



Predictors of mortality in subjects with progressive fibrosing interstitial lung diseases

Kevin K. Brown¹  | Yoshikazu Inoue²  | Kevin R. Flaherty³ |
 Fernando J. Martinez⁴ | Vincent Cottin⁵  | Francesco Bonella⁶  | Stefania Cerri⁷ |
 Sonye K. Danoff⁸ | Stephane Jouneau⁹  | Rainer-Georg Goeldner¹⁰ |
 Martin Schmidt¹¹ | Susanne Stowasser¹² | Rozsa Schlenker-Herceg¹³ | Athol U. Wells¹⁴ 

¹Department of Medicine, National Jewish Health, Denver, Colorado, USA

²Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Sakai City, Japan

³Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor, Michigan, USA

⁴Weill Cornell Medicine, New York, New York, USA

⁵National Reference Centre for Rare Pulmonary Diseases, Louis Pradel Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, Lyon, France

⁶Center for Interstitial and Rare Lung Diseases, Department of Pneumology, Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany

⁷Center for Rare Lung Disease, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy

⁸Johns Hopkins Medicine, Baltimore, Maryland, USA

⁹Department of Respiratory Medicine, Competences Centre for Rare Pulmonary Diseases, CHU Rennes, IRSET UMR 1085, Univ Rennes, Rennes, France

¹⁰Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

¹¹Boehringer Ingelheim Pharma GmbH, Ingelheim am Rhein, Germany

¹²Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

¹³Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, USA

¹⁴National Institute for Health Research Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, and National Heart and Lung Institute, Imperial College, London, UK

Correspondence

Kevin K. Brown
 Email: brownk@njhealth.org

Funding information

The INPULSIS and INBUILD trials were funded by Boehringer Ingelheim International GmbH

Associate Editor: Michael P. Keane; **Handling Editor:** Paul Reynolds

Abstract

Background and objective: Demographic and clinical variables, measured at baseline or over time, have been associated with mortality in subjects with progressive fibrosing interstitial lung diseases (ILDs). We used data from the INPULSIS trials in subjects with idiopathic pulmonary fibrosis (IPF) and the INBUILD trial in subjects with other progressive fibrosing ILDs to assess relationships between demographic/clinical variables and mortality.

Methods: The relationships between baseline variables and time-varying covariates and time to death over 52 weeks were analysed using pooled data from the INPULSIS trials and, separately, the INBUILD trial using a Cox proportional hazards model.

Results: Over 52 weeks, 68/1061 (6.4%) and 33/663 (5.0%) subjects died in the INPULSIS and INBUILD trials, respectively. In the INPULSIS trials, a relative decline in forced vital capacity (FVC) >10% predicted within 12 months (hazard ratio [HR] 3.77) and age (HR 1.03 per 1-year increase) were associated with increased risk of mortality, while baseline FVC % predicted (HR 0.97 per 1-unit increase) and diffusing capacity of the lungs for carbon monoxide (DLCO) % predicted (HR 0.77 per 1-unit increase) were associated with lower risk. In the INBUILD trial, a relative decline in FVC >10% predicted within 12 months (HR 2.60) and a usual interstitial pneumonia-like fibrotic pattern on HRCT (HR 2.98) were associated with increased

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Respirology* published by John Wiley & Sons Australia, Ltd on behalf of Asian Pacific Society of Respirology.

risk of mortality, while baseline DLCO % predicted (HR 0.95 per 1-unit increase) was associated with lower risk.

Conclusion: These data support similarity in the course of lung injury between IPF and other progressive fibrosing ILDs and the value of FVC decline as a predictor of mortality.

