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A Systematic Review and Metaanalysis of Predictors of Mortality in Idiopathic Inflammatory Myopathy–Associated Interstitial Lung Disease

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ABSTRACT. ***Objective.*** Idiopathic inflammatory myopathy (IIM)–associated interstitial lung disease (ILD) can range from rapidly progressive disease with high mortality to indolent disease with minimal morbidity. This systematic review and metaanalysis describe immunological, clinical, and radiographical predictors of mortality in IIM-ILD.

Methods. MEDLINE and Embase database searches were completed on October 18, 2021, to identify articles providing survival data according to baseline characteristics in patients with concurrent IIM and ILD. Prognostic factors common to more than 5 papers were included in the metaanalysis using a random-effects model to report odds ratios (ORs) for binary variables and Hedges *g* for continuous variables. Risk of bias was assessed using the Newcastle-Ottawa Scale score and the Egger test for publication bias.

Results. From 4433 articles, 62 papers were suitable for inclusion; among these studies, 38 different variables were considered. The OR for risk of death regarding the presence of anti–melanoma differentiation–associated protein 5 (MDA5) antibodies was 6.20 (95% CI 3.58-10.71), and anti–tRNA synthetase antibodies were found to be protective (OR 0.24, 95% CI 0.14-0.41). Neither antinuclear antibodies, anti–52-kDa Ro antigen antibodies, nor SSA significantly altered mortality, nor was MDA5 titer predictive. Examples of prognostic factors that are significantly associated with mortality in this study include the following: age; male sex; acute/subacute onset; clinically amyopathic dermatomyositis; dyspnea; ulceration; fever; raised C-reactive protein, ferritin, lactate dehydrogenase, alveolar to arterial O_2 ($A\text{-}aO_2$) gradient, ground-glass opacity on high-resolution computed tomography (HRCT), and overall HRCT score; and reduced albumin, lymphocytes, ratio of partial pressure of oxygen in the arterial blood to fraction of inspired oxygen (PF ratio), percentage predicted transfer factor for carbon monoxide, and percentage predicted forced vital capacity. Baseline surfactant protein-D and Krebs von den Lungen-6 levels were not predictors of mortality.

Conclusion. Many mortality risk factors were identified, though heterogeneity was high, with a low quality of evidence and a risk of publication bias. Studies regarding anti-MDA5 antibody–positive disease and and those from East Asia predominate, which could mask risk factors relevant to other IIM subgroups or populations.

Key Indexing Terms: idiopathic inflammatory myopathies, interstitial lung disease, metaanalysis, mortality, myositis, prognosis

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Idiopathic inflammatory myopathies (IIMs) are a heterogenous group of chronic autoimmune inflammatory disorders with multisystem involvement, including skeletal muscle, lung, and skin inflammation. Associated interstitial lung disease (ILD) is seen in approximately 40% of patients with IIM and is a negative prognostic factor.[1,2] Presentation and severity of ILD is not always predictable and can range from rapidly progressive high-fatality phenotypes to chronic indolent disease with minimal or slowly progressive effects on function. Many prognostic factors predicting likelihood of progression have been proposed, but sample sizes in individual studies are small and generalizability to real-world populations are questionable.

Several myositis-specific antibodies appear to link with phenotype and, therefore, prognosis. In particular, anti–melanoma differentiation–associated protein 5 (MDA5) antibodies are associated with rapidly progressive ILD and high mortality in

many East Asian studies,[3-6] yet there may be geographical phenotypic variation, with a few small studies suggesting that other populations may display a milder phenotype.[7,8]

Anti–aminoacyl-tRNA synthetase (ARS) antibodies are associated with an IIM phenotype termed *antisynthetase syndrome*, with common manifestations being ILD, Raynaud phenomenon, arthritis, fever, and mechanic's hands.[9,10] Whereas ILD in antisynthetase syndrome is generally considered less aggressive than in MDA5, there is heterogeneity between ARS antibodies, with anti–alanyl-tRNA synthetase (PL12) and anti–threonyl-tRNA synthetase (PL7) antibodies associated with higher prevalence and more severe lung involvement.[11,12] Additional anti–52-kDa Ro antigen (Ro52) antibodies are common in ARS and MDA5 disease. Evidence for the clinical relevance of anti-Ro52/SSA antibodies is mixed; some report an association with increased disease severity,[13,14] and others report no effect on presentation, severity, or mortality.[15]

This metaanalysis aims to consolidate evidence regarding the effect of the serological profile on short-, medium-, and long-term mortality. Secondary objectives include describing other clinical, pathological, or demographic prognostic factors.

METHODS

This review was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines.[16] The full search strategy was preregistered on the international prospective register of systematic reviews, PROSPERO (CRD42021240206). MEDLINE and Embase databases were interrogated through the Ovid and Web of Science search engines on March 18, 2021, and updated on October 18, 2021, using a predefined search protocol (Supplementary Figure S1, available from the authors upon request). The searches included key terms such as, but not limited to, the following: "myositis," "idiopathic inflammatory myopathy," "dermatomyositis," "polymyositis," OR "anti-synthetase syndrome," AND "interstitial lung disease." Articles were limited to the year 2000 onward. No language filters were applied.

Inclusion and exclusion criteria. Articles for inclusion were original cohort studies, case-control studies, randomized controlled trials (RCTs), and epidemiological studies of patients with clinically diagnosed ILD and IIMs, including dermatomyositis (DM), polymyositis (PM), clinically amyopathic DM, antisynthetase syndrome, overlap myositis, and juvenile DM. To be eligible for inclusion, articles needed to provide summary data relating to the frequency of survivors vs nonsurvivors according to baseline disease characteristics within the article or supplementary material. Case reports or series without relevant summary statistics, conference abstracts, reviews, and metaanalyses were excluded along with articles without English translation. Reference lists from relevant review articles were hand-searched for additional eligible articles.

