INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a debilitating lung disease characterised by progressive dyspnoea and exercise limitation (1). The prognosis for patients with IPF remains poor, despite the introduction of targeted antifibrotic medications. Pirfenidone and Nintedanib became widely used in clinical practise after clinical trials in 2014 demonstrated a reduction in lung function decline by up to 50% (2-4). While targeted antifibrotic therapies have been shown to enhance outcomes and prolong survival rates in patients with idiopathic pulmonary fibrosis (IPF), all while ensuring a high degree of safety and tolerability (2-5), it is important to note that these drugs, especially Nintedanib, can also cause significant side effects. These may include gastrointestinal issues, weight loss, and loss of appetite, which could potentially affect patient tolerance and overall quality of life (6, 7).

Key prognostic indicators in IPF include age at diagnosis, forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (D_LCO) (8). Computed tomography (CT) derived quantitative metrics provided by threshold-based segmentation tools relating to body composition (analytic morphomics) are gaining traction universally as providing potential disease-specific prognostic information. These tools can obtain additional information retrospectively or prospectively from routine imaging with implications on management in both pulmonary and non-pulmonary conditions (9-11). While it represents a relatively novel approach to assessing body composition, it was recently discussed in the European Working Group on Sarcopenia in Older People revision as a tool with potential for widespread utilisation in the future due to its significant correlation with whole body muscle (12).

Muscle cross-sectional area (CSA) at pre-defined vertebral levels correlates with the degree of airflow obstruction and overall mortality in chronic obstructive pulmonary disease (13). While in lung cancer surgery, sarcopenia as defined by lowest quartile of muscle CSA in the analysed cohort, showed increased post-operative complication rates and hospital stay (14). However, in IPF the significance of this additional non-routinely provided/requested morphomic information is less clear.

There is some evidence that sarcopenia predicts outcomes in IPF. Three previous studies assessing analytic morphomics in IPF demonstrated that low muscle CSA was a risk factor for mortality and a significant prognostic indicator independent of pulmonary function (15-17). Furthermore, a study evaluating sarcopenia via CT showed that patients with IPF, irrespective of treatment with antifibrotic medication had advanced

skeletal muscle loss (reduced erector spinae muscle CSA) without apparent weight loss. While this paper enrolled a cohort with IPF on antifibrotics, it failed to compare body composition between groups or segregate by type of antifibrotic (18).

Both Pirfenidone and Nintedanib have demonstrated similar levels of effectiveness and tolerability in various clinical experiments, including the landmark studies ASCEND and IMPULSIS (2, 4). In these trials, discontinuation rates for Pirfenidone stood at 14.4%, primarily due to gastrointestinal discomfort and skin-related complications, while the discontinuation rates for Nintedanib reached 19.3%, largely because of gastrointestinal discomfort and diarrhoea. However, in the absence of a direct prospective comparison between these two medicines, the ultimate decision is largely dependent on individual patient circumstances and physician judgment.

The primary aim of this study is to compare the change in muscle bulk and density in patients undergoing antifibrotic therapy with Pirfenidone, Nintedanib and patients who switched treatment from Pirfenidone to Nintedanib. An additional follow-up aim is to evaluate if knowledge of these parameters, considered with other established clinical and laboratory parameters, could aid clinicians in making an informed judgement on the antifibrotic agent of choice and subsequently advise patients accordingly. The secondary aim is to assess the variances in FVC and D_LCO with respect to the treatment agent and to investigate if there is a correlation with changes in muscle bulk and density.

CT morphomics of patients with IPF on antifibrotic medication, were obtained from routine thoracic CTs at pre-defined and previously validated vertebral levels and formed the basis for analysis in this study. Although the muscle morphomics at L3 vertebral are commonly used to diagnose sarcopenia, some studies have proposed pectoralis muscle within 1cm of the sternoclavicular joint and erector spinae muscles at T12 vertebral level may be used as a surrogate marker for diagnosis. (18, 19).

We hypothesise that changes in body composition over time, as indicated by cross-sectional muscle area and muscle density measured in Hounsfield units (HU) may be treatment-dependent. This finding may help clinicians decide which antifibrotic medication may be most suitable for patients with poor baseline muscle morphomic parameters.

MATERIALS AND METHODS

Study Type

A retrospective study was carried out in accordance with institutional review board (Clinical Research Ethics Committee) ethical approval.

Demographics

Patients with a known diagnosis of IPF confirmed at a regional ILD multidisciplinary meeting and attending a regional ILD centre for specialist management between 2014 and 2020 were included. Eighty-four patients were included in the final analysis (n=84). Only patients suitable for treatment with targeted antifibrotic medications Pirfenidone, Nintedanib or a treatment change from Pirfenidone-Nintedanib during the study period, were included. Patients whose disease was end-stage or patients who could not tolerate either medication were excluded. In addition, patients considered highly frail and patients with significant liver disease were also excluded due to the high likelihood of poor drug tolerance and worsening frailty.

