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Antibodies to Malondialdehyde-Acetaldehyde Adduct Are Associated With Prevalent and Incident Rheumatoid Arthritis–Associated Interstitial Lung Disease in US Veterans

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Objective. The objective of this study is to determine the associations of protein-specific anti–malondialdehyde-acetaldehyde (MAA) antibodies with prevalent and incident rheumatoid arthritis–interstitial lung disease (RA-ILD).

Methods. Within a multicenter, prospective cohort of US veterans with RA, RA-ILD was validated by medical record review of clinical diagnoses, chest imaging, and pathology. Serum antibodies to MAA-albumin, MAA-collagen, MAA-fibrinogen, and MAA-vimentin (IgA, IgM, and IgG) were measured by a standardized enzyme-linked immunosorbent assay. Associations of anti-MAA antibodies with prevalent and incident RA-ILD were assessed using multivariable regression models adjusting for established RA-ILD risk factors.

Results. Among 2,739 participants with RA (88% male, mean age of 64 years), there were 114 with prevalent and 136 with incident RA-ILD (average time to diagnosis: 6.6 years). Higher IgM anti–MAA-collagen (per 1 SD: adjusted odds ratio [aOR] 1.28, 95% confidence interval [CI] 1.02–1.61), IgA anti–MAA-fibrinogen (aOR 1.48, 95% CI 1.14–1.92), and IgA (aOR 1.78, 95% CI 1.34–2.37) and IgG (aOR 1.48, 95% CI 1.14–1.92) anti–MAA-vimentin antibodies were associated with prevalent RA-ILD. In incident analyses, higher IgA (per one SD: adjusted hazards ratio [aHR] 1.40, 95% CI 1.11–1.76) and IgM (aHR 1.29, 95% CI 1.04–1.60) anti–MAA-albumin antibody concentrations were associated with increased ILD risk. Participants with IgA (aHR 2.13, 95% CI 1.16–3.90) or IgM (aHR 1.98, 95% CI 1.08–3.64) anti–MAA-albumin antibody concentrations in the highest quartile had an approximately two-fold increased risk of incident RA-ILD. Across all isotypes, anti–MAA-fibrinogen, anti–MAA-collagen, and anti–MAA-vimentin antibodies were not significantly associated with incident RA-ILD.

Conclusion. Protein-specific anti-MAA antibodies to collagen, fibrinogen, and vimentin were associated with prevalent RA-ILD. IgA and IgM anti–MAA-albumin antibodies were associated with a higher risk of incident RA-ILD. These findings suggest that MAA modifications and resultant immune responses may contribute to RA-ILD pathogenesis.

The views expressed in this article are those of the author and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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INTRODUCTION

Among the most common and devastating extra-articular rheumatoid arthritis (RA) manifestations are pulmonary diseases, especially RA-associated interstitial lung disease (RA-ILD). Clinically evident RA-ILD occurs in 5% to 15% of people with RA, and subclinical disease affects up to another 30% to 40%.[1–5] Although mortality rates appear to be improving in RA, respiratory-related mortality has not improved, and RA-ILD is the most overrepresented cause of death within RA populations.[6]

Peripheral biomarkers have been investigated in RA-ILD with the goal that they may assist in RA-ILD screening.[7] The established RA autoantibodies, rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs), are present in 60% to 70% of people with RA, with ACPAs also having high disease specificity.[8,9] These autoantibodies are associated with presence of RA-ILD,[10] but, with the exception of high-titer RF, are not strongly predictive of RA-ILD development.[11] Beyond ACPAs and RF, a select number of additional autoantibodies have been studied in RA-ILD.[12–16] In addition to autoantibodies, peripheral biomarkers encompassing inflammatory cytokines, matrix metalloproteinases (MMPs), and genetic variants have also been investigated.[7,17] Most notable among these is a gain-of-function mutation in the *MUC5B* promoter region that has recently been shown to be a strong genetic risk factor for RA-ILD in a usual interstitial pneumonia (UIP) pattern.[18,19] None of these biomarkers has sufficient evidence to warrant integration into clinical care at this time, perhaps because of study cohorts frequently not being representative of broader RA populations, wide variability in RA-ILD assessment methods, limited confounder adjustment, and the paucity of evidence on predicting the development of incident RA-ILD.[7]

Apart from their clinical utility as a peripheral biomarker, ACPAs have been extensively examined for their potential roles in disease pathogenesis and whether such roles may occur in a protein-specific manner. Serum ACPAs have been shown to target multiple citrullinated proteins such as vimentin, fibrinogen, and type II collagen in RA, among others.[20–22] Profiles constructed from these antigen-specific ACPA responses have shown the ability to predict treatment responses to biologic therapies.[23] Intriguingly, proteins serving as targets of ACPA responses have been found to be shared between the lungs and joints.[24,25] These findings, along with the detection of serum ACPAs years before articular symptoms, have led to the hypothesis that immunity to citrullinated antigens may develop in the lungs. Studies in RA-associated lung diseases have further supported this hypothesis; affected lungs in patients with RA-ILD are thought to be involved in the local production of ACPAs. Furthermore, smoking, a major risk factor for RA-ILD development, increases lung tissue citrullination and oxidative stress.[26] Patients with RA-associated lung diseases have been found to have ectopic lymphoid aggregates in their lung tissues and higher levels of ACPAs in bronchoalveolar lavage fluid compared with matched serum.[27,28]

