Short running head: Predicting mortality in IIM-ILD

Full title of manuscript:

A systematic review and meta-analysis of predictors of mortality in idiopathic inflammatory myopathy-associated interstitial lung disease

Complete names of all authors: Jennifer Hannah (ORCID 0000-0002-3491-6653), Huiyi Esther Law, Tanya Gordon, Michael Rooney, April Buazon, Maryam Adas, Deepak Nagra, Christopher Stovin, James Galloway, Patrick Gordon

Key Indexing Terms: Interstitial lung disease, Idiopathic inflammatory myopathies, Myositis, Prognosis, Mortality, Meta analysis

Sources of support: JH is supported by a grant from King's College Hospital Charity. They had no role in study design, implementation, analysis or write up of this manuscript.

Initials and highest academic degrees of all authors: J Hannah MBBS MSc[1,2], H E Law MBBS[1], T Gordon[3], M Rooney[2], M Adas MBBS MSc[2], D Nagra MD[1,2], C Stovin BMBCh[1,2], A Buazon MBChB MSc [4], J Galloway MBChB PhD FRCP [1,2], P Gordon MBBS PhD FRCP [1,2]

[1]Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK

[2]Centre for Rheumatic Disease, School of Immunology & Microbial Sciences, King's College London, London, UK

[3]University of Liverpool School of Medicine, University of Liverpool, London, UK

[4]Guys and St Thomas' NHS Trust, London, UK

Conflict of interest: None declared

Corresponding author: Dr Jennifer Hannah, Department of Academic Rheumatology, Weston Education Centre, King's College London, Denmark Hill, London, SE5 9RS

Jennifer.1.hannah@kcl.ac.uk

Statement of ethics: Ethical approval was not required for this study

Abstract

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

Methods: MEDLINE and EMBASE database searches were completed on 18/10/21 for articles providing survival data according to baseline characteristics in patients with concurrent IIM and ILD. Prognostic factors common to >5 papers were included in meta-analysis using a random-effects model to report odds ratio for binary variables

and hedge's g for continuous variables. Risk of bias was assessed by Newcastle-Ottawa score and Egger's test for publication bias.

Results: From 4433 articles, 62 papers were suitable for inclusion, considering 38 different variables. OR for risk of death for anti-MDA-5 was 6.20 (3.58-10.71), and anti-tRNA-synthetase was protective OR=0.24 (0.14-0.41). ANA, Anti-Ro52 or SS-A did not significantly alter mortality, nor was MDA-5 titre predictive. Age, male gender, acute/sub-acute onset, clinically amyopathic disease, dyspnoea, ulceration, fever, raised CRP, ferritin, LDH, A-aO2 gradient, ground-glass opacities on HRCT and overall HRCT score; and reduced albumin, lymphocytes, PF ratio, %TLCO and %VC are all examples of prognostic factors significantly associated with mortality in this study. Baseline SP-D and KL-6 were not predictors of mortality.

Conclusions: Many mortality risk factors were identified, though heterogeneity was high with low quality of evidence and risk of publication bias. Anti-MDA5 disease, and studies from East Asia predominate and may mask risk factors relevant to other IIM subgroups or populations.

Introduction

The idiopathic inflammatory myopathies (IIMs) are a heterogenous group of chronic autoimmune inflammatory disorders with multi-system involvement including skeletal muscle, lung and skin inflammation. Associated interstitial lung disease (ILD) is seen in approximately 40% of IIM patients 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 impact on function. Many prognostic factors predicting likelihood of progression have been proposed, but sample sizes in individual studies are small and generalisability to real world populations questionable.

Several myositis specific antibodies appear to link with phenotype and therefore prognosis. In particular, Anti-MDA-5 is 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 other populations may display a milder phenotype.(7, 8)

Anti-tRNA-synthetase antibodies (ARS) are associated with an IIM phenotype termed anti-synthetase syndrome, with common manifestations being interstitial lung disease, Raynaud's phenomenon, arthritis, fever and mechanics hands.(9, 10) Whilst the ILD is generally considered less aggressive than in MDA-5 there is heterogeneity between ARS antibodies, with anti-PL12 and anti-PL7 associated with higher prevalence and more severe lung involvement.(11, 12) Additional anti-52kD Ro antibodies are common in ARS and MDA-5 disease. Evidence for the clinical relevance of anti-Ro/SS-A 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 meta-analysis aims to consolidate evidence regarding the impact 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.(16) Full search strategy was pre-registered on PROSPERO (CRD42021240206). MEDLINE and EMBASE databases were interrogated via the Ovid and Web of Science search engines on 18/3/2021 and updated on 18/10/2021 using a pre-defined search protocol (Supplementary data) including key terms such as (but not limited to): myositis, idiopathic inflammatory myopathy, dermatomyositis, polymyositis or anti-synthetase syndrome, AND interstitial lung disease. Articles were limited to the year 2000 onwards. No language filters were applied.

Inclusion and Exclusion Criteria

Articles for inclusion were original cohort, case-control, randomised controlled trials and epidemiological studies of patients with clinically diagnosed IIMs (including DM, PM, clinically amyopathic DM, anti-synthetase syndrome, overlap myositis and juvenile DM) and ILD. To be eligible for inclusion, articles needed to provide summary data relating to frequency of survivors vs non-survivors according to baseline disease characteristics within the article or supplementary material. Case reports or series without relevant summary statistics, conference abstracts, reviews and meta-analyses 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 independently reviewed titles and abstracts to identify those that would potentially meet inclusion criteria for full-text review (JH and PG).

Data extraction was performed onto prepopulated Excel spreadsheets (JH). Initially it was 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 was then extracted under headings covering: study design, inclusion and exclusion criteria, study duration, survival rates according to prognostic factor 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, methodology was 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 score for cohort studies which analyses bias in selection, comparability and outcome.(17) This covers selection methodology, control for confounders, and the reliability of follow up assessments and loss-to follow up.

Statistical analysis

The primary outcome of interest was mortality with primary predictor of interest being myositis-specific autoantibodies and clinical, biochemical and radiographical factors being secondary predictors of interest. Meta-analysis was performed using the meta package in Stata-16. Due to 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 pre-published protocol.

For binary variables, unadjusted incidence of mortality was calculated and results across studies pooled using a random effects model to create summary estimates for odds ratio for each baseline predicting factor with 95% confidence intervals. For continuous variables, effect size was measured with hedge's g due to discrepancies in units of measurement. Hedge's g is a measure of difference between groups calculated in terms of standard deviations. Hedge's g of 0.2-0.5, 0.5-0.8 and >0.8 imply small, medium and large effect sizes respectively.(18) A random effects model was used due to expected differences in individual study populations and methodologies.

Primary outcome was explored further through subgroup analysis according to study duration defined as short, medium and long if <1 year, 1-5 years or >5 years respectively and IIM subset. 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 is high (>50%), subgroup analysis was conducted to attempt to reduce

suspected causes of heterogeneity including study duration and disease definition. Statistical significance is set at 0.05.

Weighted linear regression test was performed to assess publication bias in funnel plots using the Egger's test.

