Clinical utility of home versus hospital spirometry in fibrotic ILD: evaluation following INJUSTIS interim analysis

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Introduction

Domiciliary monitoring of physiological variables has become routine in many chronic conditions owing to technological advances(1). Restricted clinical capacity and patient safety during the COVID-19 pandemic have identified an urgent need to consider remote lung function monitoring of chronic respiratory disease(2). Home handheld spirometry enables repeated measurements, offering opportunities for real-time disease evaluation, without the risk of nosocomial infection.

Interstitial lung disease (ILD) encompasses a heterogeneous range of immuno-inflammatory and fibrotic diseases. Forced vital capacity (FVC) correlates with outcome in ILD and remains the most commonly used biomarker of disease progression(3), with clinical trials consistently adopting hospital FVC measurements as the primary endpoint(4-6). We assessed interim data from the multi-centre It's Not Just Idiopathic Pulmonary Fibrosis Study (INJUSTIS, NCT03670576) (7) to evaluate the clinical utility of home spirometry as an alternative to hospital spirometry in participants with fibrotic ILD.

Methods

The INJUSTIS study is an ongoing multi-centre prospective, observational cohort study aiming to identify blood and physiological biomarkers that may predict disease progression in a mixed cohort of participants with multi-disciplinary confirmed fibrotic ILD (unclassifiable, hypersensitivity pneumonitis, asbestosis, rheumatoid-associated ILD and IPF) (7). A subgroup of participants possessing a smartphone were offered a portable handheld

spirometer (MIR Spirobank Smart) linked via Bluetooth to a smartphone application and asked to perform a single, blinded forced expiratory manoeuvre daily for at least three months. Hospital spirometry was collected according to international guidelines(8) at baseline and three months.

Home spirometry readings falling within the upper and lower percentile (1%/99%) of aggregated group data were excluded to limit effects of substandard blows. Baseline measurements were calculated as the mean of daily readings obtained during the first seven days. Three-month measurements were calculated as the mean of readings obtained between days 90 and 96.

Correlation and inter-observer reliability between home and hospital spirometry for corresponding timepoints were assessed using Pearson correlation and intra-class correlation coefficients in a two-way random effects model. Bland-Altman plots were generated to assess the number of measurements that were outside the 95% limits of agreement. Adherence was calculated as the number of days where a participant provided at least one reading divided by 105 days. Change in King's Brief Interstitial Lung Disease Health status questionnaire (K-BILD) over three-month was calculated according to adherence categories (<60%, 60%-80%, >80%). We assessed consistency of measures across each week of study, by calculating a weekly coefficient of variation where three or more daily values were provided. This was assessed in a generalised estimating equation population-averaged model with exchangeable correlation matrix and robust sandwich variance estimators. Association of diagnostic subgroup (IPF vs non-IPF), week and

interaction of week and subgroup were estimated. All analyses were performed using Stata v.16 (StataCorp, College Station, TX, USA).

Results

Eighty-two participants were included in analysis, of which 23 had IPF (28%) and 59 had non-IPF ILD (72%). Forty-three participants had three-month data for both home and hospital spirometry, with 19 participants excluded due to missing hospital spirometry attributable to the Covid pandemic (Table 1). Median adherence to daily home spirometry for all participants was 81% (IQR 61-94%), increasing to 91% (IQR 79-97%) in those who completed three-months. Individuals with adherence lower than 80% reported increases in symptom scores for total, activities and chest domains between baseline and three-months.

Of the total 6202 daily FVC measurements, values in the upper and lower percentiles (below 0.9L or above 5.4L) were excluded. High correlation was observed between home and hospital spirometry at baseline (r=0.89) and three-months (r=0.82) (Table 1). The intra-class correlation coefficients between hospital and home spirometry at baseline and three-months were 0.92 (95%CI 0.79-0.96) and 0.91(95%CI 0.82-0.95) respectively. Bland-Altman plots demonstrated more-than 90% of home spirometry values were within agreement limits of hospital values at both timepoints (Figure 1), though home values more frequently underestimated hospital values. The mean difference between spirometer measures of change over three months was small but variable (0.014 Litres, SD 0.49). Similar results were obtained when restricted to non-IPF participants specifically.