Although the pathogenesis of RA-ILD remains to be fully elucidated, previous studies by our group have demonstrated a potential pathogenic role of malondialdehyde-acetaldehyde (MAA) adducts in RA. In addition to being highly immunogenic byproducts of oxidative stress, MAA-modified proteins are enriched and colocalize with citrulline and immune cells in synovial tissue from patients with RA.[29,30] Circulating levels of anti-MAA antibodies are increased in RA relative to controls and are associated with, yet distinct from, both RF and ACPAs.[31] Because oxidative stress may also contribute to the development of diffuse lung diseases, our group has further examined whether these MAA adducts and their resultant immune responses are involved in RA-ILD. We found that higher concentrations of IgA and IgM serum anti–MAA-albumin antibodies, targeting a protein not implicated in RA pathogenesis, were closely associated with the presence of RA-ILD in a large RA cohort.[15] Furthermore, lung tissues from patients with RA-ILD had enhanced staining for MAA-modified proteins compared with tissues corresponding to other forms of ILD, chronic obstructive pulmonary disease, and normal lung tissues. In animal models of RA-associated lung disease, anti-MAA antibodies (and ACPAs) are induced alongside the development of lung disease.[32–34] Whether anti-MAA antibodies predict the development of incident RA-ILD and how protein-specific MAA modifications may influence antibody associations with RA-ILD are important and unanswered questions that address and advance our understanding of the pathogenesis of RA-ILD.

In this study, we aimed to evaluate whether anti-MAA antibodies targeting specific proteins implicated in RA pathogenesis would be associated with prevalent RA-ILD and the risk of developing incident RA-ILD. Based on our previous findings of IgA and IgM anti–MAA-albumin being associated with RA-ILD, we hypothesized that protein-specific anti-MAA antibodies, particularly IgA and IgM isotypes, would be associated with a higher risk of having or developing ILD in RA.

METHODS

Study population. This study included participants in the Veterans' Affairs Rheumatoid Arthritis (VARA) Registry, a multicenter, prospective cohort study of US veterans with RA initiated in 2003.[35] Participants have been diagnosed with RA by a rheumatologist and fulfill the 1987 American College of Rheumatology classification criteria.[36] At enrollment, baseline demographic data, smoking status, disease onset, medications, and comorbidities were recorded, and serum samples were collected. All participants provided written informed consent before enrollment. Institutional review board (IRB) approval is maintained by all participating study sites (VA Nebraska-Western Iowa [1576193], VA Central IRB [16194875]), and this study was approved by the VARA Scientific Ethics and Advisory Committee.

Patients and the public were not involved in the design or conduct of this study.

Measurement of anti-MAA antibodies. MAA-albumin and three protein-specific MAA modifications, MAA collagen, MAA fibrinogen, and MAA vimentin, were prepared. These proteins were chosen as antigens based on the colocalization of MAA with these proteins in RA-ILD lung tissues[15] and for their role serving as ACPA targets.[20–22] Human serum albumin (Telecris Biotherapeutics) and fibrinogen (Cayman Chemical) were modified as described previously.[31,37] Type II collagen (Chondrex) and vimentin (Cayman Chemical) were modified in a similar manner. Native collagen and vimentin were separately incubated with 2.0 mM malondialdehyde (Aldrich Chemical Co.) and 1.0 mM acetaldehyde (Aldrich Chemical Co.) in 0.1 M phosphate buffer (pH 7.2) at 37°C for three days. The protein products were then dialyzed three times in 0.1 M phosphate buffer for 24 hours at 4°C. MAA modification was confirmed via fluorescence of the dihydropyridine ring structure (excitation 398 nm and emission 460 nm) using the Turner Biosystems LS-5B spectrofluorometer.

Protein-specific anti-MAA antibodies (IgA, IgM, and IgG isotypes) were measured on the banked serum samples collected at the time of study enrollment, as described previously for albumin.[31] Enzyme-linked immunosorbent assay (ELISA) plates were coated with 2 μg/mL of native or MAA-modified forms of albumin, collagen, fibrinogen, or vimentin and incubated overnight at 4°C. Plates were then blocked with 2% casein (Sigma Aldrich) and incubated with patient serum samples for one hour. After washing, plates were incubated with a secondary horseradish peroxidase-conjugated antihuman antibody specific for IgM, IgG, or IgA (Jackson ImmunoResearch) and developed using tetramethylbenzidine substrate (BD Biosciences). Absorbance was measured at 450 nm using the MRX II microplate reader (Dyantech). A standard curve was created using known concentrations of human IgA, IgM, or IgG isotypes. Relative antibody concentrations were extrapolated and expressed as relative units based on a sample relative to the standard curve. Antibodies to corresponding native proteins were subtracted from anti-MAA antibody concentrations.

To facilitate comparisons across antibodies, anti-MAA antibody values were log-transformed and standardized for all analyses. Additionally, anti-MAA antibody values were categorized in quartiles based on previous work demonstrating that upper quartiles of anti–MAA-albumin antibodies were strongly associated with RA-ILD.[15] To quantify an overall measure of anti-MAA antibody responses, we calculated the number of anti-MAA antibodies present in high concentration and a total anti-MAA antibody score. The number of high anti-MAA antibodies was calculated as the number of antibodies in the upper two quartiles (>50%) across all isotypes of protein-specific antibodies. These scores could range from 0 to 12 and from 0 to 9 when anti–MAA-albumin was excluded. The total anti-MAA antibody score was calculated by summing the log-transformed and standardized anti-MAA antibody concentrations across all isotypes.