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

Results

On application of the search strategy 4211 articles were retrieved in the original search and a further 222 on the updated search. The screening process is summarised in Figure 1. 69 studies met the inclusion criteria reporting on 141 different potential prognostic factors. Of these 69 papers included outcomes reported in >5 papers suitable for meta-analysis.(3-6, 19-84) 5 studies were then excluded for duplicating research cohorts, leaving 62 eligible studies (Supplementary data). 11 of these studies were identified as partial duplicates, meaning they included some unique variables warranting ongoing inclusion for these variables only.

Study Features

After removing earlier studies of overlapping cohorts, average IIM-ILD mortality in the remaining included articles (n=52) was 31.32% (95%CI 26.86-35.78) but ranged from 7.32% to 72.72%. Of the 7 studies reporting mortality rates ≥50%, 2 were from intensive care unit admissions, 2 were MDA-5, and 2 were CADM populations. Most studies were from Asia (n=48), most commonly Japan (n=27) and China (n=18), only 3 studies were from elsewhere (Hungary, Mexico and France). Mortality by region was 31.49% (95%CI 26.84-36.14) in Asia, and 26.69% (95%CI 21.80-51.21) outside of Asia. 38% of studies had a follow up duration of <1 year, 35% between 1-5 years, and 19% >5 years. Four studies did not specify the follow up duration. Variables identified for extraction were summarised in the categories: antibodies, clinical features, investigations and radiology (Table 1).

Antibodies

The most consistent risk factor for mortality in IIM-ILD was the Anti-MDA5 antibody with an odds ratio for death of 6.20 (95%CI 3.58, 10.71) (Table 1 & Figure 2). Conversely having an anti-synthetase antibody was associated with a lower risk (Figure 3). There was moderate heterogeneity in these analyses. In the ARS analysis, I^2 reduced to 0% when only studies of anti-Jo1 were sub-analysed. There were insufficient data to assess if anti-Jo-1 had a reduced mortality compared to other anti-tRNA synthetases. When ARS was compared against MDA5-negative/ARS-negative patients only, the significant difference between groups was lost and I^2 measure of heterogeneity reduced to 0%, suggesting the survival benefit of ARS was strongly

influenced by the absence of anti-MDA5. Looking at studies of short-term mortality (<1 year) only, anti-MDA5 had a higher OR of death of 8.83 (95%CI 3.38, 23.06) with no impact on heterogeneity (Figure 2). All eligible studies were from Japan or China, except one of ICU admissions in France.(70) Anti-MDA5 titre showed an effect direction association with higher mortality, but this was non-significant (Figure 4). Again, all studies were from Asia. ANA does not show a significant association with mortality, but the effect direction is a reduction in mortality. In three papers reporting prognosis with SS-A it was not specified whether this was against the Ro52 or Ro60 antigen. Anti-Ro52 and SS-A showed no association with mortality when analysed either separately or together (Figure 5).

Clinical Features

Risk of death increased with age, with a mean difference of years between survivors and non-survivors of 6.56 years (95%CI 4.61-8.52). Being male, or having dyspnoea, or fever on presentation also significantly increased risk with pooled OR of 1.31, 2.24 and 2.71 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 detrimental in smokers. Specific rashes of Gottron's sign or heliotrope rash did not significantly alter risk, though patients with skin ulceration were at increased risk of dying (OR 1.97).

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). 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 1)

Biochemical Markers

Patients who died had significantly higher levels of CRP, ferritin and LDH with hedge's g coefficients conferring moderate to strong effect sizes. They had lower lymphocytes and albumin. Baseline SP-D, KL-6, ESR and CK were not found to affect outcome. (Table 1)

Pulmonary Physiology

Respiratory function testing showed baseline percentage predicted forced vital capacity (%FVC) and percentage predicted diffusion capacity (%DLCO) were lower in fatal cases. (Table 1) Alveolar-arterial gradients (A-aO2) are a measure of dysfunction of the alveolar-capillary unit. Mortality was associated with significantly higher A-aO2, and significantly lower P/F ratios.

Radiology

There was wide variation in the methodology used to describe radiology between papers. Traditional clinical diagnoses of non-specific interstitial pneumonia, usual interstitial pneumonia and organising pneumonia were not consistently reported across enough papers to permit meta-analysis. High-resolution computerised tomography (HRCT) scoring systems were widely used, but there was little concordance in methodology with Goh, Kazerooni, Ooi, Ichikado and Kinoshita scores

being used, as well as Yoshida, Sugiyama and Zou proposing their own novel scores.(65, 78, 81, 85-89) The binary presence of ground glass opacities (GGO) or GGO predominant disease on HRCT was predictive of mortality (OR 3.37) (Table 1). Additionally, the pooled effect of all GGO scoring systems strongly correlated with mortality risk with a hedges g of >1. The presence of consolidation or reticulation did not correlate with mortality. Pooling of overall HRCT scores showed a strong association with mortality with Hedge's g 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 performance of individual methods.

Risk of Bias Assessment

Funnel plots of MDA-5 and ARS meta-analyses appeared asymmetrical, confirmed by Egger's test p=0.013 and p=0.026 for MDA-5 and ARS studies respectively (Supplementary data). This could suggest publication bias within this field resulting in an overestimation of the effect size. Alternatively funnel plot asymmetry could arise from genuine heterogeneity due to there being multiple distinct subgroups of studies. On average studies had a Newcastle-Ottawa score of 3.6 out of a maximum possible of 9 stars. Yoshifuji (ASS) and Furuya (CADM/DM analysis) scored <3 stars. Sensitivity analysis removing these studies only impacted 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 impact of anti-MDA-5 on mortality dominates the picture. Anti-MDA-5 ILD appears to be an aggressive phenotype leading to high rates of mortality within the first year following diagnosis. Only 2 studies analyse outcomes beyond this with Kaplan-Meier curves of these studies showing all deaths were still within the first 20 months, implying medium term outcome for early survivors is better.(4, 90) Whilst anti-Jo-1 appears to be associated with a lower mortality, the impact of other rarer autoantibodies, both ARS and non-ARS, is difficult to elucidate. Other studies have suggested that anti-PL7 and anti-PL12 anti-synthetase syndrome may show ILD earlier in their disease course and with more severity than anti-Jo-1 positive patients.(11, 12) However there are insufficient studies addressing mortality according to ASS subtype for inclusion in this meta-analysis.

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

Several clinical factors have been shown to impact mortality. Some of this effect may be due to an association with MDA-5 disease. Patients with MDA-5 disease are more likely to be amyopathic or hypomyopathic explaining our findings of increased risk of death in CADM.(93) Likewise, fever is estimated to affect 46-69% of MDA-5 patients, and RP-ILD in 39-92%, both of which we found to be negative prognostic factors.(93) Distinctive muco-cutaneous disease including cutaneous ulceration with minimal skeletal muscle disease is a common phenotype in MDA-5 disease. Cutaneous ulceration has previously been associated with the development of ILD,(94) and our meta-analysis confirmed an association with increased mortality.

Krebs Von Den Lungen-6 (KL-6) is a lung epithelium-specific protein directly implicated in the pathogenesis of ILD and has long-been proposed as a prognostic maker in ILD, though it's relevance in IIM-ILD remains to be elucidated.(95) We did not find an association of baseline KL-6 with mortality though some studies have proposed that it is dynamic change in KL-6 which determines the prognostic relevance. Surfactant protein D (SP-D) is a biomarker of various pulmonary diseases including ARDS, chronic obstructive pulmonary disease, and systemic sclerosis associated-ILD.(96) We did not find baseline SP-D level to be a risk factor for mortality, however previous meta-analysis of SP-D in IPF found higher SP-D to predict mortality.(96) Arai et al found that although there was no difference in baseline SP-D between survivors and non-survivors,(19) increase in SP-D over the first 4 weeks was predictive of prognosis, meaning change in SP-D may be more useful.