The median coefficient of variation (CoV) for all participants was 8.2% (IQR 5.6-12.1%). A slightly higher CoV was observed in the phenotypically more diverse and larger non-IPF ILD subgroup, although no significant association with CoV was observed in longitudinal analysis (coefficient 2.11, 95%CI -1.60;5.83, p=0.144) (Figure 2). Overall, weekly CoV did not significantly change (-0.22, 95%CI -0.52;0.08, p=0.144), indicating that weekly averages reliably reflect daily values for comparison to a single time point of hospital spirometry. A suggestive, non-significant reduction in variability over time may be attributable to learning and improved technique. No interaction with ILD subgroup was observed at any week.

Discussion

Our findings in the largest prospective study of mixed fibrotic ILD support the clinical utility of home spirometry in the remote monitoring of patients. Although participants were blinded, adherence to daily spirometry remained high, and was similar to adherence rates in non-blinded studies(9). We stipulated the performance of daily measures rather than a minimum number of weekly blows,(9, 10) with reliable adherence in the three-month design. Home and hospital measurements were highly correlated at complementary time points, though home spirometry tended to underestimate measurements when compared with hospital spirometry(11). The mean difference at baseline was 0.25L lower with over 90% of measurements within agreement limits. Furthermore, although variability was observed, daily measures indicated minimal influence of time or disease and was comparable to the CoV in non-blinded studies(9). Whilst we demonstrate comparability of measurements, we emphasise the importance of longitudinal modelling of daily spirometry for clinical endpoint precision.

Recent studies using home spirometry support feasibility in idiopathic pulmonary fibrosis (IPF) (9-13), but fewer data exist regarding the acceptance of home spirometry in non-IPF ILD and its comparability to hospital spirometry(14, 15). In a single centre study of mixed fibrotic ILD, including 27 non-IPF patients, there was strong correlation between hospital and home spirometry at baseline, three-months, and six-months(15). Our results in a multi-centre comprising a larger non-IPF cohort demonstrate good agreement and inter-observer reliability between home and hospital measures of FVC in fibrotic ILD. We addressed potential bias associated with participant drop out due to falling spirometry values by asking participants to perform blinded readings in a prospective study design. Additionally, this is the first study in non-IPF ILD to explore adherence according to patient reported outcomes, describing worsening in symptoms where adherence was less than 80%.

Our study was limited by modest interim sample sizes and a restricted follow up due to interim censoring attributable to the COVID-19 pandemic. Participants were asked to perform a single reading without replication to minimise potential intrusiveness of multiple daily expiratory manoeuvres. Exclusion of participants without a smartphone may have enriched the cohort to be more technically advanced in the use of home technology. Baseline hospital spirometry was obtained pragmatically as a standard of care and the acceptable timeframe from recruitment may have contributed to larger discrepancies with home spirometry at this time point compared with three-month research visits. We were unable to validate the quality of participant attempts as the handheld device did not record flow-volume loops. It is likely these factors would be compensated in longitudinal modelling

of daily spirometry, whilst the intention here was to assess comparability to hospital spirometry when evaluated as a single value.

In summary, we demonstrate that blinded, daily home spirometry in fibrotic non-IPF ILD is feasible, reliable and within acceptable levels of agreement to hospital spirometry for clinical measurement. This is likely to be particularly relevant where clinical access or trial participation is limited due to geographical factors, patient choice, service pressures and future pandemics.