KEYWORDS

clinical trial, death, fibrosing interstitial lung disease, forced vital capacity, pulmonary fibrosis, pulmonary function test

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is, by definition, a progressive fibrosing interstitial lung disease (ILD).¹ Other chronic fibrosing ILDs may also develop a progressive phenotype characterized by an increasing extent of fibrotic features on HRCT; declining lung function; worsening symptoms, functional impairment and quality of life; and early mortality.^{2–4}

In the INPULSIS trials in subjects with IPF, and the INBUILD trial in subjects with fibrosing ILDs other than IPF who had shown progression within the previous 2 years despite management deemed appropriate in clinical practice, nintedanib reduced the rate of decline in forced vital capacity (FVC) (ml/year) over 52 weeks by approximately 50% compared to placebo.^{5–7} In the placebo groups of these trials, the rate of decline in FVC and the risk of mortality were similar and a relative decline in FVC of >10% of the predicted value was associated with a more than three-fold increase in the risk of death over 52 weeks.⁸

In addition to a decline in FVC, in subjects with fibrosing ILDs, other demographic/clinical characteristics have been associated with mortality, including higher age, more severely impaired lung function and the presence of honeycombing or traction bronchiectasis on HRCT.^{3,9–20} We used data from the INPULSIS and INBUILD trials to assess the relationship between demographic/clinical variables and mortality and to determine the relative importance of a decline in FVC after accounting for these variables.

METHODS

INBUILD and INPULSIS trials

The designs of the INBUILD trial (NCT02999178) and INPULSIS trials (NCT01335464, NCT01335477) have been published and the protocols are publicly available.^{5,6} In brief, subjects in the INPULSIS trials were aged ≥ 40 years, with IPF, FVC $\geq 50\%$ predicted and diffusing capacity of the lungs for carbon monoxide (DLCO) $\geq 30\%$ – $< 80\%$ predicted.⁵ Subjects in the INBUILD trial were aged ≥ 18 years; had a chronic fibrosing ILD other than IPF; met criteria for ILD progression within the previous 2 years, despite management deemed appropriate in clinical practice; had FVC $\geq 45\%$ predicted; and DLCO $\geq 30\%$ – $< 80\%$ predicted.⁶ The INBUILD and INPULSIS trials were conducted in accordance with the principles of the Declaration

SUMMARY AT A GLANCE

We assessed relationships between baseline and time-varying factors and mortality over 52 weeks in 1061 subjects with idiopathic pulmonary fibrosis (IPF) and 663 subjects with other progressive fibrosing interstitial lung diseases (ILDs). Our findings support similarity in the course of IPF and ILD and an association between decline in forced vital capacity and mortality.

of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization, and were approved by local authorities.

Data analysis

We analysed the relationship between baseline variables and time-varying covariates (Table 1) and time to death over 52 weeks in the INBUILD trial and, separately, in pooled data from the INPULSIS trials. Subjects who received ≥ 1 dose of nintedanib or placebo were included. Associations between variables and mortality were assessed using a Cox proportional hazards model where time-varying covariates were included using the programming statements method; missing data were not imputed.

The main model selection algorithm employed was ‘stepwise selection’, but ‘forward selection’ and ‘backward elimination’ were also utilized. Change in the Akaike information criterion was used to determine important variables. The threshold to include or remove a variable was $p = 0.05$. To evaluate the impact of a selected variable on mortality, hazard ratios (HRs) and their CIs were calculated. HRs for continuous variables reflect the impact of a unit change in the underlying variable on mortality. HRs for categorical variables reflect the impact on mortality of being in a defined group compared with the reference group, or, for time-varying covariates, of having the defined decline compared with not having that decline. Sensitivity analyses based on multiple imputation, jump to reference and copy reference²¹ were conducted to determine whether the findings were robust irrespective of the amount of missing data or the imputation method used.

TABLE 1 Overview of variables

Description	Nature
HRCT pattern (UIP-like fibrotic pattern; other fibrotic patterns) ^a	Baseline
Relative decline in DLCO ^b >15% predicted within 12 months	Time-varying
Relative decline in FVC >10% predicted within 12 months	Time-varying
Relative decline in weight >5% within 12 months	Time-varying
Age (years)	Baseline
Sex	Baseline
Treatment (nintedanib; placebo)	Baseline
FVC, ml	Baseline
FVC % predicted	Baseline
DLCO % predicted ^b	Baseline
Race (Asian; Black/African American; White)	Baseline
BMI (kg/m ²)	Baseline
Tobacco consumption (current and former; never)	Baseline
Time since diagnosis (years)	Baseline
ILD diagnosis (iNSIP, unclassifiable IIP, HP, autoimmune ILDs, other ILDs) ^a	Baseline

^aINBUILD trial only.