Dyspnoea at presentation, A/SIP (acute/subacute interstitial pneumonia), reduced FVC%, TLCO% and increasing A-a gradient were all unsurprisingly associated with mortality, with substantial effect sizes. A/SIP carries an OR of 8.31 for risk of death, the hedge's g value for difference between A-aO2 gradients is 1.00. They are all indicators of clinically active and/or significant lung disease. Likewise, the increased severity of finding on HRCT was associated with mortality. Further validation studies are required on specific HRCT scoring methods to identify those most sensitive to change and the clinical relevance. The most commonly reported score was the Kazerooni score, but this was designed for evaluation of idiopathic pulmonary fibrosis, and has not been extensively validated in IIM-ILD.(84) In the Kazerooni score, fibrotic elements such as traction bronchiectasis carry more weighting than inflammatory components ie. Ground-glass opacity and consolidation, which may be more relevant in more rapidly progressive disease such as anti-MDA-5 DM.(97)

Treatment of IIM-ILD includes corticosteroids and immunosuppressant medications such as mycophenolate, azathioprine, cyclosporin A, tacrolimus, cyclophosphamide and rituximab.(98) Efficacy of different treatments and their impact on prognosis is beyond the scope of this review, and with few randomised controlled trials 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 impact 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 these factors. Gono *et al* have already attempted this using CRP, KL-6 and MDA-5 status to predict mortality.(99) A similar 'FLAIR' score for use in CADM using ferritin, LDH, anti-MDA5, CT imaging score and RP-ILD has also been developed.(82) Our work suggests, that further features could be incorporated into these models to improve accuracy.

Limitations

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 for abstract and never formally written up. This publication bias was evident on 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 hazard ratios only 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 rapidly progressive vs chronic ILD. As well as vast variation in the way outcomes were reported, there was 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 were insufficient studies to attempt meta-regression to allow for these factors. Many studies had to be discarded as described cohorts did not all have confirmed ILD.

Overall, the total number of included patients remains small due to the rarity of IIM-ILD. The largest cohorts are from registry data, 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 outcome in the first year, and therefore of most relevance to the A/SIP patients. Longer term outlook for patients remains poorly described, particularly for those with CIP. In the primary analysis of the impact of MDA-5 on prognosis, only 3 studies looked at outcomes beyond 1 year, and no studies looked beyond 2 years.(48, 82, 100)

Despite being an uncommon variant of IIM, anti-MDA-5 positive disease has attracted a lot of research attention since its identification by Sato *et al* in 2004.(101) Since then a vast majority of research in this area has been produced in Japan and to a lesser extent China. It is thought that MDA-5 disease is more prevalent in these regions, affecting 25% of Japanese DM patients, but only 7-10% of European DM patients.(102) It also may have a more severe phenotype than cohorts elsewhere.(103, 104) This suggests an influence of genetic or environmental factors in the development and progression of disease. 91% of included studies in this meta-analysis are from East Asia, meaning that the applicability to other populations is questionable.

Conclusion

Despite limited and conflicting evidence, this study has successfully identified many potential variables of interest for developing risk prediction models in IIM-ILD. Risk factors for mortality include anti-MDA-5, male sex, increasing age, acute/sub-acute onset, CADM and to a lesser extent DM, fever or dyspnoea at presentation, raised CRP, ESR, ferritin, LDH, A-a gradient, or reduced SP-D, FVC% or TLCO%.

IIMs are a rare set of diseases and clinicians who specialise in them do not have the luxury of large randomised controlled trials to base their decisions on. The evidence base is small, and the quality of studies is low, and therefore meta-analysis is important to maximise 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 hotchpot of poorly-defined but related conditions. Heterogeneity and possible publication bias limit the interpretation of findings. MDA-5 patients and cohorts from East Asia are over-represented in the included studies, so results are likely confounded by the aggressive MDA-5 phenotype. The evidence presented in this study supports that MDA-5 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.

References

1. Sun KY, Fan Y, Wang YX, Zhong YJ, Wang GF. Prevalence of interstitial lung disease in polymyositis and dermatomyositis: A meta-analysis from 2000 to 2020. Semin Arthritis Rheum 2021;51:175-91
2. Johnson C, Pinal-Fernandez I, Parikh R, et al. Assessment of mortality in autoimmune myositis with and without associated interstitial lung disease. Lung 2016;194:733-7
3. Chen F, Wang D, Shu X, Nakashima R, Wang G. Anti-MDA5 antibody is associated with A/SIP and decreased T cells in peripheral blood and predicts poor prognosis of ILD in Chinese patients with dermatomyositis. Rheumatol Int 2012;32:3909-15
4. Gono T, Sato S, Kawaguchi Y, et al. Anti-MDA5 antibody, ferritin and IL-18 are useful for the evaluation of response to treatment in interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Rheumatology 2012;51:1563-70
5. Sato S, Masui K, Nishina N, et al. Initial predictors of poor survival in myositisassociated interstitial lung disease: A multicentre cohort of 497 patients. Rheumatology 2018;57:1212-21
6. Chen F, Zuo Y, Li S, Shi J, Wang G, Shu X. Clinical characteristics of dermatomyositis patients with isolated anti-Ro-52 antibody associated rapid progressive interstitial lung disease: Data from the largest single Chinese center. Respir Med 2019;155:127-32
7. Hall JC, Casciola-Rosen L, Samedy LA, et al. Anti-melanoma differentiation-associated protein 5-associated dermatomyositis: expanding the clinical spectrum. Arthritis Care Res 2013;65:1307-15
8. Ceribelli A, Fredi M, Taraborelli M, al. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. Clin Exp Rheumatol 2014;32:891-7
9. Connors GR, Christopher-Stine L, Oddis CV, Danoff SK. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest 2010;138:1464-74
10. Solomon J, Swigris JJ, Brown KK. Myositis-related interstitial lung disease and antisynthetase syndrome. J Bras Pneumol 2011;37:100-9
11. Pinal-Fernandez I, Casal-Dominguez M, Huapaya JA, et al. A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies. Rheumatology 2017;56:999-1007
12. Marie I, Josse S, Decaux O, et al. Comparison of long-term outcome between anti-Jo1- and anti-PL7/PL12 positive patients with antisynthetase syndrome. Autoimmun Rev 2012;11:739-45
13. La Corte R, Lo Mo Naco A, Locaputo A, Dolzani F, Trotta F. In patients with antisynthetase syndrome the occurrence of anti-Ro/SSA antibodies causes a more severe interstitial lung disease. Autoimmunity 2006;39:249-53