Demographics	All	IPF	Non-IPF	Completed 3 months
Baseline, N	82	23	59	43
Male, n (%)	59 (72%)	19 (83%)	40 (68%)	34 (79%)
Mean age (sd)	69.8 (8.1)	70.7 (7.0)	69.4 (8.5)	70.1 (7.7)
FVC, litres (sd)	2.96 (0.88)	3.38 (0.90)	2.80 (0.82)	3.01 (0.90)
FVC, % predicted (sd)	80.6 (18.0)	85.0 (15.5)	78.9 (18.7)	80.7 (20.6)
DL_{CO}, % predicted (sd)	55.1 (16.2)	54.3 (14.6)	55.4 (16.9)	52.6 (16.4)
6MWD, m (sd)	332 (101)	354 (103)	324 (100)	330 (101)
Three months, n (%)	43 (52%)	12 (52%)	31 (53%)	43 (100%)
Median Adherence, % (IQR)	81% (61-94)	79% (53-93)	85% (61-95)	91% (79-97)
Mean decline in KBILD scores	**All**	**Adherence <60%**	**Adherence 60-80%**	**Adherence >80-100%**
Total (sd)	-0.08 (6.75)	1.66 (7.31)	0.98 (6.62)	-1.25 (6.56)
Chest domain (sd)	-1.61 (18.13)	-0.39 (15.93)	3.56 (15.93)	-4.44 (19.71)
Activities domain (sd)	1.92 (12.92)	5.38 (13.78)	1.63 (12.03)	0.68 (13.11)
Psychological domain (sd)	-1.12 (10.65)	0.72 (11.33)	-1.5 (12.08)	-1.67 (9.95)

Table 1: Baseline demographics and mean change in Kings Brief Interstitial Lung Disease health related quality of life scores between baseline and 3 months visit in total and in individual domains. Adherence calculated as number of daily readings out of 105 days. Mean values presented with standard deviation (sd); median values presented with interquartile range (IQR).

		Comparison			Agreement		Pearson correlation			Intra-class coefficient
FVC sample	N	*Mean Hosp. (SD)*	*Mean Home (SD)*	*Mean diff (SD)*	*n Outside limits*	*% Within limits*	*r*	*R2*	*P*	*Coefficient (95%CI)*
All										
Baseline	*82*	*2.96 (0.88)*	*2.71 (0.86)*	*-0.26 (0.41)*	*7*	*91.5*	*0.89*	*0.79*	*<0.0001*	*0.92 (0.75;0.96)*
3 months	*43*	*2.91 (0.93)*	*2.74 (0.90)*	*-0.17 (0.52)*	*1*	*97.7*	*0.84*	*0.70*	*<0.0001*	*0.91 (0.82;0.95)*
Δ 3 months	43	-0.103 (0.27)	-0.088 (0.44)	0.014 (0.49)	3	93.0	0.11	0.01	0.50	0.18 (-0.55;0.56)
Non-IPF ILD only										
Baseline	*59*	*2.80 (0.82)*	*2.57 (0.84)*	*-0.23 (0.39)*	*4*	*93.2*	*0.89*	*0.79*	*<0.0001*	*0.92 (0.80;0.96)*
3 months	*31*	*2.83 (0.99)*	*2.63 (0.91)*	*-0.20 (0.53)*	*0*	*100*	*0.85*	*0.72*	*<0.0001*	*0.91 (0.80;0.96)*
Δ 3 months	*31*	*-0.071 (0.23)*	*-0.082 (0.35)*	*0.012 (0.40)*	*2*	*93.5*	*0.07*	*0.01*	*0.70*	*0.13 (-0.86;0.59)*

Table 2 – Comparison of FVC shown in litres after FVC <1st and >99th percentile excluded. Values shown for all patients, and for non-IPF ILD separately. Agreement after values plotted on Bland-Altman plot, with n the total number of participants with values outside limits. Correlation presented between hospital (hosp.) and home spirometry.