^bCorrected for haemoglobin.

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; iNSIP, idiopathic non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

To identify the threshold of FVC decline that was associated with the highest risk of death, the relationship between three alternative measures of FVC decline (relative decline in FVC >10% predicted within 6 months and relative decline in FVC >5% predicted within 6 and 12 months) and mortality was evaluated by: (i) replacing decline in FVC >10% predicted within 12 months with one of the alternative FVC decline measures in a model that included all other variables; (ii) including all four decline in FVC covariates in a model with all other variables; and (iii) including all four decline in FVC covariates in a model without any other variables. The decline in FVC and mortality were assessed within the same time period (i.e., 12 months).

RESULTS

Study participants

In total, 1061 and 663 subjects received ≥ 1 dose of nintedanib or placebo in the INPULSIS and INBUILD trials, respectively. Their baseline characteristics have been described.^{5,6}

Over 52 weeks, 68 subjects (6.4%) died in the INPULSIS trials and 33 subjects (5.0%) died in the INBUILD trial (27 [6.6%] subjects with a usual interstitial pneumonia [UIP]-like fibrotic pattern on HRCT and six [2.4%] subjects with other fibrotic patterns on HRCT).

TABLE 2 Association between selected variables and mortality based on data from the INPULSIS and INBUILD trials

	HR (95% CI)	p-value
Selected variables in INPULSIS		
Relative decline in FVC >10% predicted within 12 months	3.77 (2.28, 6.24)	<0.0001
Age	1.03 (1.00, 1.07)	0.037
FVC % predicted at baseline	0.97 (0.95, 0.99)	0.0007
DLCO % predicted at baseline	0.77 (0.61, 0.98)	0.033
Selected variables in INBUILD		
HRCT pattern ^a	2.98 (1.23, 7.22)	0.016
Relative decline in FVC >10% predicted within 12 months	2.60 (1.28, 5.31)	0.0085
DLCO % predicted at baseline	0.95 (0.91, 0.98)	0.0046

Abbreviations: DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; UIP, usual interstitial pneumonia.

^aHR for subjects with a UIP-like fibrotic pattern on HRCT compared with subjects with other fibrotic patterns on HRCT.

Selected variables and their association with mortality

In the INPULSIS trials, a relative decline in FVC >10% predicted within 12 months, FVC % predicted at baseline, age and DLCO % predicted at baseline were selected as variables associated with mortality (see Table S1 in the Supporting Information). A relative decline in FVC >10% predicted within 12 months (HR 3.77 [95% CI: 2.28, 6.24]) and older age (HR 1.03 [95% CI: 1.00, 1.07] per 1-year increase) were associated with a significantly increased risk of mortality, whereas higher FVC % predicted at baseline (HR 0.97 [95% CI: 0.95, 0.99] per 1-unit increase) and higher DLCO % predicted at baseline (HR 0.77 [95% CI: 0.61, 0.98] per 1-unit increase) were associated with a lower risk of mortality (Table 2).

In the INBUILD trial, a relative decline in FVC >10% predicted within 12 months, DLCO % predicted at baseline and HRCT pattern were selected as variables associated with mortality (see Table S2 in the Supporting Information). A relative decline in FVC >10% predicted within 12 months (HR 2.60 [95% CI: 1.28, 5.31]) and a UIP-like fibrotic pattern on HRCT versus other fibrotic patterns (HR 2.98 [95% CI: 1.23, 7.22]) were associated with an increased risk of mortality, while higher DLCO % predicted at baseline was associated with a lower risk of mortality (HR 0.95 [95% CI: 0.91, 0.98] per 1-unit increase) (Table 2). The same variables were selected by all the algorithms.

Sensitivity analyses assessing handling of missing data

In the INPULSIS trials, the variables selected when the multiple imputation method was used to impute missing data were consistent with the original analysis. Relative decline in DLCO >15% predicted within 12 months was selected as an

additional variable when the jump to reference and copy reference methods were used to impute missing data (see Table S3 in the Supporting Information). When the jump to reference method was used, age was only selected as a variable when the forward selection algorithm was used. In the INBUILD trial, the same variables were selected when all three imputation methods were used as in the original analysis (see Table S4 in the Supporting Information).

