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Original Research

Prognostic factors associated with mortality in acute exacerbations of idiopathic pulmonary fibrosis: A systematic review and meta-analysis

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ABSTRACT

Background: Acute exacerbations of idiopathic pulmonary fibrosis (AE-IPF) increases mortality risk, but which factors increase mortality is unknown. We aimed to perform a prognostic review of factors associated with mortality in patients with IPF.

Study design: and methods: We searched MEDLINE, EMBASE, and CINAHL for studies that reported on the association between any prognostic factor and AE-IPF. We assessed risk of bias using the QUIPS tool. We conduced pairwise meta-analyses using REML heterogeneity estimator, and GRADE approach to assess the certainty of the evidence.

Results: We included 35 studies in our analysis. We found that long-term supplemental oxygen at baseline (aHR 2.52 [95 % CI 1.68 to 3.80]; moderate certainty) and a diagnosis of IPF compared to non-IPF ILD (aHR 2.19 [95 % CI 1.22 to 3.92]; moderate certainty) is associated with a higher risk of death in patients with AE-IPF. A diffuse pattern on high resolution computed tomography (HRCT) compared to a non-diffuse pattern (aHR 2.61 [95 % CI 1.32 to 2.90]; moderate certainty) is associated with a higher risk of death in patients with AE-IPF. We found that using corticosteroids prior to hospital admission (aHR 2.19 [95 % CI 1.26 to 3.82]; moderate certainty) and those with increased neutrophils (by % increase) in bronchoalveolar lavage (BAL) during the exacerbation is associated with a higher risk of death (aHR 1.02 [1.01 to 1.04]; moderate certainty).

Interpretation: Our results have implications for healthcare providers in making treatment decisions and prognosticating the clinical trajectory of patients, for researchers to design future interventions to improve patient trajectory, and for guideline developers in making decisions about resource allocation.

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1. Background

Idiopathic pulmonary fibrosis (IPF) is associated with a poor prognosis overall, with a median survival rate of 2–3 years from the time of diagnosis [1]. Patients who experience an acute exacerbation of IPF (AE-IPF) develop a rapidly increased risk of all-cause mortality, with approximately half of patients with AE-IPF dying within 3 months of their exacerbation [2].

Currently, there are no evidence-based treatments for AE-IPF [3,4]. Although corticosteroids remain the mainstay of therapy, this treatment is supported by a weak recommendation for their use in societal clinical practice guidelines based on observational data [5]. Moreover, there is little understanding of which patients are likely to rapidly deteriorate and which factors on patient, diagnostic, and treatment levels are associated with the greatest risk of poor outcomes. Indeed, despite the overall poor prognosis of this condition, data informing prognostication following an acute exacerbation (AE) is sparse and not well summarized by the existing literature.

The existing literature includes large cohort studies reporting on multiple potential prognostic factors such as CT scan scores, age, sex, baseline lung function, frequency and severity of prior exacerbations, and prior use of immunosuppressive medications [6–9]. However, these have not been systematically evaluated or analyzed, precluding effective prognostication by clinicians. Prognostic reviews provide information pertinent to risk management (i.e., treatment decisions, resource allocation planning (i.e., clinical trial planning, end-of-life discussion) and may identify promising targets for future therapies [10].

We performed a systematic review and meta-analysis of prognostic factors associated with mortality in patients with AE-IPF including an assessment of the certainty of evidence to contextualize findings and conclusions.

2. Methods

We registered the protocol for this study on Open Science Framework (OSF) (i.e., an alternative to PROSPERO) on January 5, 2023: https://osf.io/yn7gf. Results of this systematic review are reported according to the PRISMA reporting statement [11]. We did deviate from our initial protocol, as we had initially planned to include all patients with fibrotic interstitial lung disease but due to significant patient heterogeneity, we decided to only analyze patients with IPF. Therefore, our analysis only applies to patients with a confirmed diagnosis of IPF and not to all fibrotic ILD.

2.1. Search strategy

We worked with an experienced medical librarian to develop a search strategy. We searched MEDLINE, EMBASE, and CINAHL databases from inception up to March 5th, 2023. eTable 1 presents our search strategy.

2.2. Study eligibility

We included any study that evaluated any prognostic factor (i.e., patient demographic characteristics and characteristics of patients' disease and care) for mortality in adult patients experiencing an AE-IPF. We accepted any definition of acute exacerbation for this analysis. We included cohorts of patients with non-IPF fibrotic lung disease, if the population did not make up more than 20 % of the total study population, or the study reported results stratified by IPF status. This was to avoid excluding studies that may have reported in study subgroups, but also we made a judgement that the prognostic factors would sufficiently reflect IPF patients if 20 % or less of the population were made up of different fibrotic ILD phenotypes.