Study covariates and descriptive variables. Study covariates and descriptive variables were obtained from the VARA Registry and linked veteran (VA) administrative and electronic health record data. At registry enrollment, participants' demographics (age, sex, and self-reported race), smoking status (never, former, or current), and date of RA diagnosis were recorded. At enrollment and follow-up visits, 28-joint tender and swollen counts, global assessments of disease, and acute phase reactants were obtained to calculate the Disease Activity Score in 28 joints (DAS28).[38] Anti–cyclic citrullinated peptide antibody (anti-CCP) antibodies were measured from banked serum at enrollment using a second-generation ELISA.[15] Body mass index and medication use (prednisone, methotrexate, biologics) at enrollment were obtained from linked VA medical and pharmacy records, as previously described.[39,40] UIP or non-UIP pattern was obtained from chest computed tomographic (CT) reports, with honeycombing additionally considered as evidence of UIP. The *MUC5B* rs35705950 allele variant (nucleotide Thymine) was identified by genotyping single nucleotide polymorphism using the Infinium Global Screening Array-24 v2.0 microarray (Illumina, Inc.).[19] MMP-7 was measured in plasma from enrollment using the MesoScale Discovery Platform.[17]

RA-ILD study outcomes. RA-ILD identification and validation have been described previously.[15,41,42] Possible ILD cases are identified by the presence of multiple diagnostic codes for ILD or a diagnostic code and a CT scan of the chest using linked national VA administrative data. A detailed systematic medical record review was then performed by a board-certified rheumatologist, and ILD diagnoses were considered valid if they had a treating provider diagnosis of RA-ILD and either chest CT scan findings consistent with ILD (more than 96% of cases) or a lung biopsy with histopathological features of ILD, both of which were based on clinical reports. The date of the first clinical ILD diagnosis was recorded. Indeterminate RA-ILD cases were excluded from the study (n = 13). Prevalent RA-ILD was defined as ILD present at the time of VARA enrollment. RA-ILD diagnoses were considered incident if the first clinical diagnosis was made after VARA enrollment. For the prevalent analyses, participants with incident RA-ILD were excluded. For the incident analyses, participants with prevalent RA-ILD were excluded. Given that there is often a delay in RA-ILD diagnosis, sensitivity analyses were performed one year after enrollment to distinguish prevalent versus incident ILD. Additional sensitivity analyses conducted included defining high anti-MAA above the 75th percentile, stratifying RA-ILD based on *MUC5B* status, stratifying RA-ILD based on UIP pattern, and including MMP-7 as a covariate.

Statistical analyses. Patient characteristics stratified by the development of RA-ILD were compared using chi-square tests for categorical variables or independent *t*-test for continuous variables. Anti-MAA antibodies as well as the number of high anti-MAA antibodies and anti-MAA antibody score were compared between these groups using an independent *t*-test. Correlations among isotypes (IgA, IgM, or IgG) of protein-specific anti-MAA antibodies and between anti-MAA antibodies and anti-CCP and RF were assessed using Pearson correlations.

For prevalent analyses, associations of protein-specific anti–MAA-collagen, vimentin, and fibrinogen antibody values and prevalent RA-ILD cases were examined using multivariable logistic regression models. Associations of anti–MAA-albumin antibody values in prevalent RA-ILD were reported previously.[15] For incident analyses, associations between protein-specific anti-MAA antibody concentrations and RA-ILD incidence were assessed using multivariable Cox regression models. In these analyses, participants without prevalent RA-ILD were followed from enrollment until the earliest of incident RA-ILD, death (determined through VA-maintained death records), or end of study period (June 30, 2020). Covariates in both analyses included age, sex, race (White, not White), smoking status, anti-CCP positivity, and enrollment DAS28. We adjusted for mean DAS28 in sensitivity analyses of incident RA-ILD. Cox proportional hazards models estimated incidence of developing RA-ILD by quartiles of anti-MAA antibody concentrations. Missing categorical variables were handled by the missing indicator method whereas participants with missing continuous variables (eg, DAS28) were excluded. All analyses were completed using Stata v18.0 (StataCorp).

RESULTS

Patient characteristics. The study flow diagram depicting selection of participants for incident and prevalent RA-ILD analyses is provided in Supplementary Figure 1. A total of 2,853 VARA participants had anti-MAA antibody measurements and were considered for inclusion in prevalent or incident analyses. Of the 2,717 participants included in prevalent analyses, 114 patients (4.2%) had prevalent RA-ILD at registry enrollment. Participants with RA-ILD were older (RA-ILD vs RA–no-ILD: 67.5 ± 9.8 vs 63.9 ± 11.1), more frequently had a smoking history (former: 64.9% vs 54.0%; current: 25.2% vs 24.7%), had a longer RA duration (14.4 ± 13.6 vs 11.3 ± 11.2), were more likely anti-CCP positive (86.0% vs 76.1%), had less frequent methotrexate use (14.0% vs 45.3%), and had more frequent prednisone use (65.8% vs 44.0%) (Table 1).

Among 2,739 participants without prevalent RA-ILD, 136 developed RA-ILD over 19,820 patient-years (PYs) of follow-up (crude incidence rate 6.9 per 1,000 PYs). Median time to RA-ILD incidence was 6.6 years. In contrast to those who did not develop ILD, participants developing RA-ILD tended to be more frequently male (RA-ILD vs RA-no–ILD: 94.9% vs 87.7%), be current smokers (34.5% vs 24.7%), have higher DAS28 scores (4.1±1.5 vs 3.8±1.6), and have more frequent prednisone use (59.6% vs 44.0%) (Supplementary Table 1).

Protein-specific anti-MAA antibodies and prevalent RA-ILD. Cross-sectional associations of anti–MAA-collagen, vimentin, and fibrinogen antibody values with prevalent RA-ILD after adjusting for covariates are summarized in Table 2. Higher concentrations of anti–MAA-vimentin IgA (per 1 SD: adjusted odds ratio [aOR] 1.78, 95% confidence interval [95% CI] 1.34–2.37) and IgG (aOR 1.48, 95% CI 1.14–1.92) isotypes, but not IgM, were associated with prevalent RA-ILD. The IgM isotype of anti–MAA-collagen (aOR 1.28, 95% CI 1.02–1.61) and IgA isotype of anti–MAA-fibrinogen (aOR 1.48, 95% CI 1.14–1.92) were also associated with prevalent RA-ILD. Other isotypes of anti–MAA-collagen and anti–MAA-fibrinogen were not significantly associated with prevalent RA-ILD. When analyzed as quartiles, the highest quartiles (quartile 4) of IgA and IgG anti–MAA-vimentin, IgA anti–MAA-fibrinogen, and IgM anti–MAA-collagen were strongly associated with prevalent RA-ILD (Table 3; range aOR 2.48–4.19). Trend tests across quartiles of antibodies were significant for IgA and IgG anti–MAA-vimentin, IgA and IgG anti–MAA-fibrinogen, and IgM anti–MAA-collagen. Similar findings were observed in sensitivity analyses when including individuals developing RA-ILD in the first year of follow-up (Supplementary Table 2) or when high anti-MAA was defined as greater than the 75th percentile (Supplementary Table 3).