Association between alternative categorical declines in FVC and mortality

In the INPULSIS trials, all three alternative measures of decline in FVC were consistently selected when they replaced relative decline in FVC >10% predicted within 12 months in the model (see Tables S5–S10 in the Supporting Information). In the INBUILD trial, none of the alternative measures of FVC decline was selected using the stepwise or backward selection algorithms when they replaced relative decline in FVC >10% predicted within 12 months in the model (see Tables S11–S14 in the Supporting Information). Decline in FVC >5% predicted within 12 months was selected when forward selection was used.

When all four decline in FVC variables were included in a model with all other variables, none of the alternative measures was selected in place of relative decline in FVC >10% predicted within 12 months in INPULSIS or INBUILD (see Tables S15 and S16 in the Supporting Information). When all four decline in FVC variables were included without any other variables, relative decline in FVC >10% predicted within 12 months was selected using all three selection algorithms in the INPULSIS trials (HR 4.54 [95% CI: 2.76, 7.46]; $p < 0.0001$) and the INBUILD trial (HR 2.91 [95% CI: 1.43, 5.90]; $p = 0.0031$) (see Tables S17 and S18 in the Supporting Information).

DISCUSSION

We used data from the INPULSIS trials in subjects with IPF and the INBUILD trial in subjects with progressive fibrosing ILDs other than IPF to investigate the impact of demographic and clinical variables on mortality over 52 weeks. In both the INPULSIS and INBUILD trials, a relative decline in FVC of >10% predicted within 12 months had the strongest association with mortality: compared with subjects who did not have such a decline, this decline in FVC increased the risk of death over 52 weeks by 3.8-fold in subjects with IPF and by 2.6-fold in subjects with other progressive fibrosing ILDs. This is supportive of previous studies that have consistently demonstrated an increased risk of mortality in patients with fibrosing ILDs whose FVC % predicted declined from baseline by 10% within 12 months.^{11,14,15,22–24}

A relative decline in FVC >5% predicted within 6 or 12 months and a relative decline in FVC >10% predicted within 6 months were associated with mortality when they

replaced a relative decline in FVC >10% predicted within 12 months in the model in our analyses of the INPULSIS trials, but not in the analyses of the INBUILD trial. This might have been due to the lower number of FVC declines and deaths observed in the INBUILD trial than in the INPULSIS trials. In the INPULSIS trials, the other categorical declines in FVC were not as strongly associated with mortality as a relative decline in FVC >10% predicted within 12 months. Together with evidence from previous studies, these data support the use of a relative decline in FVC >10% predicted within 12 months as a robust predictor of mortality in patients with fibrosing ILDs.

Consistent with previous studies,^{13,18,20,24–26} in our analyses, lower DLCO % predicted at baseline was associated with a higher risk of mortality over 52 weeks. Interestingly, lower FVC % predicted at baseline, which has been associated with mortality in other studies in subjects with IPF^{20,25,27} and with other fibrosing ILDs,^{3,14,16,23} was identified as a factor associated with mortality in the INPULSIS trials, but not in the INBUILD trial. This may reflect the inclusion criteria used in the INBUILD trial, which required recent progression of ILD based on decline in FVC or worsening of symptoms and abnormalities on HRCT within the 24 months prior to enrolment, and/or the difference in FVC % predicted at baseline, which was higher in the INPULSIS trials than in the INBUILD trial (mean [SD] 79.6 [17.8] vs. 69.0 [15.6] % predicted). In the INPULSIS and INBUILD trials, nintedanib reduced the rate of decline in FVC compared to placebo.^{5,6} The confounding effect of the association between treatment with nintedanib and reduced FVC decline meant that treatment with nintedanib was not selected as a variable associated with reduced mortality in these analyses.

