Impact of Interstitial Lung Disease on Mortality in ANCA-associated Vasculitis: A Systematic Literature Review and Meta-analysis

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Abstract

Background: Several retrospective series and case reports have described the association of interstitial lung disease (ILD) and ANCA-associated vasculitis (AAV). However, the relationship between the ILD and mortality in AAV patients have not been established so far. This study aims to estimate the relevance of AAV-associated-ILD and mortality risk by conducting a systematic review and meta-analysis.

Methods: A comprehensive systematic review was conducted in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses). PubMed, Embase.com and the Cochrane Library (Wiley) were searched for original observational studies. Summary estimates were derived with a random-effects model and reported as risk ratio (RR), tested for publication bias and heterogeneity.

Results: Ten retrospective cohort studies were included, comprising 526 AAV-ILD patients enrolled from 1974 to 2018. Meta-analysis yielded a pooled RR of 2.90 (95% confidence interval 1.77 to 4.74) for death among those with AAV-ILD compared with control group. Sensitivity analysis suggested that the meta-RR result was not skewed by a single dominant study.

Conclusion: ILD might be associated with a higher mortality risk in AAV patients.

Background

Anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis are immune-mediated disease that is primarily characterized by ANCA positivity and affects various organs, such as the lungs, kidneys, skin, and nervous system. Based on clinical phenotypes and pathologies, cases of AAV are divided into three diseases: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg–Strauss syndrome).^[1]

Interstitial lung disease (ILD) is a rare condition, whose prevalence and incidence rates were reported to be 97.9/100,000 and 19.4/100,000, respectively, in a recent French study.^[2] Progressive fibrosing ILD generates two main computed-tomography (CT) scan patterns: usual interstitial pneumonitis (UIP) and non-specific interstitial pneumonia (NSIP). UIP is characterized by reticular changes and honeycombing in the subpleural sections of the lower lobes on high resolution computed tomography (HRCT) whereas the radiological features of NSIP often include ground glass shadowing with features of alveolar inflammation.^[3]

During the last few years, an increasing number of publications have reported the association between ILD and AAV, particularly in anti-MPO positive AAV^[4–16]. ILD occurs concurrently or antedates MPA in the majority of affected individuals.^[4, 5, 7, 17–24] The most frequent CT scan pattern is usual interstitial pneumonia (UIP) in 43 to 83%, but other patterns (e.g. suggestive of NSIP) may be seen (5–31%).^[4, 5, 25] Progressive fibrosing ILD occurs in many systemic diseases (e.g. sarcoidosis, systemic sclerosis, rheumatoid arthritis or myositis) and is associated with shorter survival^[26]. Several case series have reported ILD seems to be a major prognostic factor in AAV patients.^[8–11, 13–16, 27–30] To further investigation, we performed a systematic literature review and meta-analysis to estimate the impact of ILD had on mortality.

Methods

A comprehensive systematic review was conducted in accordance with the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews And Meta-analyses).^[31] The review protocol was registered on 26 March 2020 in the International Prospective Register of Systematic Reviews database.

Search strategies:

The databases PubMed (N.L.M.), Embase.com and the Cochrane Library (Wiley) were searched by two authors (P.Z and J.M.) from their inception to March 2020. In brief, three search concepts were combined with the Boolean operator 'AND': (1) ANCA-associated vasculitis (AAV) or vasculitis, (2) interstitial lung disease (ILD) or pulmonary fibrosis (PF) and (3) mortality or survival rate. Search terms included indexed terms from Medical Subject Headings (MeSH) in PubMed, Emtree in EMBASE.com as well as free-text terms. The search strategy is available in Supplemental data 1. All identified studies were combined in a single reference manager file (EndNote). Abstracts for all articles of interest were reviewed for relevance, which is those that focused on the association between ILD and AAV and mortality or survival data in AAV-ILD patients. Full papers of selected abstracts were retrieved and assessed for eligibility based on the inclusion criteria.

Observational studies that met the following criteria were assessed: (1) clearly defined AAV identified by either the American College of Rheumatology 1990 classification criteria or the 2012 Chapel Hill Consensus Conference disease definitions, and (2) provided ILD-related risk ratios or hazard ratios, or can be calculated from the studies.