We excluded narrative, scoping, and systematic reviews, conference abstracts, and post-mortem investigations.

2.3. Study selection & Data extraction

Pairs of reviewers, following training and calibration exercises, worked independently and in duplicate to screen titles and abstracts of search records. Reviewers were first trained and were asked to collect studies independently. After 5 studies were screened, a separate meeting was performed to review screening and troubleshoot issues. This process was repeated twice to ensure uniformity. Subsequently, reviewers screened the full texts of records deemed potentially eligible by either reviewer at the title or abstract screening stage. Similarly, we performed the same calibration exercise as the screening process. Reviewers resolved discrepancies by discussion and, when necessary, by adjudication with a third reviewer.

Using the same procedures, we extracted information describing patient characteristics (age, sex, comorbidities), country of enrollment, severity of IPF (FVC % predicted), use of antifibrotic medications (nintedanib and pirfenidone), and diagnostic definitions for IPF.

For all studies, we extracted adjusted measures of association (e.g., adjusted odds ratios, adjusted hazard ratios, and adjusted relative risks) representing the association between any prognostic factor and all-cause mortality at the longest reported point of follow-up.

In cases where we identified more than one publication reporting on the same cohort, we assessed each for prognostic factors and included them if they reported on different prognostic factors (i.e., taking care not to include two of the same cohorts reporting on the same prognostic factors). If publications of the same cohort reported on the same prognostic factors, we used the results at the lowest risk of bias or the results at the longest reported point of follow-up, if judgements of risk of bias are similar.

2.4. Risk of bias assessments

We assessed risk of bias independently and in duplicate using the QUIPS tool, the Cochrane endorsed tool for assessing risk of bias for prognostic systematic reviews [12]. The QUIPS tool rates risk of bias as high, moderate, or low across five domains including study participation, prognostic factor measurement, outcome measurement, confounding, and statistical analysis and reporting. For the QUIPS domain of confounding, we rated studies at low risk of bias if they, at minimum, adjusted for age, sex, duration of illness, and smoking status. Reviewers resolved by discussion and, when necessary, by adjudication with a third reviewer.

2.5. Data synthesis and analysis

We reported categorical variables as proportions and percentages and continuous variables as medians and interquartile ranges (IQR) or ranges.

For every candidate prognostic factor, we presented the measure of association as either hazard ratio (HR) or odds ratio (OR) or relative risk (RR) and their corresponding 95 % confidence intervals. We standardized the direction and units of measurement for each prognostic factor. For prognostic factors of interest that were reported by more than one study, we meta-analyzed relative effects using the generic inverse variance-based method with the restricted maximum likelihood (REML) heterogeneity estimator. We chose this REML estimator over sl options because it has been shown to perform better than alternatives in a variety of scenarios, including advantages in calculating unbiased heterogeneity [13] We conducted meta-analyses of ORs, HRs, and RRs separately, consistent with Cochrane guidance, given the high event rates [14].

To explore reasons for heterogeneity, we performed pre-specified subgroup analyses comparing studies that also included non-IPF patients to those that exclusively included IPF patients, FVC (%), and risk of bias. For dichotomous subgroups, we performed subgroup analysis and for continuous subgroups (i.e., baseline FVC (%), we performed

meta-regression.

For any statistically significant subgroup effect, we assessed the credibility using principles from the ICEMAN tool [15]. For analyses with 10 or more studies, we assessed for publication bias by visually inspecting funnel plots and Eggers test [16]. We conducted all analyses in R (version 4.0.3, R Foundation for Statistical Computing), using the *meta* and *metafor* packages.

2.6. Certainty of evidence

We assessed certainty (quality) of the evidence for the association between each candidate prognostic factor and mortality using GRADE guidance for assessing the certainty of evidence of prognostic factors [17]. According to the GRADE approach for prognostic studies, evidence from observational studies starts at high certainty and may be downgraded due to considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias. We used a minimally contextualized approach for judgements of imprecision [18]. The minimally contextualized approach considers only whether confidence intervals include a minimally important effect and does not consider whether plausible effects, captured by confidence intervals, include small or large effects. We used the null effect as the threshold.

We report results using guidance from the GRADE Working Group, which involves describing the association based on the certainty of evidence (i.e., high-certainty evidence an association is present, moderate-certainty evidence an association is probably present, low-certainty evidence an association may be present and very low–certainty evidence there is an uncertain association) [19].