A higher number of elevated protein-specific (collagen, fibrinogen, vimentin) anti-MAA antibodies (range 0–9; aOR per each additional isotype: 1.18, 95% CI 1.08–1.28) and total anti-MAA antibody score (aOR 1.08, 95% CI 1.03–1.12) were both significantly associated with prevalent RA-ILD (Table 2). Comparable outcomes were observed during sensitivity analyses when stratifying prevalent RA-ILD cases by UIP pattern and *MUC5B* status and when including MMP-7 as a covariate (Supplementary Table 4).

Overall, isotypes (ie, IgA, IgM, IgG) from the same protein-specific anti-MAA antibody were weakly to moderately correlated (Pearson correlation coefficient [*r*] 0.20–0.61; Supplementary Table 5). Anti-MAA antibodies targeting different proteins (ie, albumin, collagen, fibrinogen, vimentin) were very weakly to weakly correlated (*r* –0.04 to 0.36). Furthermore, anti-MAA antibodies showed no to very weak correlations with anti-CCP (*r* 0.01 to 0.14) and RF (*r* –0.03 to 0.19) (Supplementary Table 6).

Anti-MAA antibodies and incident RA-ILD. Associations of anti-MAA antibodies with RA-ILD incidence are summarized in Figure 1. After adjusting for covariates, IgA (per 1 SD: adjusted hazards ratio [aHR] 1.40, 95% CI 1.11–1.76) and IgM (aHR 1.29, 95% CI 1.04–1.60) anti–MAA-albumin concentrations were significantly associated with higher risk of developing

Table 1. Baseline characteristics of participants stratified by prevalent RA-ILD status*

Variables	RA–no-ILD, n = 2,603	RA-ILD, n = 114	*P* value
Demographics, health behaviors			
Age, mean ± SD, y	63.9 ± 11.1	67.5 ± 9.8	<0.001
Male, n (%)	2,283 (87.7)	104 (91.2)	0.26
Race, n (%)			0.62
White	2,003 (76.9)	90 (78.9)	
Not White	600 (23.1)	24 (21.1)	
BMI, mean ± SD	28.8 ± 5.9	29.2 ± 6.2	0.49
Smoking status, n (%)			0.01
Never	535 (21.3)	11 (9.9)	
Former	1,358 (54.0)	72 (64.9)	
Current	624 (24.7)	28 (25.2)	
RA-related factors			
RA duration, mean ± SD, y	11.3 ± 11.2	14.4 ± 13.6	0.006
DAS28, mean ± SD	3.8 ± 1.6	4.0 ± 1.4	0.12
Anti-CCP positive, n (%)	1,981 (76.1)	98 (86.0)	0.02
Methotrexate use, n (%)	1,178 (45.3)	16 (14.0)	<0.001
Biologic use, n (%)	571 (21.9)	34 (29.8)	0.06
Prednisone use, n (%)	1,145 (44.0)	75 (65.8)	<0.001
ILD-related factors, n (%)			
RA-ILD pattern			–
UIP pattern	–	59 (51.8)	
Non-UIP pattern	–	55 (48.2)	
MUC5B rs3570590			<0.001
MUC5B TT/TG	412 (17.8)	42 (40.8)	
MUC5B GG	1,899 (82.2)	61 (59.2)	

* Missing values: BMI (n = 84), smoking status (n = 89), RA duration (n = 88), DAS28 (n = 239), *MUC5B* status (n = 303).
Anti-CCP, anticyclic citrullinated peptide antibody; BMI, body mass index; DAS28, disease activity score for 28 joints; GG, guanine-guanine genotype; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; TG, thymine-thymine genotype; TT, thymine-guanine; UIP, usual interstitial pneumonia.

RA-ILD. When examined as quartiles, the cumulative hazard of developing RA-ILD was increased for the highest quartile of IgA and IgM anti–MAA-albumin (Figure 2). The highest quartile of IgA (aHR 2.13, 95% CI 1.16–3.90) and IgM (aHR 1.98, 95% CI 1.08–3.64) anti–MAA-albumin were associated with an approximately two-fold higher risk of incident RA-ILD (Table 4). Concentrations and quartiles of IgG anti–MAA–albumin were not significantly associated with incident RA-ILD. Similar observations were made in sensitivity analyses when excluding participants developing RA-ILD in the first year of follow-up (Supplementary Table 7) or when high anti-MAA was defined as greater than the 75th percentile (Supplementary Table 8).

Across all isotypes, concentrations of protein-specific anti-MAA antibodies targeting collagen, fibrinogen, and vimentin were not significantly associated with the risk of incident RA-ILD (Figure 1). When examined as quartiles, there were trends for higher quartiles of protein-specific anti-MAA antibodies to confer a higher risk of incident RA-ILD (Table 4). However, only the second quartile for IgA (aHR 1.82, 95% CI 1.05–3.14) and IgM (aHR 1.94, 95% CI 1.14–3.30) anti–MAA-vimentin achieved statistical significance. Cumulative HR curves of developing RA-ILD for protein-specific anti-MAA antibodies are presented in Supplementary Figures 2 through 4, illustrating reduced RA-ILD free survival among participants with IgA or IgM anti–MAA-vimentin antibody concentrations in the second quartile.