Criteria were used for the diagnosis of ILD mostly depending on radiological evidence on chest X-ray and HRCT (such as reticular abnormality or honeycombing with or without traction bronchiectasis), which can be combined with other examination results (such as lung function testing and/or histopathology). The control group was considered to diagnose AAV with no ILD but were likely to have other common clinical manifestations, such as sinus pain, nasal discharge, or crusting, ear pain, or deafness, foot drop or wrist drop, hematuria and oliguria. Articles analyzing connective tissue disease-associated ILD (CTD-ILD) or collagen vascular disease associated ILD (CVD-ILD), and not specifically AAV-ILD, were excluded.

We also searched the reference lists of identified papers and conference abstracts for additional relevant publications. In cases of duplicate data used in more than one study, the sample with the most up-to-date data was selected for review. No additional exclusions were made on the basis of study design, quality of

the study, or duration of follow-up. The study identification and selection process are summarized in Supplemental data 2.

Data extraction:

Data were collected through a standardized extraction sheet. One reviewer (P.Z.) extracted and the second reviewer (J.M.) checked the data. Disagreements were discussed and resolved. From eligible studies, the following data were collected: year of publication, enrolment period, study design, country, sample size and demographics, mean follow-up duration, number of AAV-ILD patients, method for ILD diagnosis, survival or mortality data.

Quality assessment:

Study quality was assessed using the Newcastle-Ottawa scale (NOS).^[32] In this scale, studies are scored across three categories: selection of study groups (four questions), comparability of study groups (one question) and ascertainment of the outcome of interest (three questions) for cohort studies. Two authors (P.Z. and J.M.) performed quality scoring independently, with differences resolved by consensus.

Statistical analyses:

In this meta analyses, the outcomes of interest were pooled RR for AAV-ILD, HR were assumed to be numerically the same as the RR. Forest plots and pooled estimates were derived with inverse variance weighting and a random-effects model. The heterogeneity among studies was tested with Cochran's Q test. Significant heterogeneity was defined as a value of $P < 0.10$. The I^2 -statistic was used to quantify the heterogeneity.^[33] Source of heterogeneity was determined by subgroup analysis. All included studies were stratified according to enrolment periods (2010–2015 vs 2016–2020), center (single center vs multicenter), ethnicity (Asian vs non-Asian), covariates (covariates vs non-covariate), follow-up period (≤ 48 months vs > 48 months), and UIP pattern. Furthermore, a univariate meta-regression analysis was then used to interpret the difference in RRs between the subgroups.^[34] We evaluated the robustness of the results using jackknife sensitivity analysis, by repeated meta-RR analyses with removal of a single study in succession each time.^[35] A funnel plot was conducted to detect publication bias (i.e. bias resulting from the greater likelihood of studies with positive results to be published compared with negative results) or the small-study effect (i.e. a tendency for treatment effect estimates in small studies to differ from those in larger studies)^[36]. Furthermore, we used Egger's regression as an objective, quantitative test statistic to test for the presence of asymmetry in the data.^[37] Data analysis was performed with Review manager (RevMan) version 5.3 and Stata statistical software V.StataSE14 (stataCorp LLC, College Station, Texas, USA).

Results

A total of nine hundred records were processed for a final selection of ten articles. Most records were irrelevant, and of the 54 records were reviewed based on full text. The most frequent reasons for exclusion upon full text review were studies focusing on ANCA-positive ILD or lack of mortality data. Finally, 44 records were removed according to inclusion criteria and the remaining 10 studies were included in the meta-analysis. A list of the excluded articles is provided in Supplemental data 3.

Study characteristics:

Characteristic features of the studies included in this meta-analysis are summarized in Table 1. The studies were published between 2010 and 2019, enrolled from 1974 to 2018; All of these were retrospective cohort studies, four of which were from multicenter. Locations included 6 Asian studies, of which 4 from Japan, 1 from China and 1 from Korea, and the remaining studies came from Greece, London, Germany, Argentina respectively. The sample sizes in the individual studies ranged from 9 to 301 AAV-ILD patients and 526 in total. One study used three other control groups, including alveolar hemorrhage, bronchial asthma and pulmonary granuloma. The other study used bronchiectasis as an additional control group. Five studies adjusted mortality for BVAS, age, cardiovascular involvement, alveolar hemorrhage, serum creatinine level et al. The included studies were of high quality, scoring 7 to 9 points according to the Newcastle-Ottawa Scale.