Data extraction. Two reviewers (JH and PG) independently reviewed titles and abstracts to identify those that would potentially meet inclusion criteria for full-text review.

Data extraction was performed onto prepopulated Excel spreadsheets by one author (JH). Initially, we elucidated which prognostic factors were reported in each article. Articles were taken forward for further data extraction only if they contained a prognostic factor common to > 5 papers. Further data were then extracted under headings covering the following: study design, inclusion and exclusion criteria, study duration, survival rates according to prognostic factors, and risk of bias assessment. Extraction was independently repeated by a second reviewer, with disagreements resolved by discussion between reviewers. Where multiple studies had been published from the same research group, methodologies were compared to identify overlapping cohorts. Where cohorts overlapped, the largest sample size was selected for each variable.

Risk of bias was assessed using the Newcastle-Ottawa Scale score for cohort studies, which analyzes bias in selection, comparability, and outcome.[17] This covers selection methodology, control for confounders, the reliability of follow-up assessments, and loss to follow-up.

Statistical analysis. The primary outcome of interest was mortality; the primary predictor of interest was myositis-specific autoantibodies, and the secondary predictors of interest were clinical, biochemical, and radiographical factors. A metaanalysis was performed using the meta package in Stata 16 (StataCorp). Because of small sample sizes, prior to analysis it was decided to adjust zero cells by 0.1 rather than by 0.5 as stated in the prepublished protocol.

For binary variables, unadjusted incidence of mortality was calculated, and results across studies were pooled using a random-effects model to create summary estimates for odds ratios (ORs) for each baseline predicting factor with 95% CIs. For continuous variables, effect size was measured with Hedges *g* because of discrepancies in units of measurement. Hedges *g* is a measure of difference between groups calculated in terms of SDs. Hedges *g* values of 0.2 to 0.5, 0.5 to 0.8, and > 0.8 imply small, medium, and large effect sizes, respectively.[18] A random-effects model was used because of expected differences in individual study populations and methodologies.

The primary outcome was explored further through subgroup analysis according to IIM subset and study duration, which was defined as short (< 1 year), medium (1-5 years), and long (> 5 years). A sensitivity analysis was performed using only studies at low risk of bias.

Heterogeneity between studies was assessed using the I^2 statistic. Where heterogeneity was high (> 50%), subgroup analysis was conducted to attempt to reduce suspected causes of heterogeneity, including study duration and disease definition. Statistical significance was set at $P = 0.05$.

A weighted linear regression test was performed to assess publication bias in funnel plots using the Egger test.

There was no patient or public involvement in this study. Data used in the analyses and the analytic code are available upon reasonable request to the corresponding author.

RESULTS

After application of the search strategy, 4211 articles were retrieved from the original search, and a further 222 articles were retrieved from the updated search. The screening process is summarized in Figure 1. A total of 69 studies met the inclusion criteria and reported on 141 different potential prognostic factors. Of these, 67 papers included outcomes that were reported in > 5 papers.[3-6,19-84] In total, 5 studies were then excluded for having duplicate research cohorts, leaving 62 eligible studies (Supplementary Figures S2A,B, available from the authors upon request). In total, 11 of these studies were identified as partial duplicates, meaning that they included some unique variables warranting ongoing inclusion for these variables only.

Study features. After removing earlier studies of overlapping cohorts, the average IIM-ILD mortality in the remaining included articles (n = 52) was 31.32% (95% CI 26.86-35.78) and ranged from 7.32% to 72.72%. Of the 7 studies reporting mortality rates of 50% or higher, 2 were from intensive care unit (ICU) admissions, 2 were about MDA5 populations, and 2 were about clinically amyopathic DM (CADM) populations. Most studies were from Asia (n = 48), most commonly Japan (n = 27) and China (n = 18), and only 3 studies were from elsewhere (ie, Hungary, Mexico, and France). Mortality by region was 31.49% (95% CI 26.84-36.14) in Asia and 26.69% (95% CI