Evaluating broad anti-MAA antibody responses to modified forms of albumin, collagen, fibrinogen, and vimentin, a higher number of elevated anti-MAA antibody values (range 0–12; aHR per each additional isotype: 1.18, 95% CI 1.08–1.28) and the total anti-MAA antibody score (aHR 1.08, 95% CI 1.03–1.12) were associated with an increased risk of developing incident RA-ILD (Figure 1). When anti–MAA-albumin antibody values were excluded from these summary antibody response measures, the associations were no longer significant (data not shown). Associations of broad antibody responses with incident RA-ILD were similar in sensitivity analyses when stratifying cases by UIP pattern or *MUC5B* status, adjusting for MMP-7, and adjusting for mean DAS28 (Supplementary Table 9).

DISCUSSION

Although the pathogenic role of autoantibody responses in RA is more established, their potential contribution to RA-ILD pathogenesis is increasingly being investigated.[7] Previous studies from our group demonstrated that antibodies to anti–MAA-albumin were associated with prevalent RA-ILD, and in RA-ILD lung tissues, increased staining for MAA was detected compared with diseased and healthy control lung tissues.[15] Building on these findings, this study elucidated a potential role for novel

Table 2. Association of protein-specific anti-MAA antibody concentrations with prevalent RA-ILD*

Antibody[a]	aOR (95% CI)	*P* value
Anti–MAA-collagen (n = 2,548/n = 112 ILD)		
IgA	1.14 (0.92–1.40)	0.23
IgM	1.28 (1.02–1.61)	0.03
IgG	0.95 (0.78–1.16)	0.64
Anti–MAA-fibrinogen (n = 2,535/n = 112 ILD)		
IgA	1.48 (1.14–1.92)	0.003
IgM	1.19 (0.95–1.47)	0.13
IgG	1.15 (0.92–1.44)	0.23
Anti–MAA-vimentin (n = 2,535/n = 112 ILD)		
IgA	1.78 (1.34–2.37)	<0.001
IgM	1.11 (0.89–1.39)	0.35
IgG	1.48 (1.14–1.92)	0.003
Combined protein-specific anti-MAA (n = 2,517/n = 112 ILD)		
Sum of high anti-MAA[b]	1.18 (1.08–1.28)	<0.001
Total anti-MAA score[c]	1.08 (1.03–1.12)	0.001

* aOR, adjusted odds ratio; anti-MAA, anti–malondialdehyde-acetaldehyde adduct antibodies; RA-ILD, rheumatoid arthritis-interstitial lung disease; 95% CI, 95% confidence interval.
[a] The results on associations of anti-MAA–albumin antibody concentrations and prevalent RA-ILD were reported previously.[15]
[b] Anti-MAA antibody values were divided into quartiles, and the upper two quartiles were classified as high.
[c] Total anti-MAA score calculated from the summation of log-transformed and standardized values of protein-specific anti-MAA antibodies (collagen, fibrinogen, vimentin).

RA-related autoantibody responses to MAA adducts in a protein-specific manner as serum biomarkers for RA-ILD. Within a multicenter, prospective RA cohort of more than 2,700 participants, higher protein-specific anti-MAA antibody concentrations targeting collagen, fibrinogen, and vimentin were independently associated with the presence of ILD, findings that varied based both on the autoantibody isotype and protein antigen. Among participants without ILD at registry enrollment, IgA and IgM anti–MAA-albumin antibody concentrations were predictive of developing incident RA-ILD that was diagnosed on average 6.6 years after enrollment and independent of other RA-ILD risk factors. In contrast to antibodies directed at modified albumin, protein-specific anti-MAA antibodies targeting collagen, fibrinogen, and vimentin were not significantly associated with RA-ILD incidence. Together, these findings suggest a robust relationship between anti-MAA antibodies and RA-ILD in a protein-specific and isotype-dependent manner. Moreover, antibody responses to specific MAA-modified proteins may vary based on the stage of RA-ILD development.

Several investigations demonstrated associations of an expanded ACPA repertoire and other autoantibodies targeting post-translationally modified proteins with the presence of RA-ILD in cross-sectional studies[12–15,43] and another nested case–control study.[44] RF and anti-CCP antibodies have been further evaluated for their ability to predict incident RA-ILD with a cohort study design; only patients with RA with the highest titer of RF were found to be at increased risk for ILD, but no risk was observed related to anti-CCP concentration.[11] Given the paucity of evidence on autoantibodies predicting incident RA-ILD, it is noteworthy that we used a cohort study design to demonstrate the ability of anti–MAA-albumin antibodies to predict the development of incident RA-ILD. Another novel finding in this study was the determination that protein-specific anti-MAA antibodies targeting type II collagen, fibrinogen, and vimentin are significantly associated with established RA-ILD in an isotype-dependent manner. Characterizing these antibody responses in a protein-specific manner is essential because the previously studied target protein, albumin, does not have a known pathogenic role. The protein-specific nature of these autoantibody responses is similar to previous findings regarding ACPAs and RA-ILD.[43] As in the study by Giles et al examining multiple ACPAs,[43] overall scores for the number of antibodies targeting protein-specific anti-MAA antibodies were significantly associated with prevalent RA-ILD cross-sectionally. Together, these novel findings represent key advancements in our understanding of the timing, role, and protein-specificity of autoantibodies in RA-ILD.