Table 1
Characteristic features of the included studies

Author	Year	Country	Research Center	Cohort Type	Period	Follow-up(months)	Number of Patients	Number of ILD Patients	Number of UIP Patients	Number of Deaths (ILD vs control)	Survival rate of control group	Survival rate of IL
Tzelepis	2010	Greece	M	N-I	2003–2008	38.0	MPA 33	13	7	6 vs 1	N/A	N/A
Arulkumaran	2011	London	S	N-I	1974–2009	61.7	MPA 194	14	8	10 vs 70	1-year: 85%; 5-years:61%.	1-year:50% 5-years:20%
Ahn	2012	Korea	S	I	1994–2009	46.1	MPA 55	13	11	4 vs 2	N/A	N/A
Fernandez	2015	Argentina	S	N/A	1998–2013	61.2	MPA 28	9	8	4 vs 0	1-year: 100%, 5-years: 101%	1-year:92.3% 5-years:92%
Hirayama	2015	Japan	M	N/A	1989–2007	N/A	AAV 1147	301	N/A	118 vs 272	1-year:73.5%; 5-years:60.2%	1-year: 69.9%; 5-years:50%
Ono	2015	Japan	M	N/A	2001–2013	38.6	AAV 79	14	14	N/A	N/A	N/A
Schirmer	2016	Germany	S	N-I	1999–2013	72.0	MPA 144	17	N/A	N/A	N/A	N/A
Tashiro	2017	Japan	S	N/A	2004–2011	52.9	MPA 45	23	N/A	5 vs 4	1-year:90.9%; 5-years:81.9%	1-year:78.3% 5-years:78%
Ono	2019	Japan	M	I	2012–2018	24.2	AAV 143	63	N/A	N/A	N/A	N/A
Shi	2019	China	S	I	2012–2017	17.0	MPA 124	59	N/A	20 vs 26	1-year:89.2%	1-year:66.1%
N/A: not available; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; AAV: ANCA-associated vasculitis; MPA: microscopic polyangiitis; I: inception non-inception cohort, S: single center, M: multicenter												

Causes of death:

Table 2 details the causes of death in the included studies if were available. The majority of the deaths were respiratory failure and infectious pneumonia.

Table 2
Causes of death

Author	No. of deaths(n)	AA-ILD cohort(n)	Causes of death(n)
Tzelepis, G. E et al.	6	13	4 respiratory failure,1 lung cancer,1 sepsis.
Arulkumaran, N et al.	10	14	5 respiratory failure, 3 multi-organs failure/generalized sepsis, 2 unknown
Fernandez Casares, M et al.	4	9	4 respiratory failure
Hirayama, K et al.	118	301	21 pulmonary involvements due to vasculitis;42 both pulmonary involvements and infectious diseases; 39 infectious diseases; 16 others.
Tashiro, H et al.	5	23	1 ARDS,1 exacerbation of DAH,1 multiple organ failure,1 unknown sudden death,1 exacerbation of IP
Total	143	360	N/A
ARDS: Acute respiratory distress syndrome, DAH: diffuse alveolar hemorrhage, IP: interstitial pneumonia, N/A: not available.			

Impact of ILD on mortality in AAV:

We pooled the results of all ten studies comparing mortality risk between AAV-ILD and control groups and observed an increase in mortality among ILD, [risk ratio (RR) = 2.90; 95% confidence interval (CI) 1.77–4.74]. There was a significant heterogeneity among the studies, $I^2 = 72\%$ ($p < 0.0001$). (Fig. 1)

Sensitivity analysis:

The results of jackknife sensitivity analysis are shown in Table 3. The RRs remained significantly increased regardless of each study exclusion sequentially, with the value estimated ranging from 2.55 to 3.60 in all analyses. This suggested that the meta-RR result was robust and not skewed by a single dominant study.