Clinical Data

Data obtained from our institutional IPF database included patient demographics, baseline (t=0) blood tests (urea, creatinine, albumin), pulmonary function tests including FVC (L) and D_LCO (mmol/kPa/min), both expressed as absolute values, CT-derived morphomics, and antifibrotic treatment received during the study period. After an interval, an additional set of the same data was collected and analysed (t=1). This interval time was recorded as the duration between CT scans with separate biochemistry and pulmonary function testing occurring within three months of each CT scan, respectively (t=0) and (t=1).

Morphomic Data

Morphomic analysis was performed on previously acquired CT imaging of the thorax. All imaging data were accessible through the institutional picture archive communication system (PACS). CT images were acquired using 64-slice multidetector row CT scanners (GE Medical Systems Discovery CT 750HD, GE Medical Systems Lightspeed VCT, GE Medical discovery STE, GE Healthcare, Waukesha, WI, USA). The scan parameters were a tube voltage of 120 kVp and automated tube current modulation 50-400 mA. Of the 168 (92 Pirfenidone, 76 Nintedanib) individual images analysed, 98 (55 in Nintedanib, 43 in Pirfenidone) received intravenous contrast (Iohexol, Omnipaque 300, GE Healthcare, Waukesha, WI, USA), 22 of these were dedicated CT pulmonary angiograms and 7 were as part of combined CT thorax, abdomen, and pelvic

protocols. All included studies had a slice acquisition of 1.25 mm independent of the scan protocol. Studies that did not include the entire thorax or were deemed unsuitable for morphometric analysis, due to artefact were excluded. CT scans of the thorax were assessed by two independent pulmonary radiologists, with a specialist interest in ILD.

Images were analysed using CoreSlicer, a web-based tool that that has been validated against "slice-O-matic", a commercially available cadaver-validated image analysis software. Although CoreSlicer enables semi-automated muscle segmentation (-29 to +150 HU) and fat (-190 to -30 HU), occasional manual corrections of the areas highlighted as muscle or fat were required. This was made easily possible with the embedded brush and eraser plugins within CoreSlicer (20). On a single axial slice at the level of the lower margin of the 12th thoracic vertebrae, erector spinae muscle (ESM) cross-sectional area (CSA) and average attenuation in HU were calculated. A further single axial slice within 1 cm of the sternoclavicular joints was used to calculate these parameters for pectoralis muscle (PM) (Figure 1).

Statistical Analyses

Data compilation and statistical analysis were performed using Microsoft Excel 2011 (Microsoft Corporation, Washington, USA), Statistical Package for the Social Sciences (SPSS) version 28 (IBM, Chicago, Illinois, USA) and Jamovi version 2.3.21 (The Jamovi Project 2024, Sydney Australia). Intra-class correlation coefficient (ICC) was used to assess for interobserver bias between the two readers. Wilcoxon-signed rank, Kruskal-Wallis or the Mann-Whitney tests were used to compare median values for non-parametric data. A p-value of < 0.05 was considered significant. Bivariate analysis with Spearman rank correlation coefficient was used to determine correlation between clinical and morphomic variables and lung function. All comparisons were made using delta values, i.e., the change in the clinical/pulmonary function/morphomic parameters over the two-time points.

RESULTS

Patient Demographics

Eighty-four patients diagnosed with IPF between April 2012 and October 2020 met the criteria for inclusion. Seventy-nine per cent were male (n=66). A median age of 73 years (IQR: 66-77) and body mass index (BMI)

of 27.3 Kg/m2 (IQR: 25-30, min: 17.6, max 42.1). Sixty-nine percent (n=58) were former, 29% (n=24) never and 2% (n=2) were current smokers.

Fifty-five per cent (n=46) were initially commenced on Pirfenidone and received it exclusively throughout the study. Of the remaining 45% (n=38) on Nintedanib, 26% (n=22) received it exclusively, while 19% (n=16) represented a group who had a treatment change during the course of the study, predominantly due to drug side effects, i.e., Pirfenidone-Nintedanib (treatment change group). The median interval between imaging was 16.5 months (IQR: 11-28) (Table 1).

Entire Group

In the whole group (n=84) over the study period, FVC changed by a median of -4% (-11, +2%, $p < 0.001$), D_LCO by -9% (-24, +0.4%, $p < 0.001$) and albumin by -2% (-10, +5%, $p = 0.014$). Urea and creatinine did not significantly change (Supplementary 1).