14. Sabbagh S, Pinal-Fernandez I, Kishi T, et al. Anti-Ro52 autoantibodies are associated with interstitial lung disease and more severe disease in patients with juvenile myositis. Ann Rheum Dis 2019;78:988-95
15. Sclafani A, D'Silva KM, Little BP, et al. Presentations and outcomes of interstitial lung disease and the anti-Ro52 autoantibody. Respir Res 2019;20:256
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71
17. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013 http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
18. Bland M. An Introduction to Medical Statistics. 4th Edition ed.: Oxford University Press; 2015.
19. Arai S, Kurasawa K, Maezawa R, Owada T, Okada H, Fukuda T. Marked increase in serum KL-6 and surfactant protein D levels during the first 4 weeks after treatment predicts poor prognosis in patients with active interstitial pneumonia associated with polymyositis/dermatomyositis. Mod Rheumatol 2013;23:872-83
20. Cao H, Huan C, Wang Q, Xu G, Lin J, Zhou J. Predicting Survival Across Acute Exacerbation of Interstitial Lung Disease in Patients with Idiopathic Inflammatory Myositis: The GAP-ILD Model. Rheumatol Ther 2020;7:967-78
21. Chen IJ, Jan Wu YJ, Lin CW, et al. Interstitial lung disease in polymyositis and dermatomyositis. Clin Rheumatol 2009;28:639-46
22. Fujiki Y, Kotani T, Isoda K, et al. Evaluation of clinical prognostic factors for interstitial pneumonia in anti-MDA5 antibody-positive dermatomyositis patients. Mod Rheumatol 2018;28:133-40
23. Fujisawa T, Hozumi H, Kono M, et al. Predictive factors for long-term outcome in polymyositis/dermatomyositis-associated interstitial lung diseases. Respir Investig 2017;55:130-7
24. Fujisawa T, Hozumi H, Yasui H, et al. Clinical significance of serum chitotriosidase level in Anti-MDA5 antibody-positive dermatomyositis-associated interstitial lung disease. JRheum 2019;46:935-42
25. Furuya H, Nakajima M, Ikeda K, et al. Prognosis and treatments of patients with myositis-associated severe interstitial lung disease: A descriptive study using National Inpatient Database in Japan. Int J Rheumatol 2020;23:21-2
26. Gao X, Li Y, Jia X, et al. Predictors and Mortality of Rapidly Progressive Interstitial Lung Disease in Patients With Idiopathic Inflammatory Myopathy: A Series of 474 Patients. Front Med (Lausanne) 2020;7:363
27. Gono T, Masui K, Nishina N, et al. Risk Prediction Modeling Based on a Combination of Initial Serum Biomarker Levels in Polymyositis/Dermatomyositis-Associated Interstitial Lung Disease. Arthritis Rheumatol 2021;73(4):677-86
28. Gui X, Ma M, Ding J, et al. Cytokeratin 19 fragment is associated with severity and poor prognosis of interstitial lung disease in anti-MDA5 antibody-positive dermatomyositis. Rheumatology 2021; 60(8):3913-3922
29. Hayashi S, Tanaka M, Kobayashi H, et al. High-resolution computed tomography characterization of interstitial lung diseases in polymyositis/dermatomyositis. JRheum 2008;35:260-9
30. Hozumi H, Enomoto N, Kono M, et al. Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. PLoS One 2015;10:e0120313
31. Hozumi H, Fujisawa T, Enomoto N, et al. Clinical utility of YKL-40 in polymyositis/dermatomyositis-associated interstitial lung disease. JRheum 2017;44:1394-401
32. Hozumi H, Fujisawa T, Nakashima R, et al. Comprehensive assessment of myositis-specific autoantibodies in polymyositis/dermatomyositis-associated interstitial lung disease. Respir Med 2016;121:91-9

33. Ideura G, Hanaoka M, Koizumi T, et al. Interstitial lung disease associated with amyopathic dermatomyositis: Review of 18 cases. Respir Med 2007;101:1406-11
34. Ikeda S, Arita M, Misaki K, et al. Incidence and impact of interstitial lung disease and malignancy in patients with polymyositis, dermatomyositis, and clinically amyopathic dermatomyositis: a retrospective cohort study. Springerplus 2015;4:240
35. Ikeda S, Arita M, Morita M, et al. Interstitial lung disease in clinically amyopathic dermatomyositis with and without anti-MDA-5 antibody: To lump or split? BMC Pulm Med 2015;15:159
36. Ishida T, Kotani T, Serada S, et al. Correlation of increased serum leucine-rich α2-glycoprotein levels with disease prognosis, progression, and activity of interstitial pneumonia in patients with dermatomyositis: A retrospective study. PLoS One 2020;15:e0234090
37. Isoda K, Kotani T, Takeuchi T, et al. Comparison of long-term prognosis and relapse of dermatomyositis complicated with interstitial pneumonia according to autoantibodies: anti-aminoacyl tRNA synthetase antibodies versus anti-melanoma differentiation-associated gene 5 antibody. Rheumatol Int 2017;37:1335-40
38. Isoda K, Takeuchi T, Kotani T, et al. Pre-treatment ferritin level and alveolar-arterial oxygen gradient can predict mortality rate due to acute/subacufte interstitial pneumonia in dermatomyositis treated by cyclosporine A/glucocorticosteroid combination therapy: A case control study. PLoS ONE 2014;9:e89610
39. Jin YZ, Xie MS, Yang C, Wu RL, Zhou YB, Li XM. Prognostic value of peripheral blood markers in patients with myositis-associated interstitial lung diseases. Scand J Rheumatol 2021;
40. Kaieda S, Gono T, Masui K, Nishina N, Sato S, Kuwana M. Evaluation of usefulness in surfactant protein D as a predictor of mortality in myositis-associated interstitial lung disease. PloS one 2020;15:e0234523
41. Kang EH, Lee EB, Shin KC, et al. Interstitial lung disease in patients with polymyositis, dermatomyositis and amyopathic dermatomyositis. Rheumatology 2005;44:1282-6
42. Kobayashi NN, Takezaki S, Kobayashi I, et al. Clinical and laboratory features of fatal rapidly progressive interstitial lung disease associated with juvenile dermatomyositis. Rheumatology 2014;54:784-91
43. Koga T, Fujikawa K, Horai Y, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM. Rheumatology 2012;51:1278-84
44. Kotani T, Takeuchi T, Ishida T, et al. Increased serum LIGHT levels correlate with disease progression and severity of interstitial pneumonia in patients with dermatomyositis: A case control study. PLoS ONE 2015;10:e0140117
45. Kotani T, Takeuchi T, Yoshimatsu Y, et al. Initial limited three-level thin-section computed tomography scorings predict the prognosis of acute/subacute interstitial pneumonia in patients with dermatomyositis. Mod Rheumatol 2016;26:738-43
46. Le Goff B, Chérin P, Cantagrel A, et al. Pneumomediastinum in interstitial lung disease associated with dermatomyositis and polymyositis. Arthritis Rheum 2009;61:108-18
47. Li R, Zhu WJ, Wang F, Tang X, Luo F. AST/ALT ratio as a predictor of mortality and exacerbations of PM/DM-ILD in 1 year - A retrospective cohort study with 522 cases. Arthritis Res Ther 2020;22:202
48. Huang Y, Liu H, Wu C, et al. Ventricular arrhythmia predicts poor outcome in polymyositis/dermatomyositis with myocardial involvement. Rheumatology 2020;
49. Li Y, Wu J, Miao M, et al. Predictors of poor outcome of anti-MDA5-associated rapidly progressive interstitial lung disease in a Chinese cohort with dermatomyositis. J Immunol Res 2020;2020:2024869
50. Matsuda S, Kotani T, Ishida T, et al. Exploration of pathomechanism using comprehensive analysis of serum cytokines in polymyositis/dermatomyositis-interstitial lung disease. Rheumatology 2020;59:310-8