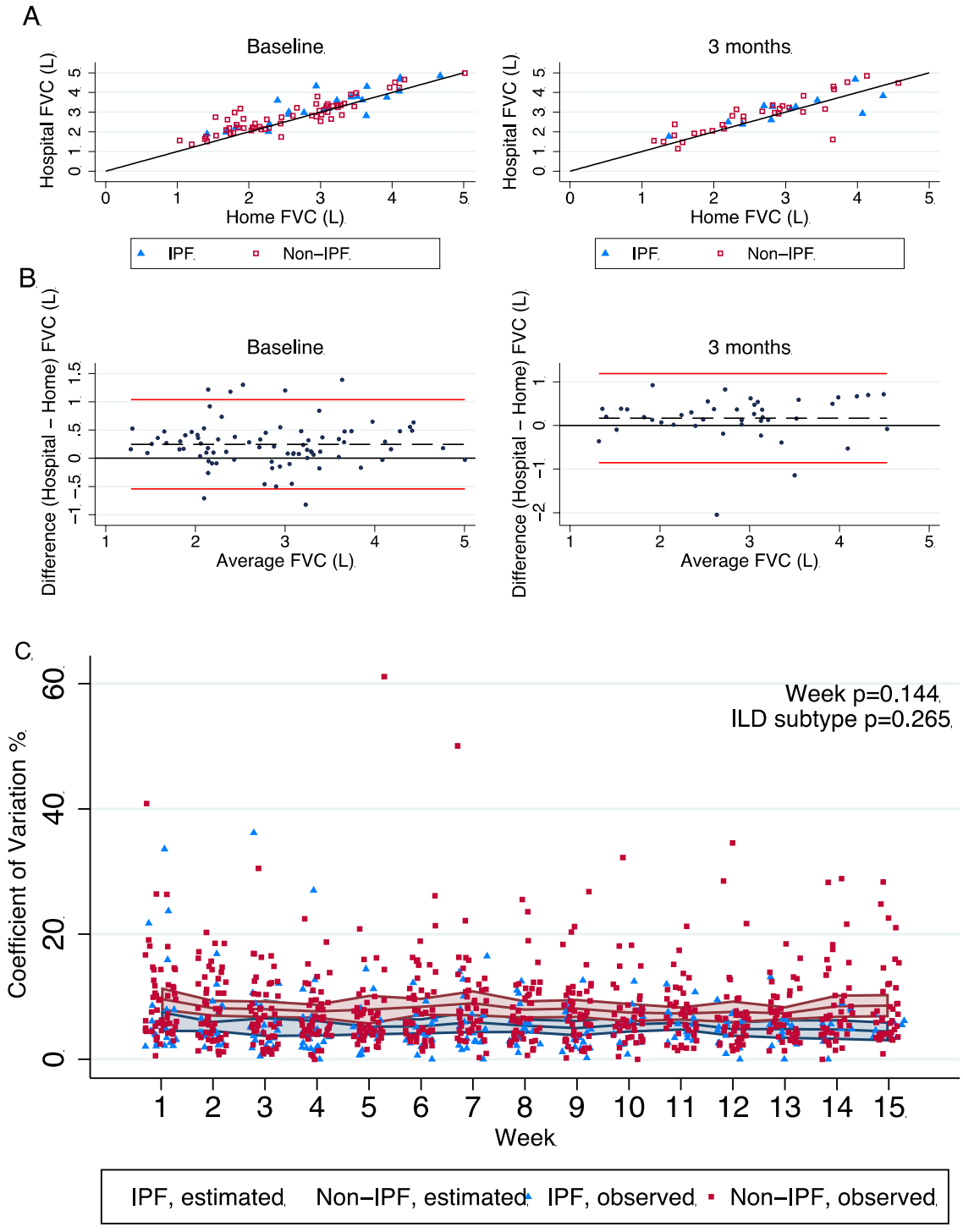

Figure 1:

A. Correlation of home and hospital FVC (litres) measurements at baseline and 3 months, coloured differently for IPF (n=23 at baseline; n=12at 3 months) and non-IPF (n=59 at baseline; n=31 at 3 months). Black reference line represents y=x.

B. Bland Altman plot for baseline and 3 months. Mean difference of hospital relative to home spirometry was 0.26L (SD 0.41) at baseline and 0.17L (SD 0.52) at 3 months. The red lines represent the 95% limits of agreement. Baseline measurements were calculated as the mean of daily readings obtained during the first seven days. Three-month measurements were calculated as the mean of readings obtained between days 90 and 96.

