Predictors of mortality in idiopathic pulmonary fibrosis: forced vital capacity decline and other surrogate endpoints – a literature review

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INTRODUCTION

- Fibrosing ILDs such as IPF are rare, debilitating diseases that result in progressive loss of lung function and are ultimately fatal. Ideally, the aim of treatment is to prolong survival, but the long follow-up and large sample sizes required to show treatment differences mean that overall survival may not be practical as an endpoint in clinical trials.

AIM

- To identify clinical trial endpoints that were most strongly associated with an increased risk of death in patients with IPF, by means of a targeted literature review.

METHODS

- Literature searches were conducted to identify studies (systematic reviews/meta-analyses, long-term [>1 year] randomized controlled trials or observational studies) from 2010 to 2023 in patients with fibrotic ILDs with any survival outcome, with or without a surrogate outcome for survival.
- Conference abstracts, case reports/series, editorials, commentaries and letters were not included.
- The following databases were searched for relevant randomized controlled trials:
  - Embase, MEDLINE In-Process Citations, MEDLINE Daily Update & Epub Ahead of Print, Cochrane Central Register of Controlled Trials, PubMed.
- Supplementary searches were undertaken on the following trial registers:
  - http://www.clinicaltrials.gov/
  - WHO International Clinical Trials Registry Platform.
- The following databases were searched for relevant systematic reviews of randomized controlled trials:
  - Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Epistemonikos, International Prospective Register of Systematic Reviews.

CONCLUSIONS

- There is a large evidence base supporting the use of FVC decline as a surrogate endpoint in IPF. Overall, a 10% decrease in FVC over 52 weeks results in a roughly three-fold increase in risk of mortality. In addition, shorter-term changes in FVC (over 3 months) have been associated with a significant increased risk of mortality.
- FVC decline and other surrogate endpoints (such as increase in CPI, decrease in DLco or decline in 6MWD) can predict mortality in IPF; however, large sample sizes may often still be required to achieve meaningful impact in these endpoints.
- The use of a second variable, in addition to FVC decline, may offer increased sensitivity to predict mortality.
- Further evaluation of composite endpoints to provide efficiency in demonstrating treatment differences in clinical trials is warranted.

RESULTS

FVC

- Evidence for association of a decline in FVC with an increased risk of death in IPF.

5% decline

	HR for mortality (95% CI)	Author
Registry	**2.73** (1.51–4.94)	Reichmann 2015[1]
Observational cohort	**1.8** (1.1–2.9)	Schmidt 2011[2]
	0.36 (0.19–0.64) (stable vs worsened)	Aono 2020[3]
	2.13 (1.20–3.92)	Taha 2020[4]

Follow-up 1–3 years

10% decline

	HR for mortality (95% CI)	Author
Randomized controlled trials	**2.2** (1.1–4.4)	Paterniti 2017[5]
	3.77 (2.28–6.24)	Brown 2022[6]
	3.56 (2.54–4.98)	Maher 2023[7]
Registry	**5.05** (2.75–9.27)	Reichmann 2015[1]
	2.8 (1.34–5.77)	Doubková 2018[8]
	1.34 (0.89–2.02)	Behr 2020[9]
Observational cohort	**2.4** (1.5–3.8)	Schmidt 2011[2]

Follow-up ≤1.6 years

15% decline

	HR for mortality (95% CI)	Author
Randomized controlled trials	**6.1** (3.1–11.8)	Paterniti 2017[5]
Observational cohort	**2.6** (1.6–4.5)	Schmidt 2011[2]

Follow-up ≤60 weeks

20% decline

	HR for mortality (95% CI)	Author
Observational cohort	**3.6** (1.9–6.9)	Schmidt 2011[2]

Follow-up ≤1 year

A pooled optimal threshold of 5.7% (relative change at 3 months, 95% CI 4.31–7 .04) was estimated for mortality in a meta-analysis[10]

DLco

- Evidence for association of a decline in DLco with an increased risk of death in IPF.