There are several potential biological mechanisms by which MAA modifications and anti-MAA antibody responses may contribute to RA-ILD pathogenesis. In vitro studies by our group previously demonstrated that MAA protein adducts activate proinflammatory and profibrotic pathways in macrophages,[37] activate extracellular matrix deposition by synovial fibroblasts,[45] and induce antibody production and T cell proliferation.[46] MAA protein adducts have been found to be enriched in lung tissues of patients with RA-ILD compared with healthy and those with non-RA diseases (chronic obstructive pulmonary disease, other ILD) controls, in which they colocalize with citrulline and extracellular matrix proteins such as type II collagen, fibronectin, and vimentin.[15] Consistent with these observations using human lung tissues, lungs from a mouse model of RA-associated lung disease also demonstrate colocalization of MAA with citrulline and extracellular matrix proteins.[34] This study appears to translate these earlier findings from lung tissues to adaptive, serologic immune responses by showing that protein-specific anti-MAA antibodies to type II collagen, fibronectin, and vimentin are strongly associated with prevalent RA-ILD, further adding to the growing body of evidence linking MAA modification and anti-MAA antibody responses to RA-ILD.

An intriguing finding in our study was that protein-specific (collagen, fibrinogen, vimentin) anti-MAA antibodies were only associated with prevalent RA-ILD, whereas antibodies to anti–MAA-albumin, a protein that represents broad anti-MAA responses, are associated with both prevalent and incident RA-ILD. In preclinical RA, ACPA epitope spreading has been demonstrated to occur and predict the onset of clinical disease.[47] Also, during the preclinical RA period, anti–MAA-albumin antibodies were elevated more proximal to the clinical onset of RA compared with ACPA and RF.[48] We speculate that MAA

Table 3. Multivariable associations of protein-specific anti-MAA antibody with prevalent RA-ILD*

Antibody	Anti-MAA–collagen[a] (n = 2,548/n = 112 RA-ILD)			Anti-MAA–fibrinogen (n = 2,535/n = 112 RA-ILD)			Anti-MAA–vimentin (n = 2,535/n = 112 RA-ILD)		
Variables	aOR	95% CI	*P* value	aOR	95% CI	*P* value	aOR	95% CI	*P* value
Quartiles for IgA									
1		1.00			1.00			1.00	
2	1.16	0.64–2.12	0.63	1.95	0.96–3.95	0.06	1.98	0.91–4.31	0.09
3	1.18	0.65–2.13	0.58	2.49	1.25–4.92	0.01	2.67	1.28–5.58	0.01
4	1.43	0.81–2.55	0.22	2.87	1.46–5.66	0.002	4.19	2.05–8.57	<0.001
P value for trend[b]			0.67			0.02			<0.001
Quartiles for IgM									
1		1.00			1.00			1.00	
2	2.16	1.15–4.08	0.02	1.10	0.61–1.98	0.75	1.00	0.53–1.90	0.99
3	1.81	0.94–3.51	0.08	1.21	0.67–2.21	0.53	1.04	0.56–1.96	0.90
4	2.48	1.31–4.69	0.01	1.51	0.85–2.67	0.16	1.75	0.99–3.10	0.06
P value for trend[b]			0.04			0.52			0.11
Quartiles for IgG									
1		1.00			1.00			1.00	
2	0.63	0.34–1.15	0.13	0.46	0.23–0.91	0.03	1.90	0.96–3.74	0.07
3	0.88	0.50–1.53	0.65	1.12	0.65–1.94	0.69	2.20	1.13–4.28	0.02
4	0.95	0.55–1.64	0.85	1.23	0.72–2.11	0.45	2.91	1.52–5.55	0.001
P value for trend[b]			0.47			0.03			0.01

* Models adjusted for age, sex, race, smoking status, anti-CCP antibody positivity, and baseline DAS28. Varying n in each analysis based on availability of specific anti-MAA antibody values. Anti-CCP, anticyclic citrullinated peptide antibody; anti-MAA, antibody to malondialdehyde-acetaldehyde; aOR, adjusted odds ratio; DAS28, disease activity score for 28 joints; ILD, interstitial lung disease; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; 95% CI, 95% confidence interval.
[a] The results on associations of anti-MAA–albumin antibody concentrations and prevalent RA-ILD were reported previously.[15]
[b] *P* value for linear trend across quartiles.

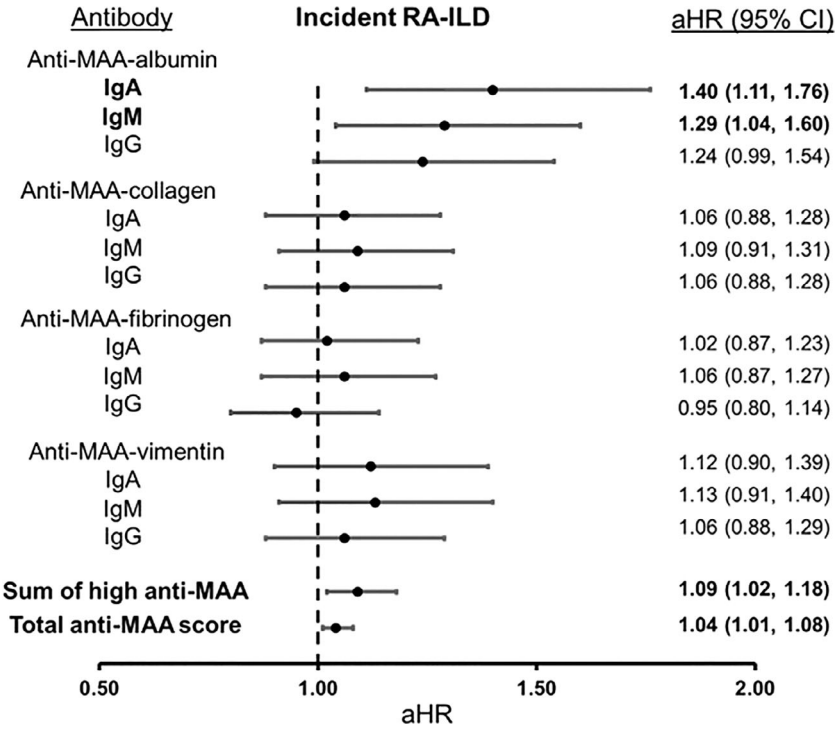

Figure 1. Protein-specific anti-MAA antibody concentrations and risk of incident RA-ILD. Values are aHR (95% CI) per 1 SD change in antibody concentration. Each antibody tested in separate Cox models adjusting for age, sex, race, smoking status, anti-CCP antibody positivity, and DAS28. aHR, adjusted hazard ratio; anti-CCP, anticyclic citrullinated peptide antibody; anti-MAA, antibody to malondialdehyde-acetaldehyde; DAS28, disease activity score for 28 joints; RA-ILD, rheumatoid arthritis-interstitial lung disease; 95% CI, 95% confidence interval.