Table 3
Sensitivity analysis

Authors	Year	RR (95% CI)	Study excluded, meta-RR (95% CI)
Tzelepis, G. E et al.	2010	9.23 [1.25, 68.11]	2.70 [1.65, 4.42]
Arulkumaran, N et al.	2011	1.84 [1.26, 2.68]	3.60 [1.81, 7.15]
Ahn, J. K. et al.	2012	5.33 [1.12, 25.44]	2.75 [1.66, 4.56]
Fernandez Casares, M et al.	2015	18.00 [1.07, 302.41]	2.72 [1.67, 4.43]
Hirayama, K et al.	2015	1.22 [1.03, 1.45]	3.47 [2.08, 5.78]
Ono, N et al.	2015	7.85 [2.14, 28.79]	2.55 [1.57, 4.12]
Schirmer, J. H et al..	2016	4.04 [1.21, 13.49]	2.79 [1.67, 4.67]
Tashiro, H et al.	2017	1.20 [0.37, 3.88]	3.24 [1.90, 5.53]
Shi, J et al.	2019	3.15 [1.44, 6.90]	2.87 [1.68, 4.88]
Ono, N et al	2019	7.55 [1.70, 33.47]	2.63 [1.61, 4.30]
all studies	/	2.90 [1.77, 4.74]	/

Subgroup analysis:

Subgroup analyses showed that meta-RR were higher in non-Asian group, multicenter group, adjusted covariates group, less follow-up period group, UIP group and in cohorts enrolled after 2015. However, meta regression analysis showed that there was no significant difference in subgroups except the follow-up period group. [Figure.2, Table 4]

Table 4
Subgroup analysis and meta-regression analysis

Study subset	No.cohorts	RR(95%CI)	I ² (%)	P(a)	P(b)
Enrollment period	10				0.80
2010–2015	6	2.73 [1.47, 5.07]	76	0.001	
2016–2019	4	3.06 [1.60, 5.84]	26	0.25	
Ethnicity	10				0.74
Asian	6	2.90 [1.36, 6.18]	76	0.0008	
non-Asian	4	3.53 [1.43, 8.74]	49	0.11	
Center	10				0.44
single center	6	2.49 [1.56, 3.97]	29	0.22	
multicenter	4	4.37 [1.14, 16.80]	82	0.0007	
Covariates	10				0.51
Covariates	6	3.59 [1.60, 8.05]	79	0.0002	
no-Covariates	4	2.43 [1.04, 5.67]	45	0.14	
Follow-up period	9				0.04
≤ 48months	5	4.83 [2.79, 8.35]	0	0.65	
>48months	4	2.19 [1.16, 4.11]	34	0.21	
Total	10	2.90 [1.77, 4.74]	72	0.0003	
P(a):p value of subgroup; P(b):p value between two subgroups.					

Assessment of publication bias:

The funnel plot is shown in Fig. 3. Visual inspection of the funnel plot was asymmetrically located. Using the Egger's test for publication bias with the 10 studies, the p-value less than 0.10 indicating that there is an evidence for publication bias. We further evaluated the number of missing studies in this meta-analysis by the application of the trim and fill method and recalculated the pooled risk estimate with the addition of those missing study. There was no significant change in the value of summary statistic, suggesting that publication bias had no significant impact on the result.

Discussion

This is the first meta-analysis of observational studies assessing the mortality risk in AAV-ILD. We found a 2.9-fold increased risk of death in patients with AAV-ILD when compared with control group. The RR remained significantly increased by sensitivity analysis, suggesting that the meta-RR result was robust and not skewed by a single dominant study. Given the heterogeneity observed in the pooled risk estimate, subgroup analysis was conducted. We further compared the RRs between the two groups by meta regression analysis, which showed that the only one difference is found in the follow-up period group. However, we still hope to explore the factors that may latently affect the prognosis of AAV-ILD patients.