Study type	Author	Follow-up	N	Findings
Registry	Doubková 2018[8]	Not reported	514	Deterioration in DLco of ≥15% at Month 12 associated with decreased overall survival • HR 3.691; 95% CI 1.491–9.134; P=0.005
	Zurkova 2019[11]	22.8 months	601	In patients treated with pirfenidone, mortality was associated with: • DLco decline ≥10% at 6, 12, 18 and 24 months (P<0.05) • DLco decline ≥15% at 6, 18 and 24 months (P<0.05), but not 12 months (P=0.182)
Retrospective cohort	Schmidt 2014[12]	Up to 4 years	734	Decline in DLco% in the previous year associated with subsequent 1-year survival (vs stable DLco) • Baseline to Year 1: HR 0.72; 95% CI 0.63–0.79; P<0.0001 • Year 1–2: HR 0.78; 95% CI 0.64–0.87; P=0.1161 • Year 2–3: HR 0.75; 95% CI 0.57–0.87; P=0.0102
	Sharp 2017[13]	22.6 months	167	Change in DLco associated with survival at 12 months • Multivariate analysis: HR 0.984; 95% CI 0.972–0.997; P=0.014
Single-center cohort	Schmidt 2011[2]	Up to 1 year	321	**Association between mortality and relative DLco decline, HR (95% CI)** **At 6 months** • 10%: 1.7 (1.1–2.5) P=0.011 • 15%: 1.6 (1.1–2.5) P=0.029 • 20%: 1.8 (1.1–3.0) P=0.030 • 25%: 2.3 (1.2–4.2) P=0.010 **At 12 months** • 10%: 2.2 (1.4–3.5) P=0.001 • 15%: 2.3 (1.5–3.7) P<0.001 • 20%: 3.0 (1.8–4.9) P<0.001 • 25%: 3.5 (2.0–6.1) P<0.001
Systematic review/meta-analysis	Khan 2022[10]	8–21 months	2,958 (23 studies)	2.5% relative decline in DLco over 3 months associated with: • 7% increased risk of mortality (HR 1.07; 95% CI 1.04–1.11) • 7% increased likelihood of disease progression (OR 1.07; 95% CI 1.02–1.12) The optimal threshold for 3-month relative decline in DLco for predicting mortality was 10.51% (95% CI 4.14–16.88; I^2=19.9%)

6MWD

- Evidence for an association of a decline in 6MWD with an increased risk of death in IPF.

Study type	Author	Follow-up	N	Findings
Randomized controlled trials	du Bois 2011[14]	72 weeks	822	Association of 24-week decline in 6MWD with risk of death at 1 year (vs decline ≤25m): • Decline >50m: HR 4.27; 95% CI 2.57–7.10; P<0.001 • Decline 26–50m: HR 3.59; 95% CI 1.95–6.63; P<0.001
	du Bois 2014[15]	24 weeks	748	Association of 24-week decline in 6MWD with risk of death at 1 year (vs decline ≤25m): • Decline >50m: HR 2.73; 95% CI 1.60–4.66; P<0.01 • Decline 26–50m: HR 2.94; 95% CI 1.56–5.53; P<0.01
	Nathan 2015[16]	48 weeks	338	Association of 24-week decline in 6MWD with risk of death at 1 year (vs decline ≤50m): • Decline >50m: HR 2.53; 95% CI 0.94–6.79; P=0.066
Prospective cohort	Brunetti 2013[17]	6–9 months	30	Positive relationship between survival and 6MWD, distance saturation product, 6MWD × body weight at 6–9 months, and a strong correlation between survival and difference in 6MWD from baseline to 6–9 months (r=0.74, P<0.006)
Retrospective cohort	Gao 2019[18]	2 years	92	• ≥5% decline in 6MWD after 1 year associated with reduced survival (38.4 months vs 46.2 months, P=0.002) • ≥5% decline in 6MWD predicted survival at 2 years (p=0.019), after adjustment for baseline age, gender, BMI, FVC and DLco • Patients with a ≥10% decline in lowest room air oxygen saturation during 6MWT had shorter survival than those without (23.8 months vs 44.3 months, P=0.005)
Systematic review/meta-analysis	Khan 2022[10]	8–21 months	2,958 (23 studies)	Increased risk of mortality associated with decline in 6MWT over 3 months seen in four cohorts (adjusted HR 1.09 per 20m decline; 95% CI 1.01–1.17)

Composite endpoints

- Summary of findings on the relationship between composite endpoints and mortality in patients with IPF.