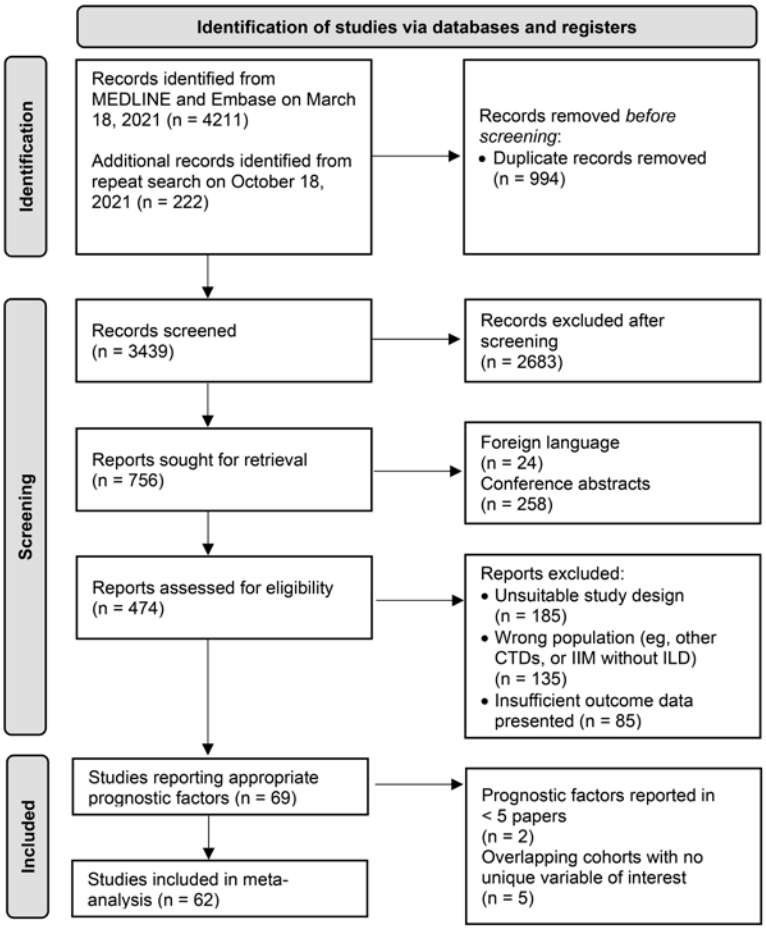

Figure 1. PRISMA flow diagram detailing study selection process. CTD: connective tissue disease; IIM: idiopathic inflammatory myopathy; ILD: interstitial lung disease; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses.

21.80-51.21) outside of Asia. In total, 38% of studies had a follow-up duration of < 1 year, 35% had a follow-up duration between 1 and 5 years, and 19% had a follow-up duration of > 5 years. In total, 4 studies did not specify the follow-up duration. Variables identified for extraction were summarized in the following categories: antibodies, clinical features, investigations, and radiology (Table).

Antibodies. The most consistent risk factor for mortality in IIM-ILD was presence of anti-MDA5 antibodies, with an OR for death of 6.20 (95% CI 3.58-10.71; Table and Figure 2). Conversely, having an antisynthetase antibody was associated with a lower risk (Figure 3). There was moderate heterogeneity in these analyses. In the ARS analysis, I^2 decreased to 0% when only studies of anti-Jo1 antibodies were subanalyzed. There were insufficient data to assess whether anti-Jo1 antibodies had a reduced mortality compared to other anti–tRNA synthetase antibodies. When ARS was compared against only patients who were negative for MDA5 or ARS, the significant difference between groups was lost and the I^2 measure of heterogeneity decreased to 0%, suggesting that the survival benefit of ARS was strongly influenced by the absence of anti-MDA5 antibodies. Looking at studies of short-term mortality (< 1 yr) only, anti-MDA5 antibodies had a higher OR of death of 8.83 (95% CI 3.38-23.06), with no effect on heterogeneity (Figure 2). All eligible studies were from Japan or China, except 1 study regarding ICU admissions in France.[70] Anti-MDA5 antibody titer showed an effect direction association with higher mortality, but this was nonsignificant (Figure 4). Again, all studies were from Asia. Antinuclear antibody did not show a significant association with mortality, but the effect direction was a reduction in mortality. In 3 papers reporting prognosis with SSA,[65,69,80] it was not specified whether this was against the Ro52 antigen or the 60-kDa Ro antigen. Anti-Ro52 antibodies and SSA showed no association with mortality when analyzed either separately or together (Figure 5).

Clinical features. Risk of death increased with age, with a mean difference between survivors and nonsurvivors of 6.56 years (95% CI 4.61-8.52; Table). Being male, having dyspnea, or having fever on presentation also significantly increased risk, with a pooled OR of 1.31 (95% CI 1.05-1.63), 2.24 (95% CI 1.11-4.53), and 2.71 (95% CI 1.65-4.47), respectively. Joint involvement, muscle symptoms, or being a current or ex-smoker did not significantly alter risk, though the suggested effect direction was protective for joint or muscle involvement and was

Table. Summary of metaanalysis results according to potential risk factors of mortality.