C. Weekly coefficient of variation (CoV) (%) in home spirometry across study time for ILD subtype. Blue and red lines represent estimated CoV (and 95% confidence intervals) in IPF and non-IPF group, respectively. Scatter points for observed individual participant weekly CoV. Number of participants included at each week (p-value for ILD subtype interaction): week 1, 76 (0.987); week 2, 72 (0.946); week 3, 73 (0.695); week 4, 69 (0.790); week 5, 70 (0.756); week 6, 69 (0.574); week 7, 68 (0.617); week 8, 65 (0.791); week 9, 63 (0.619); week 10, 59 (0.903); week 11, 58 (0.734); week 12, 58 (0.742); week 13, 55 (0.842); week 14, 52 (0.490); week 15, 46 (0.391). P values from generalised estimating equation shown for change in coefficient of variation per week, and ILD subtype (IPF and non-IPF).

References

1. Belloli EA, Wang X, Murray S, Forrester G, Weyhing A, Lin J, et al. Longitudinal Forced Vital Capacity Monitoring as a Prognostic Adjunct after Lung Transplantation. Am J Respir Crit Care Med. 2015;192(2):209-18.
2. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 2020 [Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
3. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, et al. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. European Respiratory Journal. 2010;35(4):830-6.
4. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis.[Erratum appears in N Engl J Med. 2014 Sep 18;371(12):1172]. New England Journal of Medicine. 2014;370(22):2083-92.
5. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. New England Journal of Medicine. 2019;381(18):1718-27.
6. Richeldi L, Du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. New England Journal of Medicine. 2014;370(22):2071-82.
7. Khan FS, I.//Howard, L.//McKeever, T. M.//Jones, S.//Hearson, G.//Braybrooke, R.//Edwards, C.//Jenkins, G.//Saini, G. The Its Not JUST Idiopathic pulmonary fibrosis Study (INJUSTIS): Description of the protocol for a multicentre prospective observational cohort study identifying biomarkers of progressive fibrotic lung disease. BMJ Open Respiratory Research. 2019;6 (1) (no pagination)(e000439).
8. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. The European respiratory journal. 2005;26(2):319-38.
9. Johannson KA, Vittinghoff E, Morisset J, Lee JS, Balmes JR, Collard HR. Home monitoring improves endpoint efficiency in idiopathic pulmonary fibrosis. The European respiratory journal. 2017;50(1).
10. Noth I, Cottin V, Chaudhuri N, Corte TJ, Johannson KA, Wijsenbeek M, et al. Home spirometry in patients with idiopathic pulmonary fibrosis: data from the INMARK trial. The European respiratory journal. 2021.
11. Russell AM, Adamali H, Molyneaux PL, Lukey PT, Marshall RP, Renzoni EA, et al. Daily Home Spirometry: An Effective Tool for Detecting Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2016;194(8):989-97.
12. Moor CC, Mostard RLM, Grutters JC, Bresser P, Aerts J, Chavannes NH, et al. Home Monitoring in Patients with Idiopathic Pulmonary Fibrosis. A Randomized Controlled Trial. Am J Respir Crit Care Med. 2020;202(3):393-401.
13. Marcoux V, Wang M, Burgoyne SJ, Fell CD, Ryerson CJ, Sajobi TT, et al. Mobile Health Monitoring in Patients with Idiopathic Pulmonary Fibrosis. Annals of the American Thoracic Society. 2019;16(10):1327-9.
14. Moor CC, van Leuven SI, Wijsenbeek MS, Vonk MC. Feasibility of online home spirometry in systemic sclerosis–associated interstitial lung disease: a pilot study. Rheumatology. 2020;60(5):2467-71.

15. Veit T, Barnikel M, Crispin A, Kneidinger N, Ceelen F, Arnold P, et al. Variability of forced vital capacity in progressive interstitial lung disease: a prospective observational study. Respiratory Research. 2020;21(1).