The presence of a UIP-like fibrotic pattern on HRCT has been associated with higher mortality in subjects with fibrosing ILDs,^{13,17,28–30} although this has not been observed in all studies.³ In the INBUILD trial, subjects who had a UIP-like fibrotic pattern on HRCT had approximately a three-fold higher risk of mortality over 52 weeks than subjects with other fibrotic patterns. However, it should be noted that placebo-treated subjects with other fibrotic patterns on HRCT still had a marked decline in FVC over 52 weeks (–154 ml) and that based on data from the whole INBUILD trial (median follow-up: approximately 19 months), a numerical association was observed between a relative decline in FVC >10% predicted and mortality in these subjects (HR 2.88).⁸

In our analyses, ILD diagnosis (idiopathic non-specific interstitial pneumonia, unclassifiable idiopathic interstitial pneumonia, hypersensitivity pneumonitis, autoimmune ILDs, other ILDs) was not associated with mortality. Previous analyses of data from the INBUILD trial suggest that the rate of decline in FVC was consistent across subgroups by ILD diagnosis.⁸ This suggests that once a fibrosing ILD has become progressive, the risk of mortality that it confers is similar irrespective of aetiology. It is important to bear in mind that these conclusions are based on a population of patients with fibrosing ILD that had shown progression within the prior 24 months and should not be applied to patients at diagnosis;

an accurate initial differential diagnosis of ILD remains essential.

Strengths of our analyses include the large number of subjects; the large quantity and high quality of FVC measurements collected in the setting of clinical trials; and the consistency of the findings across model selection algorithms and sensitivity analyses that investigated the impact of missing data. Limitations of our analyses include that interactions between variables were not evaluated and the small number of deaths observed over 52 weeks. The mortality rate observed in the placebo group of the INPULSIS trials was lower than that observed in large observational studies in patients with IPF,³¹⁻³³ presumably as patients with the most severe disease or certain comorbidities were not enrolled. Acute exacerbations could not be considered as a factor associated with mortality in these analyses due to the differing definitions used in the INPULSIS and INBUILD trials. The potential association between patient-reported outcomes and mortality was not evaluated.

In conclusion, these analyses of data from the INPULSIS and INBUILD trials provide further support for similarity in the course of lung injury between patients with IPF and with other forms of progressive fibrosing ILD and for the value of FVC decline as a predictor of short-term mortality in these patients.

ACKNOWLEDGEMENTS

We thank the patients who participated in the INPULSIS and INBUILD trials.

CONFLICT OF INTEREST

Research funding: The INPULSIS and INBUILD trials were funded by Boehringer Ingelheim International GmbH. The authors did not receive payment for development of this article. Writing support was provided by Julie Fleming and Wendy Morris of Fleishman-Hillard, London, UK, which was contracted and funded by Boehringer Ingelheim. Boehringer Ingelheim was given the opportunity to review the article for medical and scientific accuracy as well as intellectual property considerations.

Kevin K. Brown reports grants from NHLBI; has served on a Data Monitoring Committee for Biogen and Humanetics; has served as an advisor to AbbVie, Blade Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, DevPro Biopharma, Dispersol, Galapagos, Galecto, Huitai Biomedicine, Lilly, the Open Source Imaging Consortium, Pliant, Redx Pharma, Sanofi, Theravance, Third Pole and Translate Bio; and reports scientific collaboration with Sekisui Medical Co. Yoshikazu Inoue reports grants from the Japan Agency for Medical Research and Development and the Japanese Ministry of Health, Labour, and Welfare; and payment for lectures or advisory boards from Asahi Kasei, Boehringer Ingelheim, Galapagos, Roche, Savara Inc., Shionogi & Co, Ltd and Taiho. Kevin R. Flaherty reports grants from Boehringer Ingelheim and Roche/Genentech and consulting fees from Bellerophon, Blade Therapeutics, Boehringer Ingelheim, DevPro, Horizon Pharmaceuticals, PureHealth, Respivant, Roche/Genentech,