Of interest, mortality risks were even higher in later cohorts, that is, those with their enrolment periods that were after 2015 relative to those before 2015, although the overall comparison between the cohorts was non-significant. Over the last few decades, as treatment of AAV has evolved, disease-related mortality rates have declined. Yet, this may not be the case in individuals with AAV-ILD. In a study by Alba et al, which revealed the mortality rates of AAV-ILD patients from 2004 to 2015, suggesting no significant improvement over time.^[15] We hypothesized that this observation may due to the lack of universally accepted treatment guidelines. The effect of treatment in ILD is still controversial right now. Some studies have showed clinical or radiological improvement in 80% of patients while on immunosuppressive therapy.^[39, 40] In addition, immunosuppressive therapy might be associated with a reduction in the development of full-blown MPA, which initially presented as isolated pulmonary fibrosis with positive MPO-ANCA.^[40, 41] In sharp contrast, most of the retrospective publications reported that the disease remained unchanged or deteriorated in the majority of patients, even in presence of clinically quiescent systemic vasculitis.^[5, 19, 42] Although no clear conclusions can be drawn about the initial treatment, it is recommended that general measures are instituted as required: supplemental oxygen, pulmonary rehabilitation and influenza and pneumococcal vaccination. In the future, novel anti-fibrotic therapies (pirfenidone and nintedanib) designed for idiopathic pulmonary fibrosis might be tested in AAV-ILD. Nintedanib, an oral tyrosine kinase inhibitor has been associated stabilization of lung fibrosis. A recent double-blind, placebo-controlled, phase 3 trial, NCT0299917, has proved the efficacy of nintedanib not only in idiopathic pulmonary fibrosis but in a broad range of fibrosing lung diseases as well.^[43] Meanwhile, clinical trials (NCT03385668 and NCT02999178) are ongoing to evaluate the effect of antifibrotic drugs (pirfenidone and nintedanib) authorized for AAV in patients with lung fibrosis.^[16]

Race may also be one of the factors latent associated with AAV-ILD. Frequency of ILD in ANCA-associated vasculitis seems to be higher in Asian than in Western populations.^[4, 5, 7, 8] In a Japanese nationwide, prospective, inception cohort study of AAV (Remission Induction Therapy in Japanese Patients with ANCA-associated Vasculitis; RemIT-JAV), 39.1% patients had ILD.^[44] In contrast, ILD was observed in only 2.7% AAV patients at a renal vasculitis clinic in London.^[5] This discrepancy between Japan and other countries has been usually explained by the ethnicity and the predominance of MPO-ANCA. Hirayama K et al. reported that the 5-year survival rate was 50.2% in the patients with ILD and 73.3% in those without pulmonary involvement; ILD was added as one of the predictors of 5-year mortality. In contrast, in a retrospective study by the renal vasculitis clinic in London, there was no difference in mortality between patients with AAV-ILD and those without over the same time period.^[5] On the contrary, some European studies supported that AAV-ILD patients were more likely to have a much worse prognosis.^[4, 7, 10, 27] Therefore, we postulate that this controversy might due to small cohort size in non-Asian studies, which partly came from single center.

It was also interesting to note the trend for increased risk of death in studies that were adjusted covariates in multivariate model, RR 3.59 (95% CI 1.60–8.05). One might explain that the impact of ILD was latently masked by other factors involved and relevant RR was underestimated. Several factors may confound mortality in AAV-ILD patients, mostly including age, alveolar hemorrhage, Birmingham vasculitis activity score (BVAS), and renal involvement.^[7–10, 13, 14] First, repeated episodes of alveolar hemorrhage could be the pathogenesis of pulmonary fibrosis.^[19] However, this may lead researchers to mistakenly attribute ILD-related death to alveolar hemorrhage. Secondly, renal involvement was significantly more common in MPA, affecting 93% compared to 66% of those with GPA. Compared to GPA, serum creatine levels were significantly higher in those with MPA.^[9] Numerous patients eventually died from dialysis-related complications, thereby ignoring the potential impact of ILD. Moreover, pulmonary fibrosis (PF) occurs concurrently or antedates MPA in the majority of affected individuals.^[15] In previous reports, ILD precedes other vasculitis syndrome in 14–85% of patients.^[4, 5, 17–20, 22, 23, 25, 39, 45, 46] In those cases when pulmonary fibrosis was diagnosed before MPA, the time range from a few months to 12 years. Among the studies with short-term follow-up, the impact of ILD may be ignored for these patients has not met the diagnostic criteria of AAV yet. It is necessary for further research to explore the role of ILD in the course of AAV development by prolonging follow-up time, emphasizing on regularly radiographic images and pulmonary function tests.