51. Mejia M, Herrera-Bringas D, Perez-Roman DI, et al. Interstitial lung disease and myositis-specific and associated autoantibodies: Clinical manifestations, survival and the performance of the new ATS/ERS criteria for interstitial pneumonia with autoimmune features (IPAF). Resp Med 2017;123:79-86
52. Motegi SI, Sekiguchi A, Toki S, et al. Clinical features and poor prognostic factors of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis with rapid progressive interstitial lung disease. Eur J Dermatol 2019;29:511-7
53. Mukae H, Ishimoto H, Sakamoto N, et al. Clinical differences between interstitial lung disease associated with clinically amyopathic dermatomyositis and classic dermatomyositis. Chest 2009;136:1341-7
54. Muro Y, Sugiura K, Akiyama M. Limitations of a single-point evaluation of anti-MDA5 antibody, ferritin, and IL-18 in predicting the prognosis of interstitial lung disease with anti-MDA5 antibody-positive dermatomyositis. Clin Rheumatol 2013;32:395-8
55. Nagasaka K, Harigai M, Tateishi M, et al. Efficacy of combination treatment with cyclosporin A and corticosteroids for acute interstitial pneumonitis associated with dermatomyositis. Mod Rheumatol 2003;13:231-8
56. Nagashima T, Iwamoto M, Minota S. Gottron sign with ulceration is not a poor prognostic factor in patients with dermatomyositis and interstitial lung disease. JRheum 2017;44:1099-100
57. Nakatsuka Y, Handa T, Nakashima R, et al. Serum matrix metalloproteinase levels in polymyositis/dermatomyositis patients with interstitial lung disease. Rheumatology 2019;
58. Nara M, Komatsuda A, Omokawa A, et al. Serum interleukin 6 levels as a useful prognostic predictor of clinically amyopathic dermatomyositis with rapidly progressive interstitial lung disease. Mod Rheumatol 2014;24:633-6
59. Oda K, Kotani T, Takeuchi T, et al. Chemokine profiles of interstitial pneumonia in patients with dermatomyositis: a case control study. Sci Rep 2017;7:1635
60. Okabayashi H, Ichiyasu H, Hirooka S, et al. Clinical effects of direct hemoperfusion using a polymyxin B-immobilized fiber column in clinically amyopathic dermatomyositis-associated rapidly progressive interstitial pneumonias. BMC pulm med 2017;17:134
61. Rojas-Serrano J, Herrera-Bringas D, Mejia M, Rivero H, Mateos-Toledo H, Figueroa JE. Prognostic factors in a cohort of antisynthetase syndrome (ASS): serologic profile is associated with mortality in patients with interstitial lung disease (ILD). Clin Rheumatol 2015;34:1563-9
62. Sakamoto S, Okamoto M, Kaieda S, et al. Low positive titer of anti-melanoma differentiation-associated gene 5 antibody is not associated with a poor long-term outcome of interstitial lung disease in patients with dermatomyositis. Respir Investig 2018;56:464-72
63. Shimojima Y, Ishii W, Matsuda M, et al. Coadministration of cyclosporin A with prednisolone in acute interstitial pneumonia complicating polymyositis/dermatomyositis. Clin Med Insights Arthritis and Musculoskelet Disord 2012;5:43-52
64. Suda T, Fujisawa T, Enomoto N, et al. Interstitial lung diseases associated with amyopathic dermatomyositis. Eur Respir J 2006;28:1005-12
65. Sugiyama Y, Yoshimi R, Tamura M, et al. The predictive prognostic factors for polymyositis/dermatomyositis-associated interstitial lung disease. Arthritis Res Ther 2018;20:7
66. Sun Y, Liu Y, Yan B, Shi G. Interstitial lung disease in clinically amyopathic dermatomyositis (CADM) patients: A retrospective study of 41 Chinese Han patients. Rheumatol Int 2013;33:1295-302
67. Tada Y, Suematsu E, Ueda A, et al. Clinical factors to predict a poor prognosis and refractory disease in patients with polymyositis and dermatomyositis associated with interstitial lung disease. Clin Exp Rheum 2012;30:450
68. Tanizawa K, Nakashima R, Kubo T, et al. The prognostic value of HRCT in myositis-associated interstitial lung disease. Resp Med 2013;107:745-52
69. Váncsa A, Csípo I, Németh J, Dévényi K, Gergely L, Dankó K. Characteristics of interstitial lung disease in SS-A positive/Jo-1 positive inflammatory myopathy patients. Rheumatol Int 2009;29:989-94

70. Vojinovic T, Cavazzana I, Ceruti P, et al. Predictive Features and Clinical Presentation of Interstitial Lung Disease in Inflammatory Myositis. Clin Rev Allergy Immunol 2021;60:87-94
71. Vuillard C, Pineton de Chambrun M, de Prost N, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. Ann Intensive Care 2018;8:87
72. Wakura R, Matsuda S, Kotani T, Shoda T, Takeuchi T. The comparison of nailfold videocapillaroscopy findings between anti-melanoma differentiation-associated gene 5 antibody and anti-aminoacyl tRNA synthetase antibody in patients with dermatomyositis complicated by interstitial lung disease. Sci Rep 2020;10:15692
73. Wang K, Zhao J, Chen Z, et al. CD4+CXCR4+ T cells as a novel prognostic biomarker in patients with idiopathic inflammatory myopathy-associated interstitial lung disease. Rheumatology 2019;58:511-21
74. Won Huh J, Soon Kim D, Keun Lee C, et al. Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Resp Med 2007;101:1761-9
75. Xu A, Ye Y, Fu Q, et al. Prognostic values of anti-Ro52 antibodies in anti-MDA5-positive clinically amyopathic dermatomyositis associated with interstitial lung disease. Rheumatology 2021;60:3343-51
76. Yamaguchi K, Yamaguchi A, Onuki Y, et al. Clinical features of dermatomyositis associated with anti-MDA5 antibodies by age. Mod Rheumatol 2021;31:177-85
77. Ye S, Chen XX, Lu XY, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. Clin Rheumatol 2007;26:1647-54
78. Yoshida N, Okamoto M, Kaieda S, et al. Association of anti-aminoacyl-transfer RNA synthetase antibody and anti-melanoma differentiation-associated gene 5 antibody with the therapeutic response of polymyositis/dermatomyositis-associated interstitial lung disease. Respir Investig 2017;55:24-32
79. Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. Autoimmunity 2006;39:233-41
80. Zhang T, Zhang J, Liu X, et al. A clinical analysis of prognostic factors for dermatomyositis-associated interstitial lung disease. Int J Clin Exp Med 2018;11:5903-11
81. Zou J, Guo Q, Chi J, Wu H, Bao C. HRCT score and serum ferritin level are factors associated to the 1-year mortality of acute interstitial lung disease in clinically amyopathic dermatomyositis patients. Clin Rheumatol 2015;34:707-14
82. Lian X, Zou J, Guo Q, et al. Mortality Risk Prediction in Amyopathic Dermatomyositis Associated With Interstitial Lung Disease: The FLAIR Model. Chest 2020;158:1535-45
83. Wu W, Xu W, Sun W, et al. Forced vital capacity predicts the survival of interstitial lung disease in anti-MDA5 positive dermatomyositis: a multi-centre cohort study. Rheumatology 2021;25
84. Xu W, Wu W, Zhang D, et al. A novel CT scoring method predicts the prognosis of interstitial lung disease associated with anti-MDA5 positive dermatomyositis. Sci Rep 2021;11:17070
85. Kazeroni EA MF, Flint A, et al. Thin section CT Obtained at 10-mm Increments versus Limited Three-Level Thin-Section CT for Idiopathic Pulmonary Firbosis: Correlation with Pathological Scoring. AJR 1997:977-83
86. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248-54
87. Ooi G, Mok M, Tsang K, et al. Interstitial lung disease in systemic sclerosis: An HRCT-clinical correlative study. Acta Radiologica 2003;44:258-64
88. Ichikado K, Suga M, Müller NL, et al. Acute interstitial pneumonia: comparison of high-resolution computed tomography findings between survivors and nonsurvivors. Am J Respir Crit Care Med 2002;165:1551-6
89. Kinoshita F, Hamano H, Harada H, et al. Role of KL-6 in evaluating the disease severity of rheumatoid lung disease: comparison with HRCT. Respir med 2004;98:1131-7