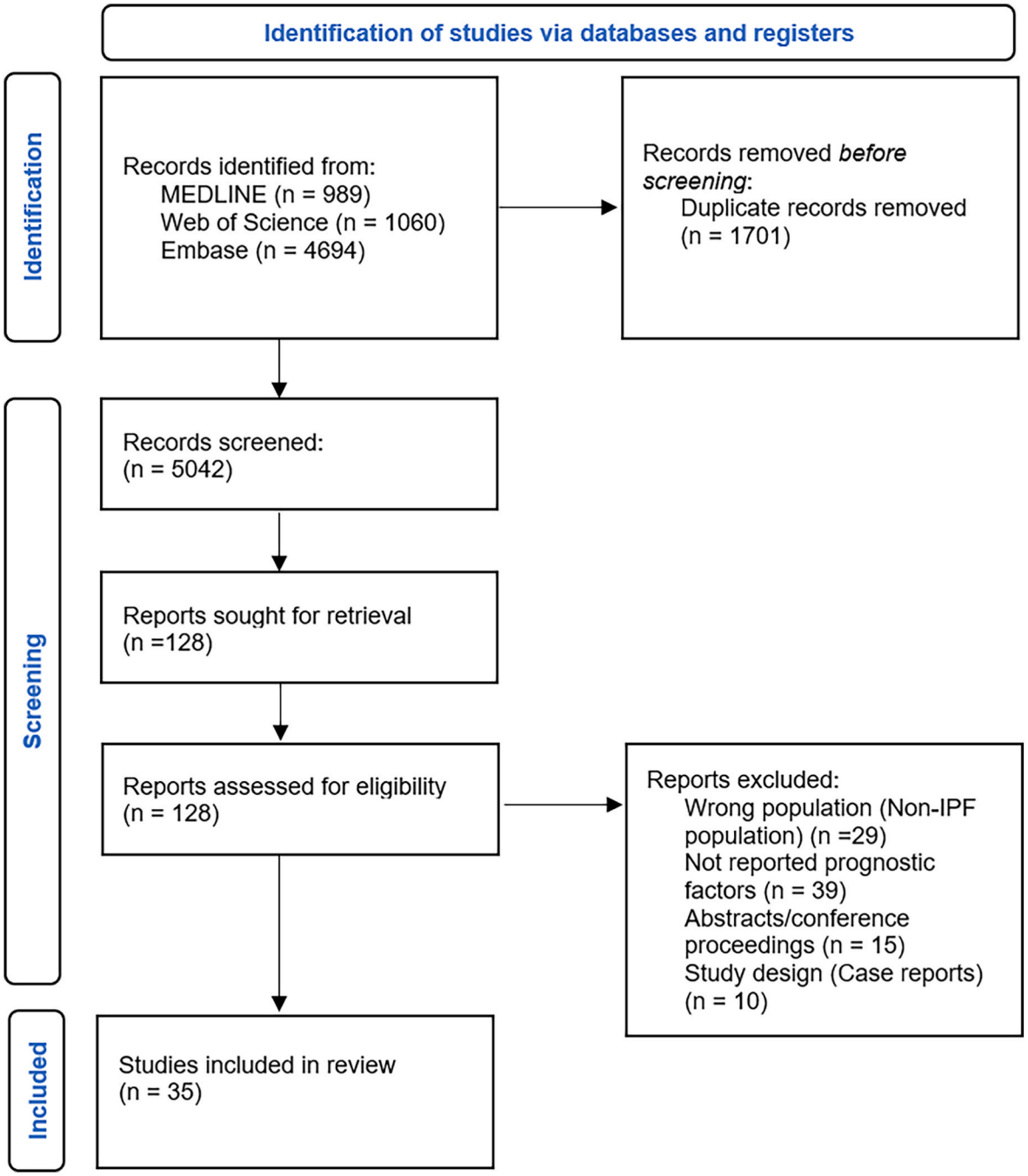

Fig. 1. PRISMA flow diagram of included studies.

3. Results

We included 35 publications reporting on 25 unique cohorts from 1990 to 2022. Fig. 1 presents more details on the study inclusion and exclusion criteria.

The mean age of patients ranged between 64.6 and 78.5 years old across studies. Patients enrolled were predominately male, with males accounting for 55.9 %–91.5 % of the study cohorts. The baseline FVC mean ranged from 53.7 to 79.6 % predicted. Across studies, 4.2 %–62 % used anti-fibrotic medications.

Patients were predominantly enrolled from Japan (76 %), followed by South Korea (12 %), China (4 %), USA (4 %) and Canada (4 %). eTable 2 presents more details on the included studies [6,20–49].

3.1. Risk of bias

We rated most cohorts at low risk of bias (77.2 %) and rated eight at moderate risk of bias (22.8 %) due to concerns related to residual confounding in the multivariate analyses. eTable 3 presents more detail on our risk of bias assessments.