Shionogi & Co, Ltd and United Therapeutics. Fernando J. Martinez has served on a Data Safety Monitoring Board, advisory board or steering committee for Afferent/Merck, Bayer, Biogen, Boehringer Ingelheim, Nitto, Respivant, Roche and Veracyte; and has received consulting fees or payment for presentations from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Bridge Biotherapeutics, CSL Behring, DevPro, IQVIA, Roche/Genentech, Sanofi, Shionogi & Co, Ltd, twoXAR, United Therapeutics and Veracyte. Vincent Cottin reports grants from Boehringer Ingelheim; consulting or lecturing fees from Actelion, AstraZeneca, Boehringer Ingelheim, Novartis, Roche/Promedior and Sanofi; support for attending meetings from Actelion, Boehringer Ingelheim and Roche/Promedior; and has served on a steering committee, advisory board, Data Safety Monitoring Board or adjudication committee for Actelion, Bayer/Merck Sharp & Dohme, Bristol-Myers Squibb, Celgene, FibroGen, Galapagos, Galecto, Novartis, Roche/Promedior and Shionogi and Co, Ltd. Francesco Bonella has received speakers fees from Boehringer Ingelheim, Fujirebio, Galapagos and Roche; support for attending meetings from Boehringer Ingelheim and Roche; and has acted as an advisor for Boehringer Ingelheim, Bristol-Myers Squibb, Fujirebio, Galapagos, GlaxoSmithKline, Roche and Takeda. Stefania Cerri reports payment for presentations from Boehringer Ingelheim. Sonye K. Danoff has been a clinical trial investigator or has served on a clinical trial coordinating committee for Boehringer Ingelheim, Bristol-Myers Squibb and Roche/Genentech; has received consulting fees, presenting fees or support for attending meetings from Boehringer Ingelheim, the France Foundation and Lupin Pharma; has served on a Data Safety Monitoring Board or advisory board for Galecto and Galapagos; and has acted as an advisor for the American Thoracic Society and Pulmonary Fibrosis Foundation. Stephane Jouneau reports grants from AIRB, Boehringer Ingelheim, LVL, Novartis and Roche; payment for lectures or speaker bureaus from Actelion, AIRB, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Genzyme, GlaxoSmithKline, LVL, MundiPharma, Novartis, Pfizer, Roche and Sanofi; support for attending meetings from Boehringer Ingelheim and Roche; and participation on advisory boards for Boehringer Ingelheim, Novartis and Roche. Rainer-Georg Goeldner, Martin Schmidt and Susanne Stowasser are employees of Boehringer Ingelheim. Rozsa Schlenker-Herceg was an employee of Boehringer Ingelheim at the time this research was conducted. Athol U. Wells reports consulting or speaker fees from Blade Therapeutics, Boehringer Ingelheim and Roche.

AUTHOR CONTRIBUTION

Kevin K. Brown: Conceptualization (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Yoshikazu Inoue:** Conceptualization (supporting); investigation (equal); visualization (supporting); writing – review and editing (supporting). **Kevin R. Flaherty:** Conceptualization (supporting); visualization (supporting); writing – review and editing (supporting). **Fernando J. Martinez:** Conceptualization (supporting); visualization (supporting); writing – review and editing

(supporting). **Vincent Cottin**: Conceptualization (supporting); investigation (equal); visualization (supporting); writing – review and editing (supporting). **Francesco Bonella**: Investigation (equal); visualization (supporting); writing – review and editing (supporting). **Stefania Cerri**: Investigation (equal); visualization (supporting); writing – review and editing (supporting). **Sonye K. Danoff**: Investigation (equal); visualization (supporting); writing – review and editing (supporting). **Stephane Jouneau**: Investigation (equal); visualization (supporting); writing – review and editing (supporting). **Rainer-Georg Goeldner**: Conceptualization (equal); data curation (equal); formal analysis (lead); methodology (equal); visualization (equal); writing – original draft (supporting); writing – review and editing (supporting). **Martin Schmidt**: Data curation (equal); methodology (equal); visualization (supporting); writing – review and editing (supporting). **Susanne Stowasser**: Conceptualization (supporting); visualization (supporting); writing – review and editing (supporting). **Rozsa Schlenker-Herceg**: Conceptualization (equal); project administration (lead); supervision (lead); visualization (equal); writing – original draft (lead); writing – review and editing (supporting). **Athol U. Wells**: Conceptualization (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (supporting).