90. Li S, Sun Y, Shao C, Huang H, et al. Prognosis of adult idiopathic inflammatory myopathy-associated interstitial lung disease: A retrospective study of 679 adult cases. Rheumatology 2021;60:1195-204
91. Decker P, Moulinet T, Lopez B, et al. Clinical significance of anti-Ro52 (TRIM21) antibodies in adult patients with connective tissue diseases. Eur J Intern Med 2021;91:45-52
92. Xing X, Li A, Li C. Anti-Ro52 antibody is an independent risk factor for interstitial lung disease in dermatomyositis. Respir Med 2020;172:106134
93. Kurtzman DJ, Vleugels RA. Anti-Melanoma differentiation–associated gene 5 (MDA5) dermatomyositis: a Concise review with an emphasis on distinctive clinical features. J Am Acad Dermatol 2018;78:776-85
94. Narang NS, Casciola-Rosen L, Li S, Chung L, Fiorentino DF. Cutaneous ulceration in dermatomyositis: association with anti–melanoma differentiation–associated gene 5 antibodies and interstitial lung disease. Arthritis Care Res 2015;67:667-72
95. Ishikawa N, Hattori N, Yokoyama A, Kohno N. Utility of KL-6/MUC1 in the clinical management of interstitial lung diseases. Respir investig 2012;50:3-13
96. Wang K, Ju Q, Cao J, Tang W, Zhang J. Impact of serum SP-A and SP-D levels on comparison and prognosis of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Medicine 2017;96
97. Kazerooni EA, Martinez FJ, Flint A, et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. AJR Am J Roentgenol 1997;169:977-83
98. Barba T, Fort R, Cottin V, et al. Treatment of idiopathic inflammatory myositis associated interstitial lung disease: A systematic review and meta-analysis. Autoimmun Rev 2019;18:113-22
99. Gono T, Masui K, Nishina N, et al. Risk Prediction Modeling Based on a Combination of Initial Serum Biomarker Levels in Polymyositis/Dermatomyositis–Associated Interstitial Lung Disease. Arthritis Rheumatol 2021;73:677-86
100. Gono T, Masui K, Nishina N, et al. Risk prediction modeling based on a combination of initial serum biomarkers in myositis-associated interstitial lung disease. Arthritis Rheumatol 2020;
101. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. Arthritis Rheum 2005;52:1571-6
102. Mehta P, Machado PM, Gupta L. Understanding and managing anti-MDA 5 dermatomyositis, including potential COVID-19 mimicry. Rheumatol Int 2021:1-16
103. Ceribelli A, Fredi M, Taraborelli M, et al. Prevalence and clinical significance of anti-MDA5 antibodies in European patients with polymyositis/dermatomyositis. Clin Exp Rheumatol 2014;32:891-7
104. Hall JC, Casciola-Rosen L, Samedy LA, et al. Anti–melanoma differentiation–associated protein 5–associated dermatomyositis: expanding the clinical spectrum. Arthritis Care Res 2013;65:1307-15

Table 1. Summary of meta-analysis results according to potential risk factors of mortality. Statistically significant factors highlighted in bold typeface.

	Risk Factor for mortality	Number of studies	n	I^2	Odds Ratio	Hedge's g	95% CI
Antibodies	**MDA-5**	**16**	**1383**	**39.3%**	**6.20**		**3.58, 10.71**
	ARS	**16**	**3128**	**31.1%**	**0.24**		**0.14, 0.41**
	MDA5-/ARS- vs ARS	5	597	0.0%	1.54		0.84, 2.83
	Jo-1 vs Non-Jo-1	**5**	**714**	**0.0%**	**0.33**		**0.14, 0.77**
	Ro52 or SS-A	8	1206	40.0%	1.15		0.54, 2.46
	ANA	9	566	0.0%	0.75		0.50, 1.13
	MDA5 Titre	7	335	93.5%		0.42	-0.09, 0.94
Clinical features	**Age**	**28**	**1269**	**44.8%**		**6.56**	**4.61, 8.52**
	Male	**30**	**2289**	**0.0%**	**1.31**		**1.05, 1.63**
	A/SIP	**24**	**968**	**27.9%**	**8.31**		**4.79, 14.41**
	CADM vs DM/PM*	**25**	**2467**	**40.3%**	**1.56**		**1.07, 2.29**
	DM (excluding CADM) vs PM	**14**	**1598**	**0.0%**	**2.48**		**1.86, 3.30**
	Disease duration at baseline (weeks)	6	419	13.53		-0.11	-0.33, 0.10
	Dyspnoea	**5**	**189**	**0.0%**	**2.24**		**1.11, 4.53**
	Ulceration	**6**	**828**	**0.0%**	**1.97**		**1.28, 3.04**
	Gottron's sign	5	348	0.0%	1.72		0.88, 3.35
	Heliotrope Rash	5	348	18.5%	1.37		0.77, 2.45
	Joint involvement	7	492	0.0%	0.72		0.46, 1.14
	Fever	**10**	**896**	**29.2%**	**2.71**		**1.65, 4.47**
	Muscle involvement	7	844	20.2%	0.68		0.41, 1.13
	Ex/Current Smoker	6	259	0.0%	1.17		0.57, 2.43
Investigations	**CRP**	**15**	**831**	**0.0%**		**0.32**	**0.13, 0.51**
	CK	19	1100	0.0%		0.02	-0.11, 0.15
	KL-6	14	490	71.7%		0.05	-0.25, 0.34
	Albumin	**7**	**482**	**90.2%**		**-0.67,**	**-1.00, -0.34**
	SP-D	7	511	0.0%		-0.06	-0.49, 0.37
	Ferritin	**19**	**993**	**67.9%**		**0.90**	**0.53, 1.28**
	Lymphocytes	**7**	**378**	**0.0%**		**-0.46**	**-0.70, -0.23**
	LDH	**18**	**1034**	**35.2%**		**0.53**	**0.27, 0.79**
	ESR	9	575	43.1%		0.56	-0.24, 1.36
	A-aO2 gradient	**5**	**140**	**62.3%**		**1.00**	**0.33, 1.67**
	PF Ratio	**6**	**306**	**84.4%**		**-0.72**	**-1.29, -0.15**
	FVC%	**13**	**703**	**85.3%**		**-0.54**	**-0.93, -0.15**
	DLCO%	**12**	**617**	**45.3%**		**-0.45**	**-0.72, -0.18**
Radiology	**GGO score**	**5**	**415**	**0.00%**		**1.10**	**0.84, 1.37**
	GGO presence	**9**	**244**	**8.71%**	**3.37**		**1.41, 8.03**
	Consolidation presence	6	131	43.34%	0.70		0.14, 3.44
	Reticulation presence	6	172	57.18%	1.05		0.15, 7.20
	Overall HRCT score	**8**	**628**	**45.74**		**0.96**	**0.68, 1.24**