3.2. All-cause mortality

3.2.1. Patient factors

We found that long-term use of supplemental oxygen at baseline (aHR 2.52 [95 % CI 1.68 to 3.80]; moderate certainty), and a diagnosis of IPF as compared to other (aHR 2.19 [95 % CI 1.22 to 3.92]; moderate certainty) was associated with a higher risk of death in patients with AE-IPF.

Patients ⩾81 years old, as compared with younger patients, was associated with a higher risk of death in patients with AE-IPF (aOR 2.98 [95 % CI 2.48 to 3.58]; moderate certainty).

Fig. 2 and eFigs. 1–11 present the forest plots. Table 1 presents the hazard ratios analysis and Table 2 presents the odds ratio analysis.

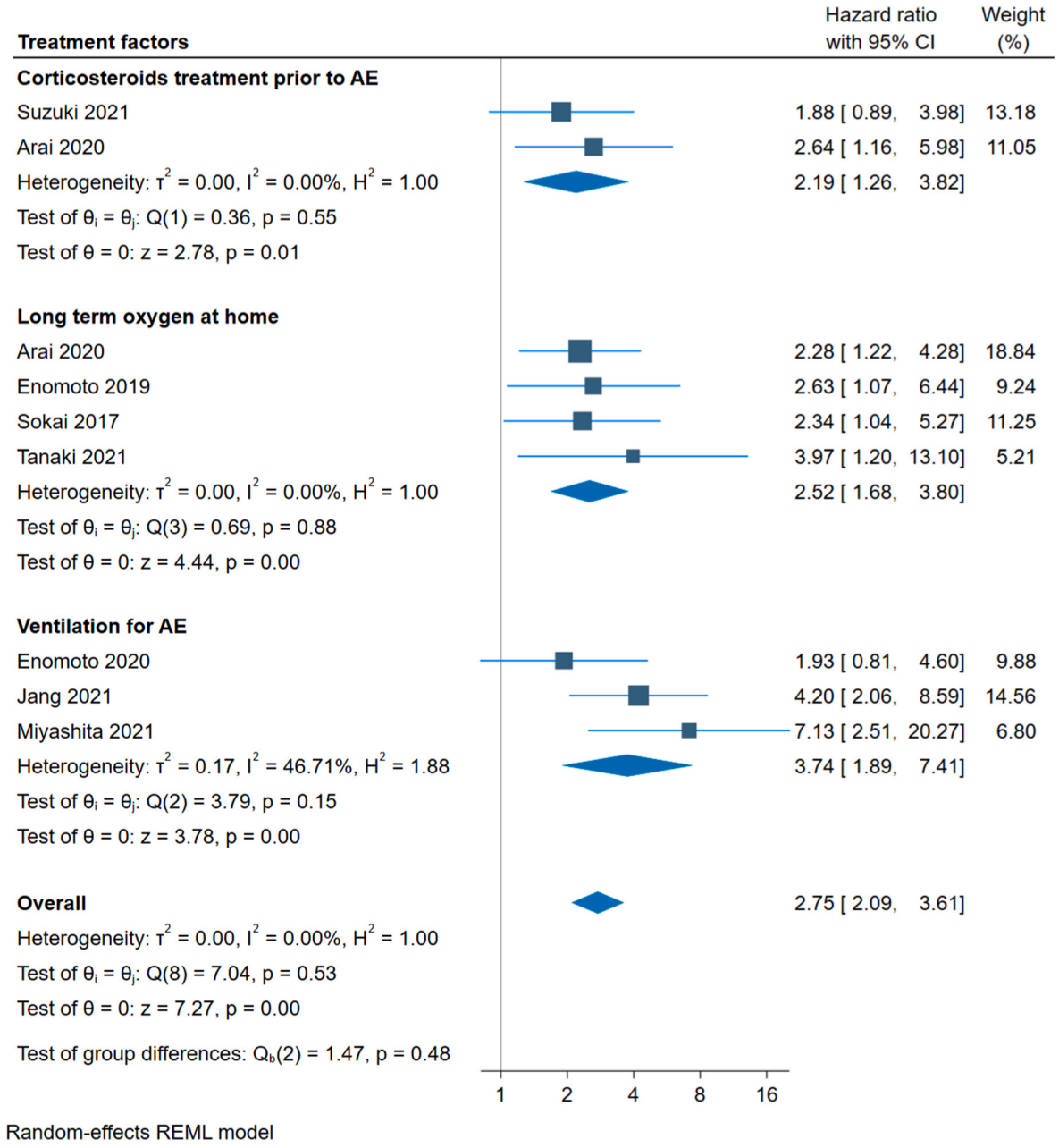

Fig. 2. Forest plot of treatment factors associated with mortality.

Table 1
Prognostic factors pooled by adjusted hazard ratios and 95 % confidence intervals.