Risk Factor for Mortality	Studies, n	Participants, n	I^2, %	OR	Hedges *g*	95% CI
Antibodies						
MDA5	16	1383	**39.3**	**6.20**	—	**3.58 to 10.71**
ARS	16	3128	**31.1**	**0.24**	—	**0.14 to 0.41**
MDA5/ARS– vs ARS+	5	597	0.0	1.54	—	0.84 to 2.83
Jo1 vs Non-Jo1	5	714	**0.0**	**0.33**	—	**0.14 to 0.77**
Ro52 or SSA	8	1206	40.0	1.15	—	0.54 to 2.46
ANA	9	566	0.0	0.75	—	0.50 to 1.13
MDA5 titer	7	335	93.5	—	0.42	–0.09 to 0.94
Clinical features						
Age	28	1269	**44.8**	—	**6.56**	**4.61 to 8.52**
Male sex	30	2289	**0.0**	**1.31**	—	**1.05 to 1.63**
A/SIP	24	968	**27.9**	**8.31**	—	**4.79 to 14.41**
CADM vs DM/PM	25	2467	**40.3**	**1.56**	—	**1.07 to 2.29**
DM (excluding CADM) vs PM	14	1598	**0.0**	**2.48**	—	**1.86 to 3.30**
Disease duration at baseline, wks	6	419	13.53	—	–0.11	–0.33 to 0.10
Dyspnea	5	189	**0.0**	**2.24**	—	**1.11 to 4.53**
Ulceration	6	828	**0.0**	**1.97**	—	**1.28 to 3.04**
Gottron sign	5	348	0.0	1.72	—	0.88 to 3.35
Heliotrope rash	5	348	18.5	1.37	—	0.77 to 2.45
Joint involvement	7	492	0.0	0.72	—	0.46 to 1.14
Fever	10	896	**29.2**	**2.71**	—	**1.65 to 4.47**
Muscle involvement	7	844	20.2	0.68	—	0.41 to 1.13
Ex/current smoker	6	259	0.0	1.17	—	0.57 to 2.43
Investigations						
CRP	15	831	**0.0**	—	**0.32**	**0.13 to 0.51**
CK	19	1100	0.0	—	0.02	–0.11 to 0.15
KL-6	14	490	71.7	—	0.05	–0.25 to 0.34
Albumin	7	482	**90.2**	—	**–0.67**	**–1.00 to –0.34**
SP-D	7	511	0.0	—	–0.06	–0.49 to 0.37
Ferritin	19	993	**67.9**	—	**0.90**	**0.53 to 1.28**
Lymphocytes	7	378	**0.0**	—	**–0.46**	**–0.70 to –0.23**
LDH	18	1034	**35.2**	—	**0.53**	**0.27 to 0.79**
ESR	9	575	43.1	—	0.56	–0.24 to 1.36
A-a O_2 gradient	5	140	**62.3**	—	**1.00**	**0.33 to 1.67**
P/F ratio	6	306	**84.4**	—	**–0.72**	**–1.29 to –0.15**
FVC%	13	703	**85.3**	—	**–0.54**	**–0.93 to –0.15**
TLCO%	12	617	**45.3**	—	**–0.45**	**–0.72 to –0.18**
Radiology						
GGO score	5	415	**0.00**	—	**1.10**	**0.84 to 1.37**
GGO presence	9	244	**8.71**	**3.37**	—	**1.41 to 8.03**
Consolidation presence	6	131	43.34	0.70	—	0.14 to 3.44
Reticulation presence	6	172	57.18	1.05	—	0.15 to 7.20
Overall HRCT score	8	628	**45.74**	—	**0.96**	**0.68 to 1.24**

Values in bold are statistically significant. A-a: alveolar to arterial; ANA: antinuclear antibody; A/SIP: acute/subacute interstitial pneumonia; ARS: aminoacyl-tRNA synthetase; CADM: clinically amyopathic dermatomyositis; CK: creatine kinase; CRP: C-reactive protein; DM: dermatomyositis; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; GGO: ground-glass opacity; HRCT: high-resolution computed tomography; KL-6: Krebs von den Lungen-6; LDH: lactate dehydrogenase; MDA5: melanoma differentiation–associated protein 5; OR: odds ratio; P/F: PaO_2 (partial pressure of oxygen in the arterial blood)/FiO_2 (fraction of inspired oxygen); PM: polymyositis; Ro52: 52-kDa Ro antigen; SP-D: surfactant protein-D; TLCO: transfer factor for carbon monoxide for carbon monoxide;.

detrimental in smokers. Specific rashes of Gottron sign or heliotrope rash did not significantly alter risk, though patients with skin ulceration were at increased risk of dying (OR 1.97, 95% CI 1.28-3.04).

Patients with acute or subacute presentation, defined as progressive respiratory symptoms within 3 months of presentation, had a poor prognosis compared to those with a more chronic onset (OR 8.31, 95% CI 4.79-14.41). Patients with CADM were at higher risk of death than those with classical DM or PM, and DM conferred a higher risk than PM (Table).

Biochemical markers. Patients who died had significantly higher levels of C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH), with Hedges *g* coefficients conferring moderate to strong effect sizes. They had lower lymphocytes and albumin.