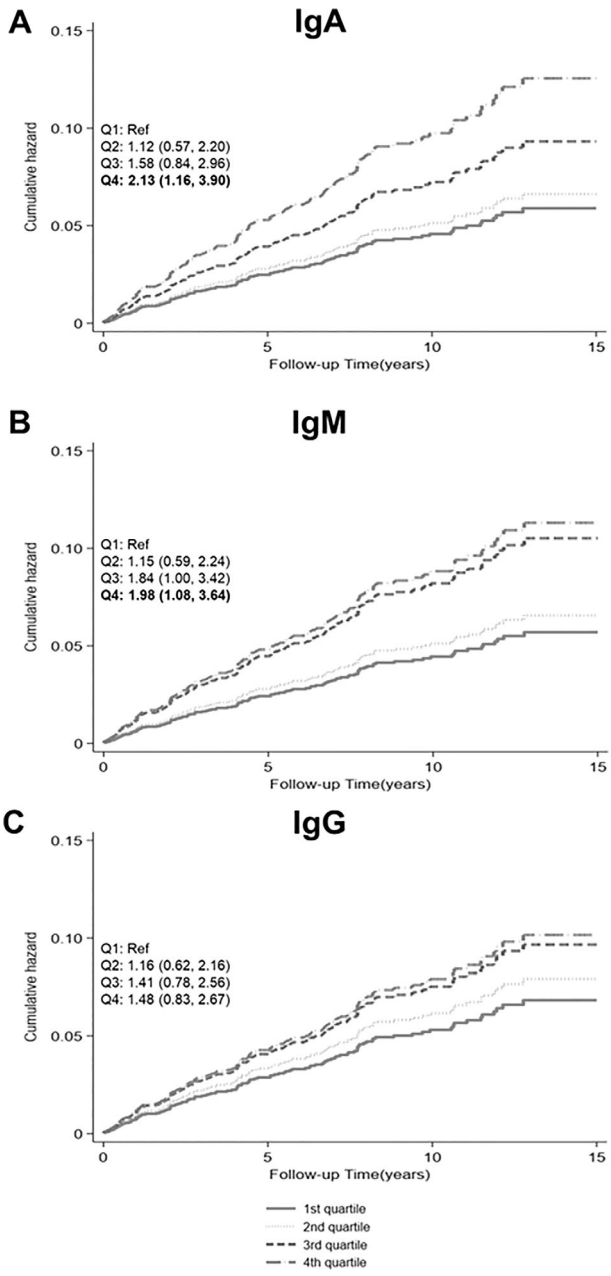

Figure 2. Anti-MAA-albumin antibody concentrations and cumulative hazard of developing RA-ILD. Cumulative hazard ratios by quartiles of (A) IgA, (B) IgM, and (C) IgG anti-MAA-albumin antibody concentrations. Values are aHR (95% CI) from Cox regression models adjusted for age, sex, race, smoking status, anti-CCP antibody positivity, and DAS28. Line patterns: solid line, 1st quartile; dotted line, 2nd quartile; dashed line, 3rd quartile; dashed/dot line, 4th quartile. aHR, adjusted hazard ratio; anti-CCP, anticyclic citrullinated peptide antibody; anti-MAA, antibody to malondialdehyde-acetaldehyde; DAS28, disease activity score for 28 joints; Q1, 1st quartile; Q2, 2nd quartile; Q3, 3rd quartile; Q4, 4th quartile; RA-ILD, rheumatoid arthritis patients with interstitial lung disease; Ref, referent; 95% CI, 95% confidence interval.

modification and anti-MAA antibodies are likely acting in conjunction with citrullination and ACPAs to facilitate loss of immune tolerance. This is consistent with previous reports showing colocalization of MAA and citrulline in lung tissue of patients with RA-ILD,[15] enhanced proinflammatory and profibrotic cellular responses to dually (MAA and citrulline) modified proteins,[30,37,45] and increased ACPA responses in mice immunized with MAA and citrulline modified albumin.[30] It is possible that MAA modification and anti-MAA antibody responses are initiating and expanding in the subclinical phase of RA-ILD (recognizing the majority of RA-ILD occurs after articular disease onset). Broader MAA epitope antibodies (reflected by anti–MAA-albumin) may capture these early autoantibody responses in the subclinical phase. After epitope spreading has occurred, additional protein-specific anti-MAA antibody responses would be detected in established RA-ILD. Longitudinal studies with serial biospecimens during the subclinical phases of RA-ILD are needed to further test this hypothesis and elucidate the potential contribution of anti-MAA antibodies to RA-ILD onset.