Factors	Number of studies	aHR (95 % CI	GRADE	Narrative summary
Patient factors				
PF ratio (per 10 units)	9	1.00 (0.99–1.00)	Moderate	PF ratios (per 10-unit increase) are probably not associated with an increased risk of death.
Age	9	1.00 (0.99–1.02)	Moderate	Age (per year increase) are probably not associated with an increased risk of death)
Male sex	8	0.97 (0.61–1.56)	Low	Male (versus female) may not be associated with an increased risk of death.
Smoking history/ current smoker (vs never smoker)	6	0.70 (0.36–1.36)	Very low	A smoking history has an uncertain prognostic effect on mortality.
FVC (% predicted)	5	0.99 (0.98–1.01)	Moderate	Baseline FVC (%) is probably not associated with an increased risk of death.
Long-term oxygen at home	4	2.52 (1.68–3.80)	Moderate	Long-term oxygen at home (versus none) is probably associated with an increased risk of death.
Confirmed IPF (vs other)	4	2.19 (1.22–3.92)	Moderate	A confirmed diagnosis of IPF (versus not) is probably associated with an increased risk of death.
BMI (kg/m)	2	0.96 (0.91–1.02)	Moderate	BMI (per unit of kg/m) may not be associated with an increased risk of death.
DLCO (% predicted)	2	1.01 (1.00–1.03)	Moderate	Baseline DLCO (% predicted) probably is not associated with an increased risk of death.
Laboratory factors				
LDH (U/L)	7	1.00 (1.00–1.00)	Moderate	LDH (per U/L) is probably not associated with an increased risk of death.
KL-6	5	0.99 (0.98–1.00)	Moderate	KL-6 (per unit increase) probably is not associated with an increased risk of death.
WBC (cells/uL)	3	1.03 (0.99–1.07)	Moderate	WBC (per increase in cells/uL) probably is not associated with an increased risk of death.
CRP (per mg/dL)	3	1.02 (0.99–1.07)	low	CRP (per unit crease in mg/dL) is probably associated with an increased risk of death.
IgG	1	0.99 (0.98–1.00)	Very low	IgG (per unit increase) has an uncertain association with an increased risk of death.
D-dimer	2	1.04 (1.01–1.06)	Low	Increase in D-dimer (per unit increase) probably is not associated with an increased risk of death.
ΔLDH (U/L)	2	1.00 (1.00–1.01)	Low	Change in LDH (per unit increase) may not predict a higher risk of death.
Radiologic factors				
CT score (per unit)	6	1.14 (1.02–1.27)	Low	CT scores (per unit increase) probably is associated with an increased risk of death.
Consolidation score (%)	3	1.00 (0.97–1.03)	Very low	Consolidations scores (per % increase in score) has an uncertain association with risk of death.
HRCT with diffuse pattern (vs. non-diffuse)	3	2.61 (1.32–5.17)	Moderate	HRCT with diffuse pattern (vs. non-diffuse) probably is associated with an increased risk of death.
Extent of honeycombing	1	0.96 (0.91–1.01)	Low	Extent of honeycombing (% increase) may not be associated with an increased risk of death.
HRCT with diffuse pattern (vs. Peripheral)	2	2.34 (0.99–5.55)	Low	HRCT with a diffuse pattern (vs. peripheral) may be associated with an increased risk of death.
Treatment factors				
Requiring invasive mechanical ventilation	3	3.74 (1.89–7.41)	Moderate	Requiring invasive mechanical ventilation at AE (vs none) probably is associated with an increased risk of death.
Steroid use prior to AE (vs. None)	2	2.19 (1.26–3.82)	Moderate	Prior use of steroids (vs. None) probably is associated with an increased risk of death.
Period from admission to commencement of treatments for AE (per day)	1	1.12 (1.01–1.26)	Low	An increased period from admission to start of treatment may be associated with an increased risk of death.
Scoring systems				
JRS score before AE	2	1.31 (0.90–1.90)	Low	Higher JRS scores before AE may be

(*continued on next page*)

Table 1 (*continued*)

Factors	Number of studies	aHR (95 % CI	GRADE	Narrative summary
				associated with increased risk of death.
Bronchial alveolar lavage				
BAL neutrophils %	3	1.02 (1.01–1.04)	Moderate	BAL neutrophils (% increase) is probably associated with an increased risk of death.
BAL lymphocytes %	2	0.98 (0.96–1.00)	Low	BAL lymphocytes (% increase) is probably not associated with an increased risk of death.