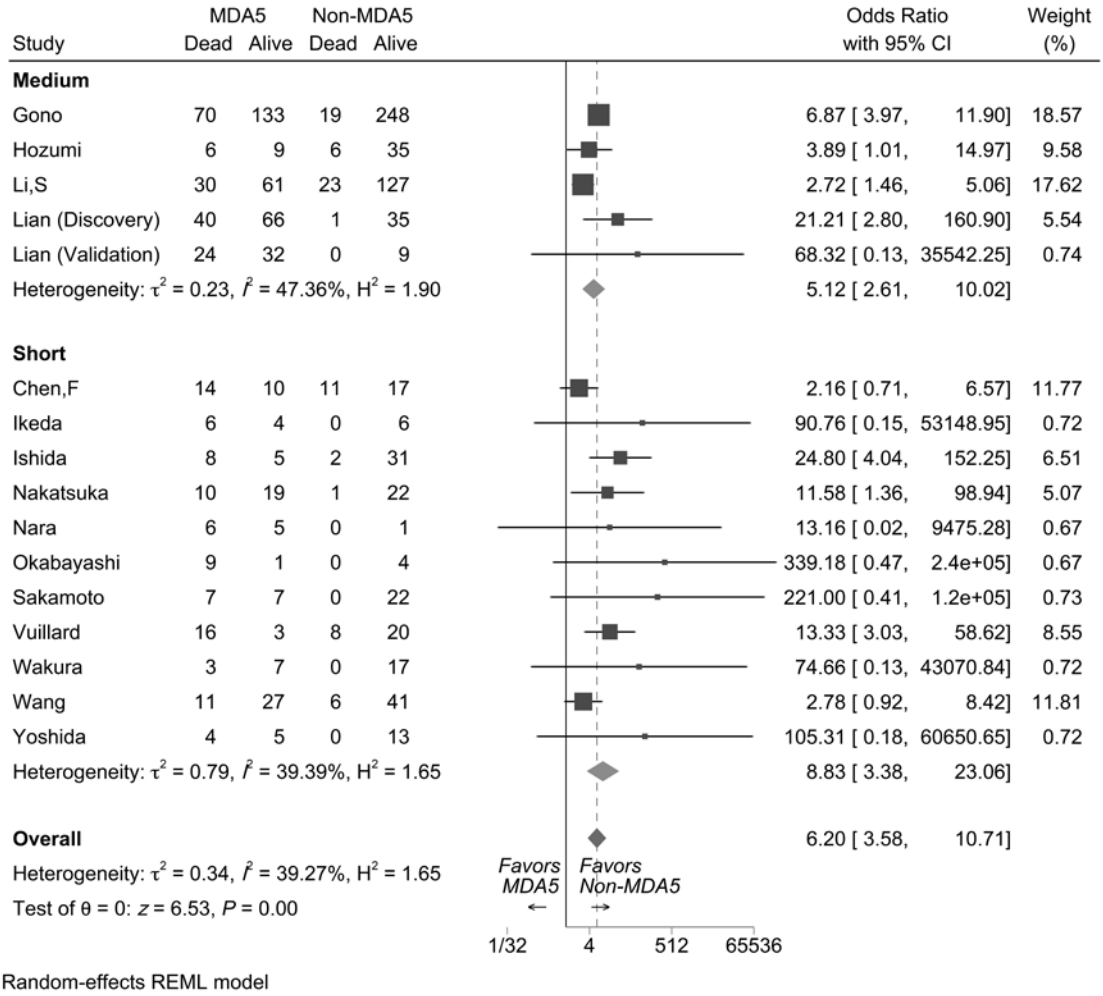

Figure 2. Forest plot showing increased odds of mortality with anti-MDA5 antibody divided by study duration of < 1 year (short) or between 2-5 years (medium). MDA5: melanoma differentiation–associated protein 5; REML: restricted maximum likelihood.

Baseline surfactant protein-D (SP-D) levels, Krebs von den Lungen-6 (KL-6) levels, erythrocyte sedimentation rate (ESR), and creatine kinase levels were not found to affect outcome (Table).

Pulmonary physiology. Respiratory function testing showed that baseline percentage predicted forced vital capacity (FVC%) and percentage predicted transfer factor for carbon monoxide (TLCO%) were lower in fatal cases (Table). Alveolar to arterial (A-a) O_2 gradients are a measure of dysfunction of the alveolar-capillary unit. Mortality was associated with significantly higher A-a O_2 gradients and significantly lower ratios of partial pressure of oxygen in the arterial blood to fraction of inspired oxygen (PF ratio).

Radiology. There was wide variation in the methodology used to describe radiology between papers. Traditional clinical diagnoses of nonspecific interstitial pneumonia, usual interstitial pneumonia, and organizing pneumonia were not consistently reported across enough papers to permit a metaanalysis. High-resolution computed tomography (HRCT) scoring systems were widely used, but there was little concordance in methodology with scores from Kazerooni et al,[85] Goh et al,[86] Ooi et al,[87] Ichikado et al,[88] and Kinoshita et al [89] being used, as well as Yoshida et al,[78] Sugiyama et al,[65] and Zou et al[81] proposing their own novel scores. The binary presence of ground-glass opacity (GGO) or GGO predominant disease on HRCT was predictive of mortality (OR 3.37, 95% CI 1.41-8.03; Table). Additionally, the pooled effect of all GGO scoring systems strongly correlated with mortality risk, with a Hedges $g > 1$. The presence of consolidation or reticulation did not correlate with mortality. Pooling of overall HRCT scores showed a strong association with mortality, with a Hedges g of 0.96, confirming that HRCT analysis can be a useful predictor of outcome, but because of difference in scoring methodologies, we are unable to confirm the performance of individual methods.

Risk of bias assessment. Funnel plots of MDA5 and ARS meta-analyses appeared asymmetrical, confirmed by the Egger test for MDA5 ($P = 0.02$) and ARS ($P = 0.03$) studies (Supplementary Figures S3 and S4, available from the authors upon request). This could suggest publication bias within this field, resulting in an overestimation of the effect size. Alternatively, funnel plot