Study type	Author	Follow-up	N	Findings
Registry	Chandel 2023[19]	1 year	516	DO-GAP: c-statistic 0.73; 95% CI 0.70–0.76; GAP: c-statistic 0.67; 95% CI 0.64–0.71
Randomized controlled trial	Durheim 2015[20]	Up to 60 weeks	510	A composite of early respiratory hospitalization or disease progression: HR 5.65; 95% CI 2.19–14.56; P=0.0003; c-statistic 0.843
Prospective cohort	Manzetti 2022[21]	3 years	109	Prediction of 3-year lung transplant-free survival, score at time of diagnosis: • RISE: sensitivity 94%; specificity 57%; AUC 0.81. GAP: sensitivity 88%; specificity 52%; AUC 0.74 Prediction of 3-year lung transplant-free survival, 12-month changes in score: • RISE: sensitivity 68%, specificity 82%; AUC 0.75. GAP: sensitivity 48%; specificity 80%; AUC 0.64
Retrospective cohort	Schmidt 2011[2]	Up to 1 year	321	**Association with overall mortality at 12 months, HR (95% CI)** **Overall population** • ≥5-point increase in CPI: 2.1 (1.3–3.5; P=0.004) • 10% decline in FVC: 2.4 (1.5–3.8; P<0.001) • 15% decline in DLco: 2.3 (1.5–3.7; P<0.001) **Patients with no emphysema** • ≥5-point increase in CPI: 4.4 (1.8–10.7) • Decline in FVC: 2.6 (0.8–2.6) • Decline in DLco: 2.8 (1.3–4.4)
	Jacob 2017[22]	30 months	283	**Independent predictors of mortality, HR (95% CI)** • CPI: 1.05 (1.02–1.07; p<0.001); PVV: 1.23 (1.08–1.40; P=0.001); honeycombing: 1.18 (1.06–1.32; p=0.002); three-group staging system: 2.23 (1.85–2.69; P<0.0001)
	Sverzellati 2020[23]	Up to 26 months	58	**Association with the outcome of death or lung transplant, HR (95% CI)** • FVC ≥10% decline + ≥20% relative increase in CALIPER total lung fibrosis: 10–14 months – 14.9 (3.9–56.8) • FVC ≥10% decline + visual disease progression: 10–14 months – 48.1 (7.9–260) • FVC trend increase + VRS relative increase ≥20%: 22–26 months – 15.1 (2.7–59.5) • FVC trend increase + visual disease progression: 22–26 months – 15.6 (2.8–86.6)

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REFERENCES

1. Reichmann WM, et al. BMC Pulm Med 2015; 15:167;
2. Schmidt SL, et al Eur Respir J 2011; 38:176–183;
3. Aono Y, et al. Ther Adv Respir Dis 2020; 14:1753466620953783;
4. Taha N, et al. Respir Res 2020; 21:119;
5. Paterniti MO, et al. Ann Am Thorac Soc 2017; 14:1395–1402;
6. Brown KK, et al. Respirology 2022; 27:294–300;
7. Maher TM, et al. Respirology 2023; 28:1147–1153;
8. Doubková M, et al. Clin Respir J 2018; 12:1526–1535;
9. Behr J, et al. Eur Respir J 2020; 56:1902279;
10. Khan FA, et al. Am J Respir Crit Care Med 2022; 205:936–948;
11. Zurkova M, et al. Respir Res 2019; 20:16;
12. Schmidt SL, et al. Chest 2014; 145:579–585;
13. Sharp C, et al. ERJ Open Res 2017; 3:00096–02016;
14. du Bois RM, et al. Am J Respir Crit Care Med 2011; 183:1231–1237;
15. du Bois RM, et al. Eur Respir J 2014; 43:1421–1429;
16. Nathan SD, et al. Respir Med 2015; 109:914–922;
17. Brunetti G, et al. Eur Respir J 2013; 42:P3693;
18. Gao J, et al. Eur Respir J 2019; 54:PA1356;
19. Chandel A, et al. ERJ Open Res 2023; 9:00124–02023;
20. Durheim MT, et al. Lancet Respir Med 2015; 3:388–396;
21. Manzetti GM, et al. Eur Respir J 2022; 60:1881;
22. Jacob J, et al. Eur Respir J 2017; 49:1601011;
23. Sverzellati N, et al. Eur Radiol 2020; 30:2669–2679.

ABBREVIATIONS

6MWD, 6-minute walk distance; 6MWT, 6-minute walk time; AUC, area under the curve; BMI, body mass index; CI, confidence interval; CPI, composite physiologic index; DLco, diffusing capacity of the lung for carbon monoxide; DO-GAP, Distance-Oxygen-Gender-Age-Physiology; FVC, forced vital capacity; GAP, Gender-Age-Physiology; HR, hazard ratio; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; OR, odds ratio; PVV, pulmonary vessel volume; RISE, risk stratification score; VRS, vessel-related structures (computer-derived variable).

DISCLOSURES

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