Note: aHR = adjusted hazard ratios risk, CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development and Evaluation. All included estimates are network estimates.
High certainty (very confident that true effect lies close to that of effect estimate), moderate certainty (moderately confident in effect estimate; the true effect is likely to be close to effect estimate, but there is a possibility that it is substantially different), low certainty (confidence in the effect estimate is limited; true effect may be substantially different from the effect estimate) or very low certainty: (very little confidence in the effect estimate; true effect is likely to be substantially different from the effect estimate).

3.2.2. *Laboratory factors*

We found that increases (per mg/L) in CRP and D-dimer (per unit increase) were associated with an increased risk of death (aOR 1.11 [95 % CI 1.03 to 1.19]; moderate certainty).

eFigs. 1–11 present the forest plots. Table 1 presents the hazard ratios analysis.

3.2.3. *Radiographic factors*

A higher CT score (i.e., extent of fibrosis) (per unit) (aHR 1.14 [95 % CI 1.02 to 1.27]; low certainty) and a diffuse pattern on high resolution computed tomography (HRCT) compared to a non-diffuse pattern (aHR 2.61 [95 % CI 1.32 to 2.90]; moderate certainty) was associated with a higher risk of death in patients with AE-IPF.

For HRCT with a diffuse pattern vs non-diffuse, we found similar results in studies reporting OR (aOR 2.53 [95 % CI 1.32 to 4.86]; moderate certainty).

Fig. 3 and eFigs. 1–11 present the forest plots. Table 1 presents the hazard ratios analysis and Table 2 presents the odds ratio analysis.

3.2.4. *Treatment factors*

We found that patients who required invasive mechanical ventilation on hospital admission (aHR 3.74 [95 % CI 1.89 to 7.41]; moderate certainty), those that were using corticosteroids prior to hospital admission (i.e., pre-exacerbation) (aHR 2.19 [95 % CI 1.26 to 3.82]; moderate certainty) and those with increased neutrophils (by % increase) in bronchoalveolar lavage (BAL) during the exacerbation had a higher risk of death (aHR 1.02 [1.01 to 1.04]; moderate certainty).

Fig. 2 and eFigs. 1–11 present the forest plots. Table 1 presents the hazard ratios analysis.

3.2.5. *Subgroup analyses*

There were no credible subgroup effects based on risk of bias or baseline FVC (% predicted). eTables 4-5 present these analyses.

Table 2
Prognostic factors pooled by adjusted odds ratios and 95 % confidence intervals.

Factors	Number of studies	aOR (95 % CI	GRADE	Narrative summary
Patient factors				
Age	4	0.99 (0.95–1.04)	Moderate	Age (per increase in year) is probably not associated with an increased risk of death.
Age ⩾81	1	2.98 (2.47–3.59)	Low	Patients aged 81 years or older may be associated with an increased risk of death compared to patients aged <81
Male (vs. Female)	3	2.37 (0.73–7.69)	Low	Being male (versus female) may be associated with an increased risk of death.
PF ratio (per 10 units)	4	0.99 (0.99–0.99)	Moderate	PF ratios (per 10 unit increase) is probably not associated with a higher risk of death.
Lung cancer (vs. None)	2	4.90 (0.67–35.61)	Low	Having lung cancer (versus not) may be associated with a higher risk of death.
Laboratory factors				
CRP (mg/dL)	5	1.11 (1.03–1.19)	Moderate	CRP (per increase in mg/dL) is probably associated with an increased risk of death.
LDH (U/L)	3	1.00 (1.00–1.00)	Moderate	LDH (per increase in U/L) is probably not associated with an increased risk of death.
KL-6	2	1.00 (1.00–1.00)	Moderate	KL-6 (per unit increase) may not be associated with an increased risk of death.
SP-D (ng/mL)	1	1.00 (1.00–1.00)	Low	SP-D (per unit increase) may not be associated with an increased risk of death.
Δ LDH, 1 week	2	1.02 (0.99–1.05)	Low	Change in LDH at 1 week (per unit increase) may be associated with an increased risk of death.
Radiologic factors				
HRCT with diffuse pattern (vs. non-diffuse)	2	2.53 (1.32–4.86)	Moderate	HRCT with diffuse pattern (vs. non-diffuse) is probably associated with an increased risk of death.
Scoring systems				
Charlson Comorbidity Index score	2	1.39 (1.22–1.60)	Low	The Charlson Comorbidity Index Score may be associated with an increased risk of death.

Note: aOR = adjusted odds ratios risk, CI = confidence interval, GRADE = Grading of Recommendations, Assessment, Development and Evaluation. All included estimates are network estimates.
High certainty (very confident that true effect lies close to that of effect estimate), moderate certainty (moderately confident in effect estimate; the true effect is likely to be close to effect estimate, but there is a possibility that it is

substantially different), low certainty (confidence in the effect estimate is limited; true effect may be substantially different from the effect estimate) or very low certainty: (very little confidence in the effect estimate; true effect is likely to be substantially different from the effect estimate).

