001

Definition of abbreviations: CI = confidence interval; ILAs = interstitial lung abnormalities; MESA = Multi-Ethnic Study of Atherosclerosis; MMP-7 = matrix metalloproteinase-7. Models were adjusted for age, sex, race, body mass index, smoking status, cigarette pack-years. P value for the interaction between log MMP-7 and smoking status for dyspnea was 0.34. P value for the interaction between log MMP-7 and smoking status for cough was 0.01. P values for the interaction between log MMP-7 and smoking status for ILA was 0.06.

ILAs

In fully adjusted models, each natural log increment in serum MMP-7 was associated with a 1.5-fold increased odds of ILA (95% CI = 1.1–2.1; $P = 0.01$, Table 3) at 10-year follow-up. The adjusted association was stronger among never-smokers (odds ratio = 2.3; 95% CI = 1.4–3.9; $P = 0.001$) than among ever-smokers (odds ratio = 1.1; 95% CI = 0.8–1.7; $P = 0.002$; P for interaction, 0.06).

All-Cause Mortality

There were 191 deaths among the 1,227 MESA participants during 13,782 person-years of follow-up (crude mortality rate 13.9 per 1,000 person-years; 95% CI = 8.5–22.7 per 1,000 person-years). Each natural log increment in serum MMP-7 was associated with a 3.7-fold increased rate of death (unadjusted hazard ratio [HR] = 3.7; 95% CI = 3.4–4.1; $P < 0.001$; Table 4). In a fully adjusted model, each natural log increment in serum MMP-7 was associated with a 2.2-fold increased rate of death (HR = 2.2; 95% CI = 1.9–2.4; $P < 0.001$; Figure 1). There was evidence of effect modification by smoking (P for interaction, 0.01). The association between serum MMP-7 and mortality was higher among never-smokers (HR = 2.6; 95% CI = 2.1–3.2; $P < 0.001$) than among ever-smokers (HR = 2.0; 95% CI = 1.7–2.4; $P < 0.001$).

We performed two *post hoc* sensitivity analyses. First, we additionally adjusted for FVC in the subset that underwent spirometry ($n = 697$). The HR for death per natural log increment in serum MMP-7 in this fully adjusted model was 2.5 (95% CI = 1.9–3.2; $P < 0.001$). In a fully adjusted model, we also additionally adjusted for the Agatston coronary artery calcium score and self-reported history of cancer. The HR for mortality per natural log increment in serum MMP-7 was 2.0 (95% CI = 1.7–2.2; $P < 0.001$).

Discussion

We have shown that higher serum MMP-7 levels are associated with lower FVC, a higher prevalence of both self-reported exertional dyspnea and ILAs on CT, and a higher all-cause mortality rate among middle-aged and older community-dwelling adults sampled without regard to respiratory symptoms or disease. Overall, our findings provide support for the hypothesis that serum MMP-7 levels are a useful biomarker of ECM remodeling in

Table 4. Association between Serum Matrix Metalloproteinase-7 Level and All-Cause Mortality in 1,227 Multi-Ethnic Study of Atherosclerosis Participants over 12.2 Years of Follow-Up

Measure		
No. of deaths		191
No. at risk		1,227
Person-years of follow-up		13,782
Mortality rate (95% CI) per 1,000 person-years		13.9 (8.5–22.7)

Model	HR for Death (95% CI)	P Value
Unadjusted		
Overall	3.7 (3.4–4.1)	<0.001
Ever-smokers	4.0 (3.5–4.6)	<0.001
Never-smokers	3.8 (3.2–4.4)	<0.001
Adjusted*		
Overall	2.2 (1.9–2.4)	<0.001
Ever-smokers	2.0 (1.7–2.4)	<0.001
Never-smokers	2.6 (2.1–3.2)	<0.001

Definition of abbreviations: CI = confidence interval; HR = hazard ratio.

All covariates were measured at baseline examination in 2000–2002. P value for the interaction between matrix metalloproteinase (MMP)-7 and smoking status was 0.01. Each HR is expressed per natural log unit increment in MMP-7.

*Adjusted for age, sex, race/ethnicity, body mass index, smoking status, pack-years, and study site.

the lung, a precursor of clinically evident pulmonary fibrosis (22). Measurement of serum MMP-7 levels may potentially aid in the selection of adults for ILD prevention strategies and/or serve as a marker of response to preventative therapies.