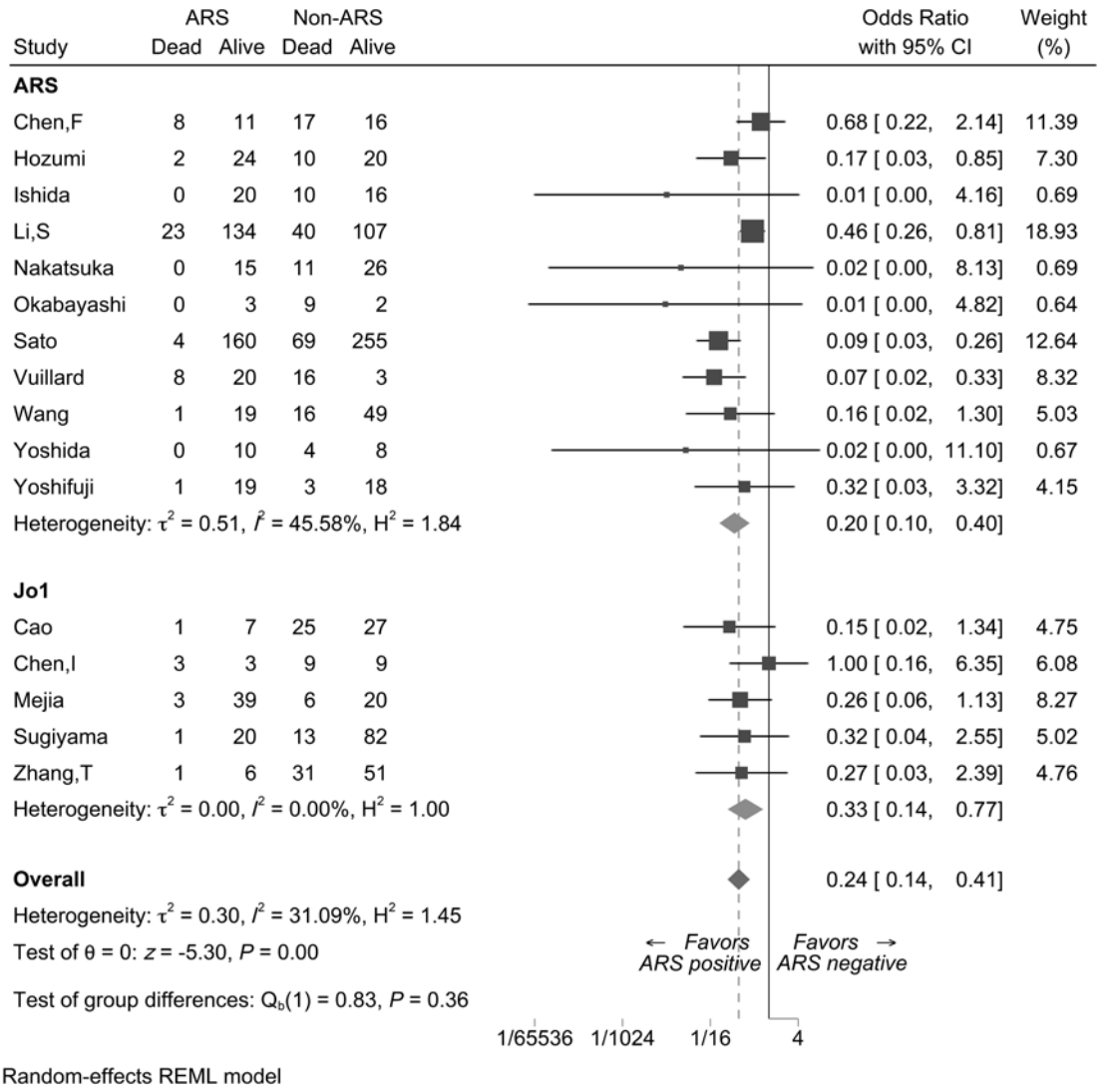

Figure 3. Forest plot showing a reduced risk of death in those with an ARS antibody. Heterogeneity can be reduced by subanalyzing only those with anti-Jo1. ARS: aminoacyl-tRNA synthetase; REML: restricted maximum likelihood.

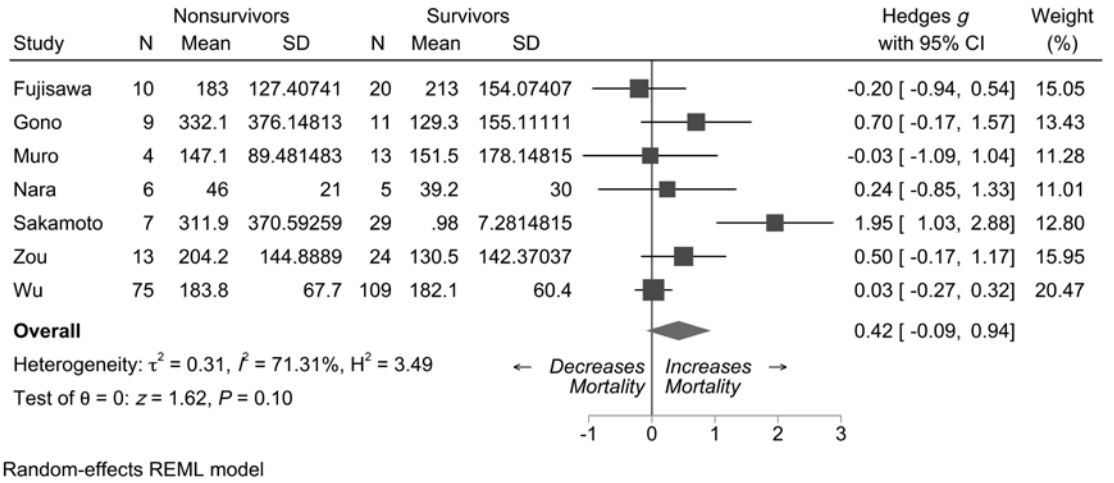

Figure 4. Forest plot of MDA5 titer showing pooled effect on odds ratio. MDA5: melanoma differentiation–associated protein 5; REML: restricted maximum likelihood.