4. Discussion

4.1. Main findings

We present a comprehensive systematic review and meta-analysis, including 35 studies with over 18,000 patients, reporting on several important prognostic factors associated with increased mortality risk in patients with AE-IPF. This analysis is the most robust and comprehensive analysis to date. It highlights the existing prognostic factors in the existing literature, with potentially clinically important factors and highlighting the significant limitations of current evidence synthesis in this research space.

We found that long-term use of supplemental oxygen, a diagnosis of IPF, higher CT scores (i.e., measure of the degree of fibrosis), diffuse patterns on HRCT, the requirement of invasive mechanical ventilation at the onset of admission, the use of corticosteroids prior to admission, and increased neutrophils in BAL were associated with a higher risk of mortality from AE-IPF. This may reflect the degree of inflammation associated with the AE-IPF or concomitant infection in patients with AE-IPF.

Furthermore, we identified more additional prognostic factors that may be associated the risk of death but with less certainty, which require additional validation and research. Future studies can address the validity of these prognostic factors as well as address more clinically useful prognostic factors.

4.2. In relation to previous studies

Currently, there is limited understanding of prognostic factors for AE-IPF. In contrast, our understanding of the prognostic factors for IPF in general is further along than in patients with AE-IPF. For example, clinicians regularly use the Gender-Age-Physiology (GAP) index and staging system, combined with clinical features to determine prognosis, and therapeutic options. Knowledge of these prognostic factors help guide management with introduction of anti-fibrotic and transplantation work-up as well [50,51]. Despite a need for similar validated tools and factors, there is currently a dearth of evidence based prognostic factors for clinicians to utilize.

The literature and available tools for AE-IPF are limited. This is in part due to a lack of attention to evidence synthesis in this area. We identified only one prior prognostic review on this topic [52], which presented similar prognostic factors as our analysis but did not include as many including radiographic factors and lack some methodological advantages of our analysis including the use of QUIPS and GRADE. Furthermore, the use of prognostic factors is challenging because we currently do not have evidence-based treatments for AE-IPF, making the utility of prognostic factors less apparent [53]. However, the identification and rigorous analysis of prognostic factors can also aid researchers in determining the highest risk patients and which ones may benefit more from treatment than others.

4.3. Strengths and limitations

One of the key strengths of our study is the number of included studies, which improves the certainty of our results. We also performed this review with independent double-screening for the inclusion of