Although ours is the first such study in community-dwelling adults, our findings

are consistent with previous work in disease states. Serum MMP-7 levels are elevated in IPF, rheumatoid arthritis-associated ILD, and scleroderma-associated ILD—in some cases to levels similar to those observed in our cohort (9, 22–25). Higher serum MMP-7 levels are associated with reduced lung function and higher mortality in IPF and

Figure 1. Continuous associations between log matrix metalloproteinase (MMP)-7 and mortality. Model adjusted for age, sex, race/ethnicity, smoking status, smoking pack-years, body mass index, and study site. P for association, <0.001. Solid lines, overall effect estimates; dashed lines, 95% confidence interval (CI) bands. Each vertical hashmark in the rug plot along the x-axis represents one study participant. One outlier was excluded. HR = hazard ratio.

with dyspnea in patients with systemic sclerosis (26). Serum MMP-7 levels are also elevated in adults with familial subclinical ILD and in individuals at risk for ILD, a finding concordant with ours (27). Our study expands these previous findings to the general population and suggests that serum MMP-7 levels may be a biomarker of subclinical ILD.

MMP-7 is a member of a family of 28 enzymes responsible for cleaving ECM proteins (28). It is normally expressed at low levels in the pulmonary epithelium and is responsible for turnover and degradation of connective tissue, as well as maintenance of epithelial integrity and repair (29). MMP-7 is among the most differentially overexpressed proteins in IPF lung, and regulates ECM remodeling in ILD through various mechanisms (7, 9). For example, it mediates E-cadherin shedding in injured lung epithelium, contributing to epithelial repair (14), activates pro-TNF- α and osteopontin (15), and cleaves syndecan-1, contributing to local neutrophil influx and injury (16). Our findings suggest that increased MMP-7 activity in the lung may contribute to the early biological pathways that lead to pulmonary fibrosis.

We observed contradictory—and unexplained—effects of smoking on the associations of serum MMP-7 levels with lung function (stronger effect among smokers) and with ILA (stronger effect among never-smokers). The stronger association between greater serum MMP-7 levels and lower FVC among smokers is consistent with prior work showing stronger associations of subclinical ILD with lower FVC among smokers (2, 6), and

may reflect smoking-related remodeling of the pulmonary ECM. On the other hand, we observed a complex relationship between MMP-7 levels, smoking status, and ILA that was unexpected. Higher serum MMP-7 levels were associated with ILA overall and among never-smokers, but were not associated with ILA in smokers, the group we would have expected to observe the strongest association. It is possible that nonpulmonary sources contribute to serum MMP-7 levels in smokers (30). We are cautious to not overinterpret this hypothesis generating subgroup analysis due to the possibility of type 1 error. Notably, the consistency of the association between serum MMP-7 and mortality among both smokers and never-smokers provides evidence supporting the potential clinical relevance of serum MMP-7 in this population.

Our study had a number of limitations. First, our analyses were restricted to MESA participants with complete outcome data in each analysis. However, the differences in the baseline characteristics of those with and without missing outcome data were modest, suggesting that our findings are not unduly influenced by selection bias. Second, unmeasured and residual confounding could explain some or even all of the findings in this observational study. Nevertheless, our findings are consistent with previous studies that have established serum MMP-7 levels as a serum biomarker of IPF. Third, we lacked lung pathology to correlate with ILA. Fourth, because MMP-7 levels tend to be lower in serum than in plasma (8), our findings cannot be directly compared with much of the previous

literature that has focused on plasma of MMP-7. Fifth, we lacked data on baseline comorbidities, including autoimmune diseases, which could have influenced MMP-7 levels, ILA, and mortality. Finally, we lacked serial measurement of serum MMP-7, limiting our ability to examine associations between longitudinal trends in MMP-7 and both subclinical and clinical measures of ILD. Longitudinal comparisons of serum MMP-7 and ILA might yield important insights into whether serum MMP-7 is a marker of “active” subclinical ILD.

In summary, our data support the hypothesis that serum MMP-7 levels are a biomarker of subclinical ILD linked to lower FVC, exertional dyspnea, ILA, and mortality in community-dwelling adults. Serum MMP-7 levels may be an indirect measure of ECM remodeling in the lung, permitting translational and epidemiological studies of subclinical ILD without subjecting study participants to radiation from CT scanning. Future studies should focus on whether serum MMP-7, perhaps combined with other demographic, genetic, and radiologic factors, can identify adults at risk for clinically evident ILD, serving as an enrichment strategy for ILD prevention clinical trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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