Although our findings demonstrate robust associations of anti-MAA antibodies and RA-ILD, the clinical relevance of these findings remains to be determined. Anti-MAA antibodies are not specific for RA or RA-ILD, having been detected in other disease conditions.[46,49,50] Although many peripheral biomarkers have been studied in RA-ILD, none possess the necessary attributes to support clinical implementation at this time.[7] Our findings suggest that the assessment of anti-MAA antibodies to facilitate RA-ILD screening will likely require measuring all isotypes (IgA, IgM, IgG) of protein-specific anti-MAA antibodies or global anti-MAA antibody responses such as anti–MAA-albumin to get a broad assessment of anti-MAA antibody responses and optimize sensitivity for detecting RA-ILD risk. Moreover, the best performance is anticipated to be achieved by combining anti-MAA antibody measurement with other peripheral biomarkers in a panel and assessment of clinical risk factors. Whether other protein-specific anti-MAA antibodies may have a higher specificity for RA-ILD is uncertain, though specificity is less important than sensitivity in RA-ILD screening. Additional studies are warranted to develop RA-ILD biomarker panels and effective RA-ILD screening strategies.

There are limitations to this study. The population comprised US veterans who were predominantly men, which may limit generalizability. However, RA-ILD prevalence is higher in men compared with women.[1] Identification of RA-ILD was retrospective, which may result in misclassification. The most likely type of misclassification would be considering subclinical or mild RA-ILD as no-ILD, which would bias our results toward the null. Misclassification of ILD diagnosis date may also have occurred given the often insidious onset of RA-ILD. We performed sensitivity analyses using one year after registry enrollment to distinguish prevalent versus incident RA-ILD, but further studies are needed to characterize autoantibody responses before RA-ILD onset with prospective RA-ILD assessment. Although we were able to account for smoking status, we did not have data on pack-years of smoking or other occupational and military inhalant exposures. Anti-MAA antibody responses to collagen, fibrinogen, and

Table 4. Multivariable associations of protein-specific anti-MAA antibody with incident RA-ILD*

Antibody	Anti-MAA–albumin (n = 2,154/n = 126 RA-ILD)			Anti-MAA–collagen (n = 2,548/n = 126 RA-ILD)			Anti-MAA–fibrinogen (n = 2,535/n = 126 RA-ILD)			Anti-MAA–vimentin (n = 2,535/n = 126 RA-ILD)		
Variables	aHR	95% CI	*P* value	aHR	95% CI	*P* value	aHR	95% CI	*P* value	aHR	95% CI	*P* value
Quartiles for IgA												
1		1.00			1.00			1.00			1.00	
2	1.12	0.57–2.20	0.73	0.59	0.33–1.03	0.06	1.13	0.69–1.87	0.62	1.82	1.05–3.14	0.03
3	1.58	0.84–2.96	0.15	0.86	0.52–1.41	0.55	1.01	0.60–1.69	0.98	1.36	0.77–2.41	0.29
4	2.13	1.16–3.90	0.01	1.15	0.72–1.84	0.56	0.96	0.56–1.64	0.88	1.62	0.92–2.87	0.10
P value for trend[a]			0.02			0.11			0.48			0.17
Quartiles for IgM												
1		1.00			1.00			1.00			1.00	
2	1.15	0.59–2.24	0.68	0.74	0.43–1.27	0.27	1.16	0.68–1.98	0.59	1.94	1.14–3.30	0.01
3	1.84	1.00–3.42	0.05	1.00	0.61–1.68	0.98	1.52	0.90–2.55	0.11	1.43	0.81–2.53	0.22
4	1.98	1.08–3.64	0.03	1.36	0.84–2.19	0.21	1.42	0.83–2.41	0.20	1.31	0.73–2.33	0.37
P value for trend[a]			0.04			0.16			0.38			0.08
Quartiles for IgG												
1		1.00			1.00			1.00			1.00	
2	1.16	0.62–2.16	0.65	0.79	0.39–1.36	0.39	0.70	0.41–1.21	0.20	1.21	0.72–2.04	0.46
3	1.41	0.78–2.56	0.26	0.93	0.55–1.56	0.78	1.10	0.68–1.80	0.69	1.51	0.92–2.48	0.10
4	1.48	0.83–2.67	0.19	1.36	0.84–2.21	0.22	0.96	0.58–1.60	0.89	0.93	0.52–1.65	0.80
P value for trend[a]			0.50			0.18			0.40			0.22

* Models adjusted for age, sex, race, smoking status, anti-CCP antibody positivity, and baseline DAS28. Varying n in each analysis based on availability of specific anti-MAA antibody values. aHR, adjusted hazard ratio; anti-CCP, anticyclic citrullinated peptide antibody; anti-MAA, antibody to malondialdehyde-acetaldehyde; DAS28, disease activity score for 28 joints; ILD, interstitial lung disease; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; 95% CI, 95% confidence interval.
[a] *P* value for linear trend across quartiles.

vimentin were investigated, but other target proteins may be of interest, which will require future studies. Healthy controls and those with other non-RA diseases were not included in this study, and future work will aim to define cut-points to discriminate from healthy controls. Finally, although we used a large, prospective RA cohort, some estimates were imprecise with wide CIs, which limits their interpretation.

In conclusion, anti–MAA-collagen, fibrinogen, and vimentin antibodies were independently associated with prevalent RA-ILD in a large, multicenter, cohort of US veterans with RA. Additionally, higher concentrations of IgA and IgM anti–MAA-albumin antibodies were associated with incident RA-ILD risk in this cohort. The relationships of anti-MAA antibody responses with RA-ILD were both protein and isotype dependent. These findings warrant further evaluation of these autoantibody responses in the pathogenesis of RA-ILD. Together with clinical factors and other peripheral biomarkers, comprehensive autoantibody measurement may be valuable for RA-ILD risk stratification and screening in RA populations.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Aripova had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Aripova, Thiele, Duryee, Ascherman, Cannon, Wysham, Kerr, Monach, Baker, Poole, Mikuls, England.

Acquisition of data. Aripova, Thiele, Duryee, Hunter, Mikuls, England.

Analysis and interpretation of data. Aripova, Thiele, Duryee, Yang, Roul, Ascherman, Matson, Kunkel, Cannon, Wysham, Kerr, Monach, Baker, Poole Mikuls, England.

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