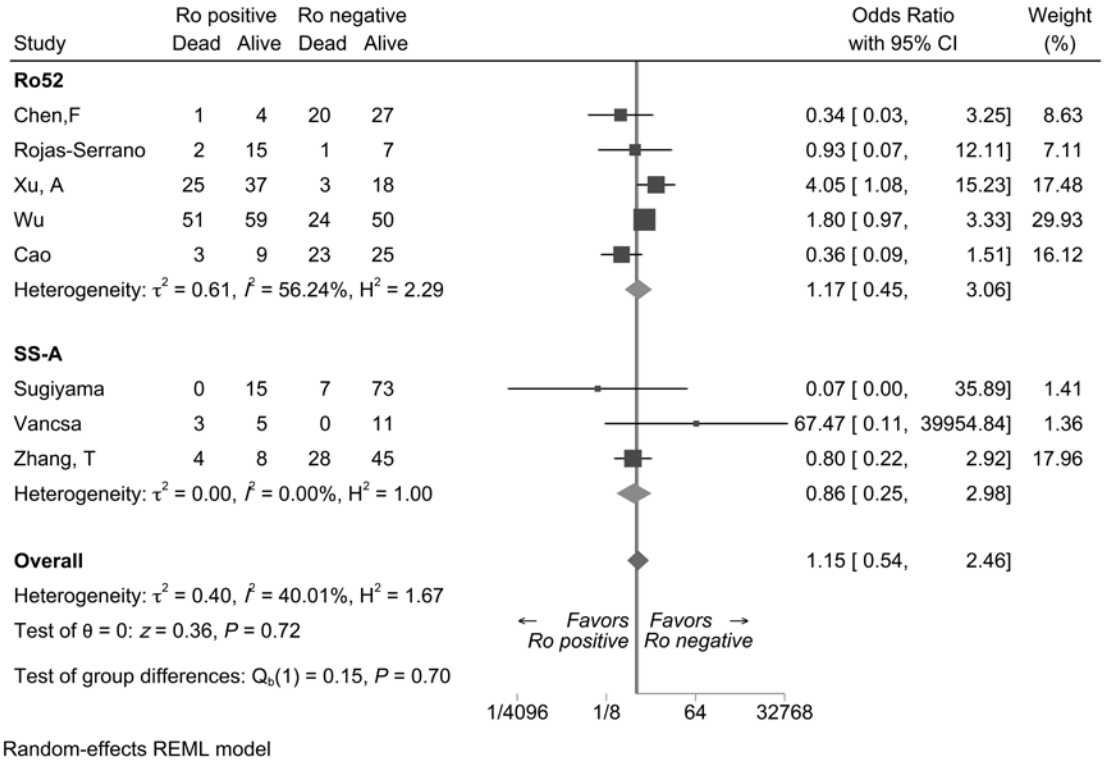

Figure 5. Forest plot showing there is no effect of Ro52 or SSA on mortality. REML: restricted maximum likelihood; Ro52: 52-kDa Ro antigen.

asymmetry could arise from genuine heterogeneity as a result of there being multiple distinct subgroups of studies. On average, studies had a Newcastle-Ottawa Scale score of 3.6 out of a maximum possible score of 9 stars. Two studies scored less than 3 stars each.[25,79] Sensitivity analysis after removing these studies only affected DM vs PM analysis (reduced OR by 0.02), with no change to the significance of the result.

DISCUSSION

Research in the field of IIM-ILD is complicated by the heterogeneity between groups. The strong effect of anti-MDA5 antibodies on mortality dominates the picture. ILD with anti-MDA5 antibodies appears to be an aggressive phenotype leading to high rates of mortality within the first year following diagnosis. Only 2 studies analyzed outcomes beyond this, with Kaplan-Meier curves of these studies showing that all deaths still occurred within the first 20 months, implying that a medium-term outcome for early survivors is better.[4,90] Whereas the presence of anti-Jo1 antibodies appears to be associated with lower mortality, the effect of other rarer autoantibodies, both ARS and non-ARS, is difficult to elucidate. Other studies have suggested that anti-PL7 and anti-PL12 antisynthetase syndrome may show ILD in patients earlier in their disease course and with more severity than in patients who were positive for anti-Jo1.[11,12] However, there are insufficient studies addressing mortality according to ARS subtype for inclusion in this metaanalysis.

Anti-Ro52 antibodies occur in one-third of patients with connective tissue disease (CTD) and are associated with ILD at CTD diagnosis.[91] The presence of anti-Ro52 antibodies in IIM increases the likelihood of developing ILD.[92] Whereas some studies have drawn links to increased ILD severity, an increased rate of rapidly progressive ILD (RP-ILD), and an increased likelihood of deterioration in patients who were positive for anti-Ro52 antibodies, our results did not demonstrate an increase in mortality.[12,75,91,92]

Several clinical factors have been shown to affect mortality. Some of these effects may be due to an association with MDA5 disease. Patients with MDA5 disease are more likely to be amyopathic or hypomyopathic, which explains our findings of an increased risk of death in CADM.[93] Likewise, fever is estimated to affect 46% to 69% of patients with MDA5 and 39% to 92% of patients with RP-ILD, both of which we found to be negative prognostic factors.[93] Distinctive mucocutaneous disease, including cutaneous ulceration with minimal skeletal muscle disease, is a common phenotype in MDA5 disease. Cutaneous ulceration has previously been associated with the development of ILD,[94] and our metaanalysis confirmed an association with increased mortality.

KL-6 is a lung epithelium–specific protein directly implicated in the pathogenesis of ILD and has long been proposed as a prognostic marker in ILD; however, its relevance in IIM-ILD remains to be elucidated.[95] We did not find an association of baseline KL-6 levels with mortality, though some studies have proposed that it is a dynamic change in KL-6 levels that determines the prognostic relevance. SP-D is a biomarker of various pulmonary diseases, including acute respiratory distress

syndrome, chronic obstructive pulmonary disease, and systemic sclerosis–associated ILD.[96] We did not find baseline SP-D levels to be a risk factor for mortality; however, a previous metaanalysis of SP-D in idiopathic pulmonary fibrosis (IPF) found that higher SP-D levels predicted mortality.[96] Arai et al[19] found that although there was no difference in baseline SP-D levels between survivors and nonsurvivors, an increase in SP-D levels over the first 4 weeks was predictive of prognosis, meaning that changes in SP-D levels may be more useful.