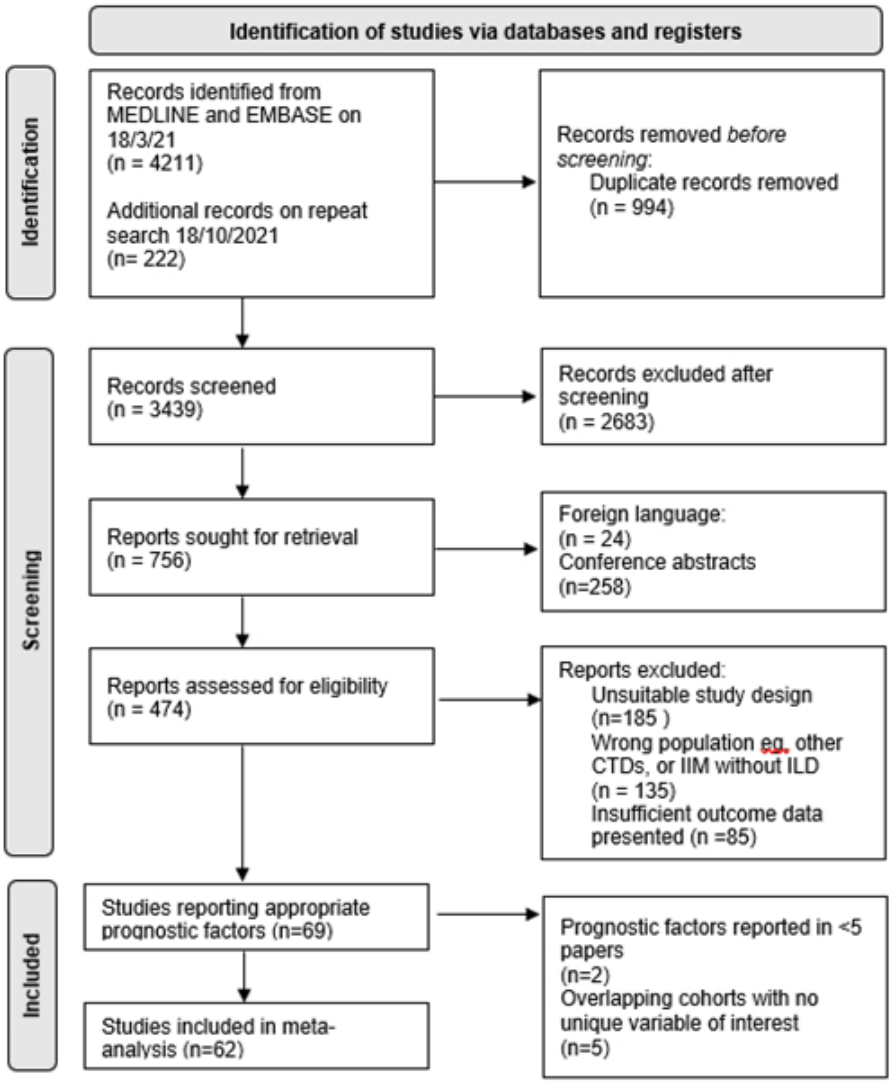

Figure 1. PRISMA flow diagram detailing study selection process

147x172mm (96 x 96 DPI)

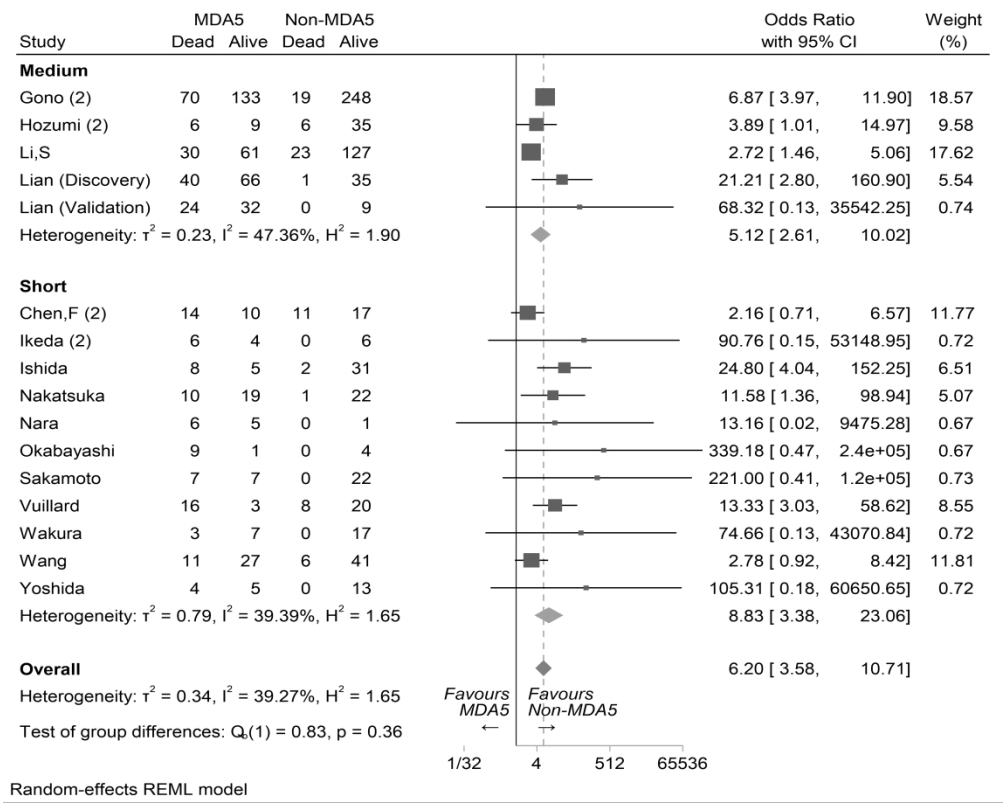

Figure 2. Forest plot showing increased odds of mortality with anti-MDA5 antibody divided by study duration of <1 year (Short) or between 2-5 years (Medium)

159x128mm (600 x 600 DPI)