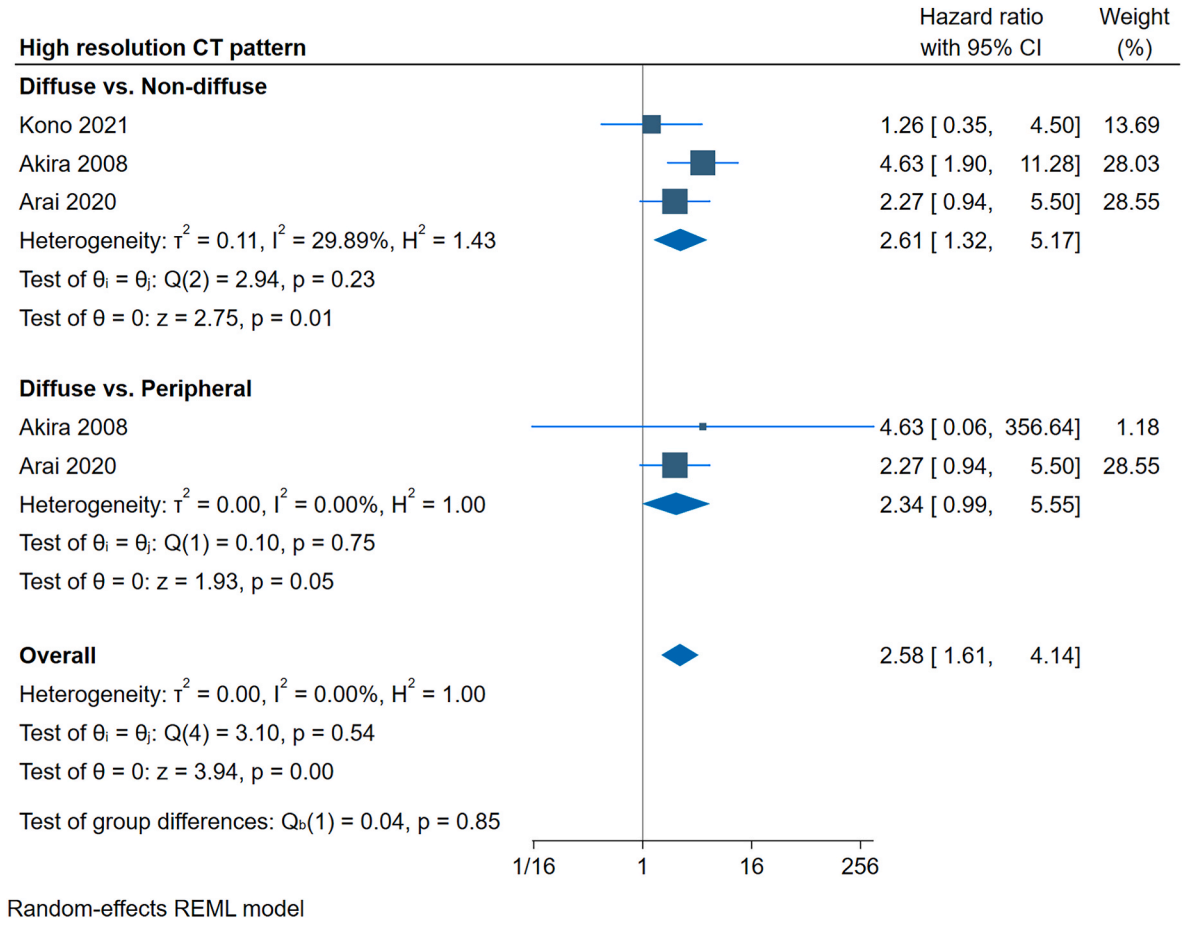

Fig. 3. Forest plot of high-resolution CT pattern factors and mortality.

articles. We analyzed the data using QUIPS tool and assessed the certainty of the evidence using the GRADE approach.

However, there are notable limitations to our study. Firstly, a substantial number of the studies included in the analysis were from Japan and South Korea, potentially skewing the data towards these populations and limiting the generalizability of our results. As such, our findings might not accurately represent other demographic and geographic populations.

Secondly, our study revealed a moderate risk of bias due to residual confounding in some of the included cohorts. This stems from the inherent limitation of these studies, however, we accounted for this in our rating of the certainty of the evidence and were able to offer estimates with moderate certainty evidence.

Third, we identified some treatment related factors that may have little clinical significance. For example, we found that patients presenting with AE-IPF already on corticosteroids had worse outcomes. This is not surprising and probably represents data prior to 2012 when PANTHER-IPF was published [54]. Current IPF treatment guidelines do not support the use of corticosteroids in IPF.

While we aimed for a comprehensive analysis, not all potential prognostic factors could have been included and furthermore, not all of them are clinically useful. For instance, other therapeutic interventions, comorbidities, and genetic factors were not systematically evaluated, which could limit the applicability of our results. In addition, although we identified bronchoscopy as a prognostic factor, bronchoscopy is often not done for practical and patient safety reasons. This highlights the need for future studies to include factors with these parameters in mind. Future studies should also aim to address these limitations by including more diverse population groups and expanding on the factors analyzed.

4.4. Future Directions

The findings from this systematic review and meta-analysis have important implications for future research. The identification of these prognostic factors can guide future investigations into the complex pathophysiology of AE-IPF. There are active trials including the EXAFIP2 trial investigating the use of corticosteroids versus placebo in patients with IPF that would benefit from a better understanding of patient prognostic factors to help guide treatment decisions.

Importantly, we did not identify any prognostic factors that had high certainty evidence. Future studies should take care to adjust appropriately for important prognostic factors of mortality when reporting on prognostic factors to improve the certainty of the evidence going forward.

5. Conclusion

The identified prognostic factors can guide patient management and inform future research in IPF. Long-term use of supplemental oxygen, a diagnosis of IPF, higher CT scores, a diffuse pattern on HRCT, requirement of invasive mechanical ventilation at onset of admission, use of corticosteroids prior to admission, and increased neutrophils in BAL are all associated with higher mortality risk.

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Data sharing

Request can be made to the corresponding author.

Ethics

Not applicable.

CRediT authorship contribution statement

Tyler Pitre: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Daniel Lupas:** Writing – review & editing, Writing – original draft, Resources, Project administration, Data curation. **Ibrahim Ebeido:** Writing – review & editing, Writing – original draft, Resources, Investigation, Data curation. **Alexander Colak:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Mihir Modi:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **George V. Kachkovski:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Sydney B. Montesi:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Yet H. Khor:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Leticia Kawano-Dourado:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Conceptualization. **Gisli Jenkins:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Jolene H. Fisher:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **Shane Shapera:** Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Conceptualization. **Bram Rochwerg:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis. **Rachel Couban:** Writing – review & editing, Writing – original draft, Software, Resources, Formal analysis, Conceptualization. **Dena Zeraatkar:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107515.

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