Dyspnea at presentation, acute/subacute interstitial pneumonia (A/SIP), reduced FVC%, reduced percentage predicted TLCO%, and an increasing A-a O_2 gradient were all unsurprisingly associated with mortality, with substantial effect sizes. A/SIP carries an OR of 8.31 for risk of death, and the Hedges *g* value for the difference between A-a O_2 gradients is 1.00. They are all indicators of clinically active and/or significant lung disease. Likewise, increased GGO and overall severity scores on HRCT was associated with mortality. Further validation studies are required regarding specific HRCT scoring methods to identify those most sensitive to change and their clinical relevance. The most commonly reported score was the Kazerooni score, but this was designed for evaluation of IPF and has not been extensively validated in IIM-ILD.[84] In the Kazerooni score, fibrotic elements, such as traction bronchiectasis, carry more weight than inflammatory components (ie, GGO and consolidation), which may be more relevant in more rapidly progressive disease, such as DM with anti-MDA5 antibodies.[85]

Treatment of IIM-ILD includes corticosteroids and immunosuppressant medications, such as mycophenolate, azathioprine, cyclosporine A, tacrolimus, cyclophosphamide, and rituximab.[97] The efficacy of different treatments and their effects on prognosis are beyond the scope of this review, and with few RCTs in this area, substantial uncertainty remains about the best treatment options. Clinician choice is primarily influenced by perceived disease severity and physician experience. Improved risk stratification at an early stage through clarification of valuable prognostic factors may affect choice of timing and strength of therapeutic intervention.

Overall, with so many factors contributing to mortality risk, a risk prediction model could be constructed to take into account all of these factors. Gono et al[27] have already attempted this using CRP, KL-6, and MDA5 status to predict mortality. A similar "FLAIR" score for use in CADM using ferritin, LDH, anti-MDA5 antibodies, CT imaging scores, and RP-ILD has also been developed.[82] Our work suggests that further features could be incorporated into these models to improve accuracy.

Regarding limitations in this study, most included studies were retrospective, making causality inferences difficult. During the search stages, it was evident that a large number of studies in this area are submitted as abstracts and are never formally written up. This publication bias was evident on the funnel plots of the primary outcomes. Additionally, there was large variability in the way results were presented, making many seemingly relevant articles unsuitable for inclusion, including many that presented results graphically or with only hazard ratios, without providing the raw data. Short-term mortality is not the only outcome of interest to patients with IIM-ILD; many articles looked at alternative measures of outcome, such as pulmonary function deterioration, radiographic progression, or the development of RP-ILD vs chronic ILD. As well as vast variation in the way outcomes were reported, there was an equally huge variation in the inclusion criteria between studies. Some cohorts were unselected PM and DM populations, whereas others defined entry by antibody subset, presentation (ie, A/SIP only), or severity (ie, ICU only). There was an insufficient number of studies needed to attempt a meta-regression to allow for these factors. Many studies had to be discarded, as patients in described cohorts did not all have confirmed ILD.

Overall, the total number of included patients remains small because of the rarity of IIM-ILD. The largest cohorts are from registry data, assessment of which may prove the most effective and efficient way of investigating the rarer subtypes of IIM-ILD.

Long-term follow-up data are lacking, with most of the studies looking at outcomes in the first year; these studies are, therefore, of the most relevance to patients with A/SIP. A longer-term outlook for patients remains poorly described, particularly for those with chronic interstitial pneumonia. In the primary analysis of the effect of MDA5 on prognosis, only 3 studies looked at outcomes beyond 1 year, and no studies looked at outcomes beyond 2 years.[48,82,98]

Despite being an uncommon variant of IIM, anti-MDA5 antibody–positive disease has attracted a lot of research attention since its identification and description by Sato et al in 2005.[99] Since then, a vast majority of research in this area has been produced in Japan and to a lesser extent in China. It is thought that MDA5 disease is more prevalent in these regions, affecting 25% of Japanese patients with DM but only 7% to 10% of European patients with DM.[100] It also may have a more severe phenotype than cohorts elsewhere.[7,8] This suggests an influence of genetic or environmental factors in the development and progression of disease. In total, 91% of included studies in this metaanalysis were from East Asia, meaning that the applicability to other populations is questionable.

In conclusion, despite limited and conflicting evidence, this study has successfully identified many potential variables of interest for developing risk prediction models for IIM-ILD. Risk factors for mortality include anti-MDA5 antibodies, male sex, increasing age, acute/subacute onset, and CADM. Risk factors also included, to a lesser extent, DM; fever or dyspnea at presentation; raised CRP, ESR, ferritin, LDH, or A-a O_2 gradient; or reduced SP-D, FVC%, or TLCO%.

IIMs are a rare set of diseases, and clinicians who specialize in them do not have the luxury of large RCTs on which to base their decisions. The evidence base is small, and the quality of studies is low; therefore, metaanalyses are important for maximizing the understanding of what has been published, not just to help clinicians understand the disease but also to inform the design of future research.

IIM-ILD is a hodgepodge of poorly defined but related conditions. Heterogeneity and possible publication bias limit the interpretation of findings. Patients with MDA5 and cohorts from East Asia are overrepresented in the included studies, so

results are likely confounded by the aggressive MDA5 phenotype. The evidence presented in this study supports the idea that MDA5 confers a very different disease phenotype. This highlights the need to separate phenotypes in clinical studies, as well as the need for more diverse international myositis-ILD cohorts and well-designed prospective studies.

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