Current studies suggest that ILD, especially UIP, mainly affects the long-term course. Our study confirmed that the RR-value tend to be higher in UIP group, even higher in the group which has shorter follow-up period, suggesting that ILD is not only associated with long-term prognosis, but also a risk factor for poor prognosis within 48 months. Pulmonary fibrosis frequently exists before systemic involvement, which might aggravate the possibility of respiratory failure and pulmonary infection, most of which need to use intravenous corticosteroids and immunosuppressive therapy. Among the causes of death in AAV-ILD patients, respiratory failure and infectious diseases of the ILD are among the most frequent causes of death.^[4, 5, 7, 12] In the series of MPA patients with pulmonary fibrosis, one-third of them developed chronic respiratory insufficiency requiring long-term oxygen therapy and 31–85% died during the follow-up period.^[5, 7, 17, 25, 41, 47] Meanwhile, Infectious complications are associated with mortality in AAV patients over the first year after diagnosis, and maintenance therapy with corticosteroids increases the incidence rate of infections.^[8, 13, 28, 47, 48]

The strengths of our meta-analysis include the thorough systematic literature review, duplicate abstraction, careful exclusion of studies on overlapping populations, evaluation of study quality using the Newcastle-Ottawa scale. Both sensitivity and subgroup analysis were applied to evaluate the stability and heterogeneity of findings. Although there is an evidence for publication bias, no significant change in the recalculated value of the summary statistic by the application of the trim and fill method, suggesting that publication bias had no significant influence on the result.

Our meta-analysis has few limitations. The follow-up period of studies is different, which may affect the result of meta-analysis. However, we have already adopted appropriate statistical methods to minimize the bias. Firstly, sensitivity analysis suggested that this conclusion is relatively stable and not affected by a single test. Secondly, we conducted subgroup analysis according to follow-up months, which reveals that each groups of RR values, regarding to follow-up period no more than 48 months and longer than 48 months, were higher than control group. Therefore, we still have reason to believe that this result has a certain reference value. Another limitation is that the values we used to assess prognostic factors were not identical, including risk ratios or hazard ratios. However, we choose the covariate adjusted HR to reduce the heterogeneity of the result as far as possible. At the same time, a particularity of this systemic review needs to be considered, for the outcome is rare in all populations and subgroups under review, one can generally ignore the distinctions among various measures of relative risks, such as odd ratios, risk ratio and hazard ratio.^[48] Moreover, no studies adjusted for respiratory physiology. Homma S et al, reported that causes of death in AAV-ILD include progressive deterioration of pulmonary function,^[47] suggesting latter studies should concentrate on the relationship between pulmonary function and mortality.

Conclusion

In summary, our meta-analysis indicated that ILD is a complication of AAV that might associated with poor prognosis. The risk of death in AAV-ILD patients remains relatively high over time, which warrants further investigation to create optimum treatment protocols for this special subpopulation of AAV patients.

Abbreviations

AAV: ANCA-associated vasculitis; ILD: interstitial lung disease; PF: pulmonary fibrosis; RR: risk ratio; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; UIP: usual interstitial pneumonia; NSIP non-specific interstitial pneumonia; HRCT: high resolution computed tomography; CTD: connective tissue disease; CVD: collagen vascular disease.

Declarations

Contributors:

GW planned the study. JM helped guide the study and assisted in data collection.

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Competing interests:

There are no competing interests for any author.

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Ethics approval and consent to participate:

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Consent for publication:

The manuscript has been read and approved for publication by all the authors.

Availability of data and material:

All data and materials in this manuscript are available.

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Figures

Figure 1

Meta-analysis of studies examining association between AAV-associated-ILD and mortality.

Figure 3

Funnel plot of AAV-associated-ILD and mortality.

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