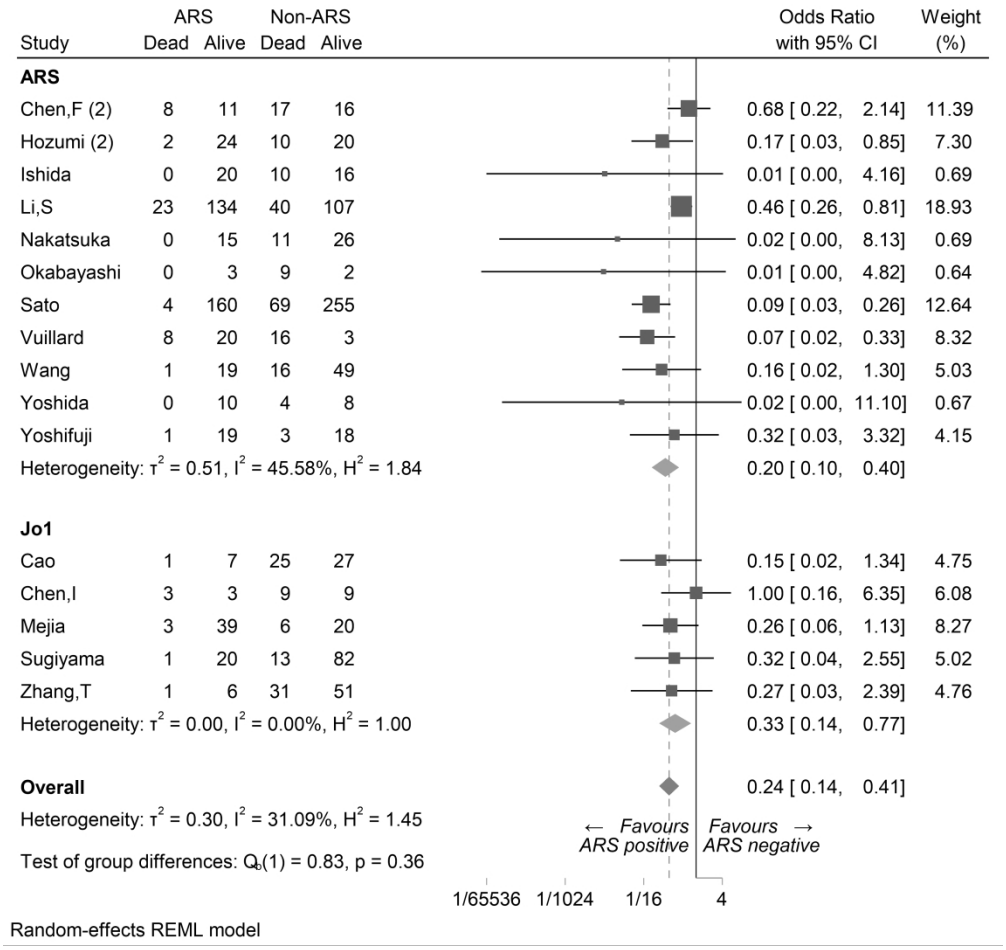

Figure 3. Forest plot showing a reduced risk of death in those with an ARS antibody. Heterogeneity can be reduced by sub analysing only those with anti-Jo1

159x151mm (600 x 600 DPI)

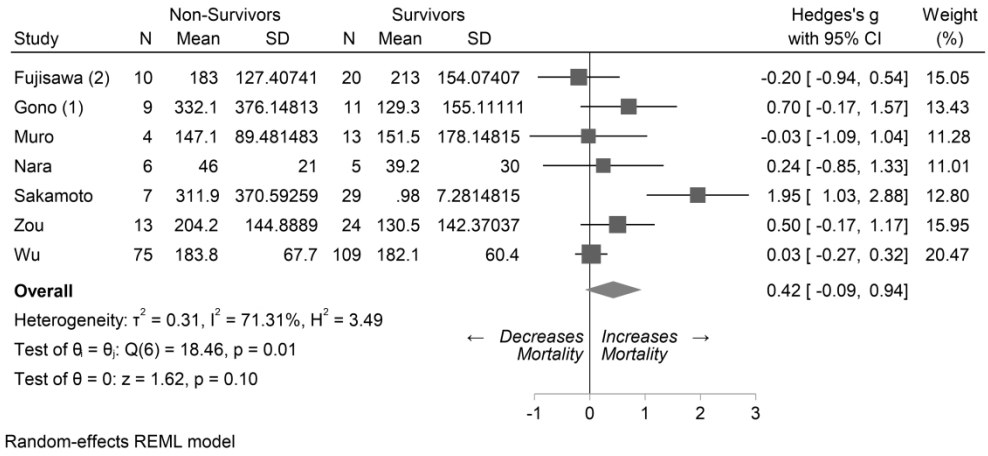

Figure 4. Forest plot of MDA5 titre showing pooled effect on odds ratio

159x74mm (600 x 600 DPI)

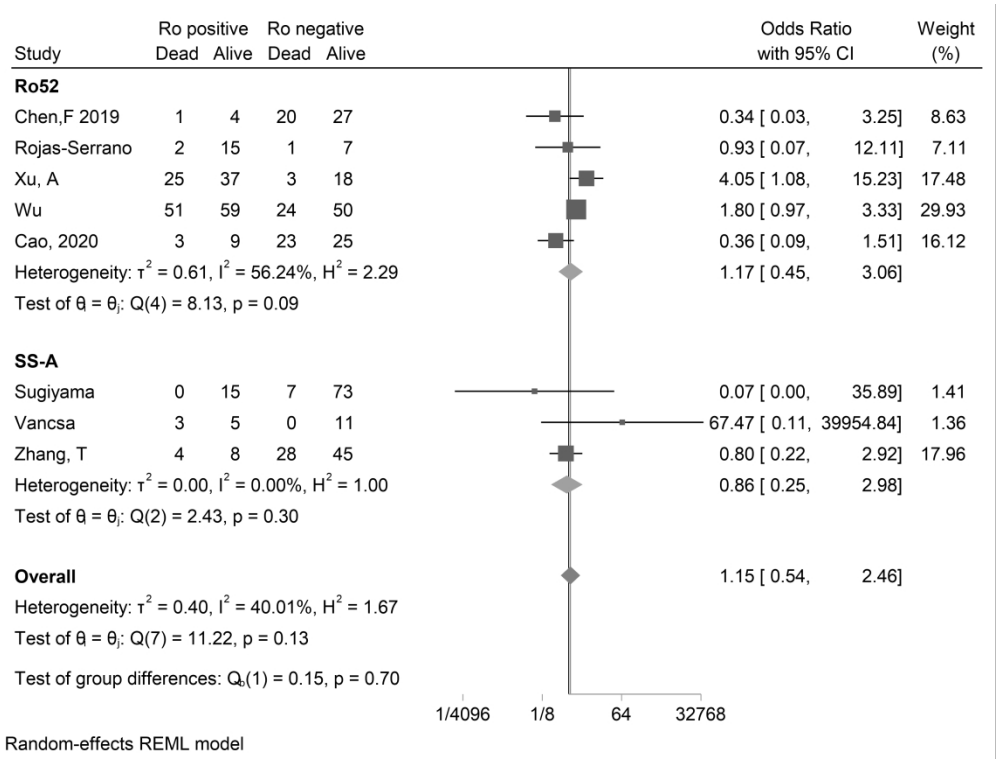

Figure 5. Forest plot showing there is no effect of Ro52 or SS-A on mortality

159x120mm (600 x 600 DPI)