DATA AVAILABILITY STATEMENT

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to relevant material, including participant-level clinical study data, as needed by them to fulfil their role and obligations as authors under the ICMJE criteria. Clinical study documents and participant clinical study data are available to be shared on request after publication of the primary manuscript in a peer-reviewed journal, and if regulatory activities are complete and other criteria met as per the BI Policy on Transparency and Publication of Clinical Study Data (<https://www.mystudywindow.com/msw/datasharing>). Bona fide, qualified scientific and medical researchers are eligible to request access to the clinical study data with corresponding documentation describing the structure and content of the data sets. Upon approval, and governed by a legal agreement, data are shared in a secured data-access system for a period of 1 year, which may be extended upon request. Prior to providing access, clinical study documents and data will be examined, and, if necessary, redacted and de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of informed consent. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing>.

HUMAN ETHICS APPROVAL DECLARATION

The INBUILD and INPULSIS trials were conducted in accordance with the principles of the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on

Harmonization, and were approved by local authorities. The protocols were approved by an Independent Ethics Committee and/or Institutional Review Board at all the participating centres. All subjects provided written informed consent.

Clinical trial registration: INBUILD trial (NCT02999178) and INPULSIS trials (NCT01335464, NCT01335477) at clinicaltrials.gov.

ORCID

Kevin K. Brown  <https://orcid.org/0000-0002-9209-3261>
 Yoshikazu Inoue  <https://orcid.org/0000-0003-3994-874X>
 Vincent Cottin  <https://orcid.org/0000-0002-5591-0955>
 Francesco Bonella  <https://orcid.org/0000-0001-7579-9767>
 Stephane Jouneau  <https://orcid.org/0000-0002-1949-3461>
 Athol U. Wells  <https://orcid.org/0000-0003-2108-6248>

REFERENCES

- Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198:e44–68.
- Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ, IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J*. 2018;51(5):pii:1800692.
- Nasser M, Larrieu S, Si-Mohamed S, Ahmad K, Boussel L, Brevet M, et al. Progressive fibrosing interstitial lung disease: a clinical cohort (the PROGRESS study). *Eur Respir J*. 2021;57:2002718.
- Wijssenbeek M, Cottin V. Spectrum of fibrotic lung diseases. *N Engl J Med*. 2020;383:958–68.
- Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370:2071–82.
- Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. *N Engl J Med*. 2019;381:1718–27.
- Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. 2020;8:453–60.
- Brown KK, Martinez FJ, Walsh SLF, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. *Eur Respir J*. 2020;55:2000085.
- Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*. 2003;168:543–8.
- Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2003;168:538–42.
- Richeldi L, Ryerson CJ, Lee JS, Wolters PJ, Koth LL, Ley B, et al. Relative versus absolute change in forced vital capacity in idiopathic pulmonary fibrosis. *Thorax*. 2012;67:407–11.
- Walsh SL, Sverzellati N, Devaraj A, Wells AU, Hansell DM. Chronic hypersensitivity pneumonitis: high resolution computed tomography patterns and pulmonary function indices as prognostic determinants. *Eur Radiol*. 2012;22:1672–9.
- Ryerson CJ, Urbania TH, Richeldi L, Mooney JJ, Lee JS, Jones KD, et al. Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Respir J*. 2013;42:750–7.
- Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid

- arthritis-associated interstitial lung disease. *Eur Respir J*. 2016;47:588–96.
15. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. *Arthritis Rheumatol*. 2017;69:1670–8.
 16. Gimenez A, Storrer K, Kuranishi L, Soares MR, Ferreira RG, Pereira CAC. Change in FVC and survival in chronic fibrotic hypersensitivity pneumonitis. *Thorax*. 2018;73:391–2.
 17. Adegunsoye A, Oldham JM, Bellam SK, Montner S, Churpek MM, Noth I, et al. Computed tomography honeycombing identifies a progressive fibrotic phenotype with increased mortality across diverse interstitial lung diseases. *Ann Am Thorac Soc*. 2019;16:580–8.
 18. Chan C, Ryerson CJ, Dunne JV, Wilcox PG. Demographic and clinical predictors of progression and mortality in connective tissue disease-associated interstitial lung disease: a retrospective cohort study. *BMC Pulm Med*. 2019;19:192.
 19. Singh N, Varghese J, England BR, Solomon JJ, Michaud K, Mikuls TR, et al. Impact of the pattern of interstitial lung disease on mortality in rheumatoid arthritis: a systematic literature review and meta-analysis. *Semin Arthritis Rheum*. 2019;49:358–65.
 20. Snyder L, Neely ML, Hellkamp AS, O'Brien E, de Andrade J, Conoscenti CS, et al. Predictors of death or lung transplant after a diagnosis of idiopathic pulmonary fibrosis: insights from the IPF-PRO Registry. *Respir Res*. 2019;20:105.
 21. Cro S, Morris TP, Kenward MG, Carpenter JR. Reference-based sensitivity analysis via multiple imputation for longitudinal trials with protocol deviation. *Stata J*. 2016;16:443–63.
 22. du Bois RM, Weycker D, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med*. 2011;184:1382–9.
 23. Volkman ER, Tashkin DP, Sim M, Li N, Goldmuntz E, Keyes-Elstein L, et al. Short-term progression of interstitial lung disease in systemic sclerosis predicts long-term survival in two independent clinical trial cohorts. *Ann Rheum Dis*. 2019;78:122–30.
 24. Krauss E, El-Guelai M, Pons-Kuehnemann J, Dartsch RC, Tello S, Korfei M, et al. Clinical and functional characteristics of patients with unclassifiable interstitial lung disease (uILD): long-term follow-up data from European IPF Registry (eurIPFreg). *J Clin Med*. 2020;9:2499.
 25. Doubková M, Švancara J, Svoboda M, Šterclová M, Bartoš V, Plačková M, et al. EMPIRE Registry, Czech part: impact of demographics, pulmonary function and HRCT on survival and clinical course in idiopathic pulmonary fibrosis. *Clin Respir J*. 2018;12:1526–35.
 26. Kim HC, Lee JH, Chae EJ, Song JS, Song JW. Long-term clinical course and outcome of interstitial pneumonia with autoimmune features. *Respirology*. 2020;25:636–43.
 27. Jo HE, Glaspole I, Grainge C, Goh N, Hopkins PM, Moodley Y, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J*. 2017;49:1601592.
 28. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics – a large multicentre UK study. *Rheumatology (Oxford)*. 2014;53:1676–82.
 29. Walsh SL, Sverzellati N, Devaraj A, Keir GJ, Wells AU, Hansell DM. Connective tissue disease related fibrotic lung disease: high resolution computed tomographic and pulmonary function indices as prognostic determinants. *Thorax*. 2014;69:216–22.
 30. Salisbury ML, Gu T, Murray S, Gross BH, Chughtai A, Sayyoub M, et al. Hypersensitivity pneumonitis: radiologic phenotypes are associated with distinct survival time and pulmonary function trajectory. *Chest*. 2019;155:699–711.
 31. Jo HE, Glaspole I, Moodley Y, Chapman S, Ellis S, Goh N, et al. Disease progression in idiopathic pulmonary fibrosis with mild physiological impairment: analysis from the Australian IPF registry. *BMC Pulm Med*. 2018;18:19.
 32. Behr J, Prasse A, Wirtz H, Koschel D, Pittrow D, Held M, et al. Survival and course of lung function in the presence or absence of antifibrotic treatment in patients with idiopathic pulmonary fibrosis: long-term results of the INSIGHTS-IPF registry. *Eur Respir J*. 2020;56:1902279.
 33. Tran T, Šterclová M, Mogulkoc N, Lewandowska K, Müller V, Hájková M, et al. The European MultiPartner IPF registry (EMPIRE): validating long-term prognostic factors in idiopathic pulmonary fibrosis. *Respir Res*. 2020;21:11.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Brown KK, Inoue Y, Flaherty KR, Martinez FJ, Cottin V, Bonella F, et al. Predictors of mortality in subjects with progressive fibrosing interstitial lung diseases. *Respirology*. 2022; 27:294–300. <https://doi.org/10.1111/resp.14231>