The PMA changed by -6% (-15, +6%, $p = 0.022$) and ESMA by -7% (-19, +8%, $p = 0.015$). Density in each muscle group did not significantly change (Supplementary 1).

There were no direct correlations between morphomic and pulmonary function metrics (Supplementary 2).

The intra-class correlation coefficients between readers for the analysed morphomics were excellent (R-values > 0.9) (Supplementary 3).

Trichotomized Treatment Group Comparison

Patients in the Pirfenidone group had a more marked decrease in FVC with a median change in FVC of -0.14L ($p = 0.031$) compared with -0.04L and -0.05L in the Nintedanib and Pirfenidone-Nintedanib treatment change group respectively. However the difference was only statistically significant when comparing Pirfenidone with Nintedanib (p = 0.029). Pirfenidone also showed a more marked median decrease in D_LCO of -1.90 mmol/kPa/min compared with -0.93 mmol/kPa/min and -0.45 mmol/kPa/min in the Nintedanib and Pirfenidone-Nintedanib treatment change group respectively. This difference was statistically significant when comparing Pirfenidone with the treatment switch group (p = 0.048)

The change PMA and ESMA was significant when comparing the three treatment groups ($p < 0.0017$ and 0.008 respectively). However, Post-Hoc testing did not find any significant differences in PMA or ESMA

between the Nintedanib and Pirfenidone groups. Although there was a statistically significant difference seen in the PMA and ESMA when comparing the Pirfenidone group with those that switched treatment, this is to be expected as those that experienced significant side effects and could no longer tolerate the drug, switched treatments. Kruskal-Wallis testing of PM and ESM change in attenuation found no statistically significant difference between the three treatment groups. The Pirfenidone group had a median change in PMA of -1.11 cm^2 (-3.9, +4.21) and ESMA of -0.36 cm^2 (-3.94, +2.77). The Nintedanib group had far larger median change in PMA of -6.47 cm^2 (-8.79, +4.57) and ESMA of -2.43 cm^2 (-6.43, + 5.81), however this difference between the two groups was not statistically significant. This may be due to the relatively small sample size of patients in the Nintedanib group and the small effect size of the change in PMA and ESMA (Glass's Δ = -0.489 and -0.247 respectively).In the Pirfenidone-Nintedanib treatment change group, the median change in PMA was -4.49 cm^2 (-8.96, -1.70) and ESMA -5.30 cm^2 (-6.57, -2.38) (Table 2), (Figure 2).

Stratified subgroup analysis with inclusion of pre-treatment BMI reveals a statistically significant greater PMA loss in the Nintedanib group as compared to the Pirfenidone group (Mean difference, -4.97, p = 0.015) when the BMI was <30. This was not seen in those with a pre-treatment BMI of ≥30. While subgroup analysis with BMI groups with clinically relevant cut offs of <25, 25-30 and >30 was originally planned, this was not possible due to the small number of patients with BMIs of <25 (1 in the Nintedanib group and 6 in the treatment switch group). Therefore, the authors decided on a BMI of 30 as the cut off to compare obese vs non obese patients. Change in ESMA was not statistically different in between the Nintedanib and Pirfenidone groups in either the <30 BMI or ≥30 BMI category. Comparison of those who switched treatment (i.e. those previously on Pirfenidone) with Nintedanib showed no statistically significant difference in change in ESMA and PMA in either the <30 or >30 pre-treatment BMI categories.

Treatment Group Correlation

There were no direct correlations between pulmonary function and morphomics. Although one may expect a linear relationship between muscle bulk loss and decline in respiratory function, the data from our patient cohort did not support this hypothesis. It is likely, the effect of antifibrotics on muscle tissue is independent to its effect on pulmonary architecture. (Supplementary 2)

DISCUSSION

The IPF group represent a patient cohort who are routinely exposed to thoracic CT for qualitative analysis of lung parenchymal disease. Easily attainable quantitative morphomic data is often neglected or, if not, done in a descriptive ad-hoc and non-objective manner (20). This 'real life' study demonstrates that patients with IPF receiving antifibrotic therapy exhibit a decrease in pectoral and erector spinae musculature cross sectional area, evident on morphomic analysis. The progressive decline in pulmonary function demonstrated in our patient cohort over the study period is a hallmark of IPF. There were no direct morphomic correlations with pulmonary function, suggesting morphomic variables as independent risk factors.

As shown in previous studies, there was no statistically significant difference in loss/preservation of pulmonary function (FVC and D_LCO) between the Pirfenidone and Nintedanib group.

However, in terms of morphomics, the results show that differences exist in rate of muscle bulk loss depending on the treatment received. Although when considering the groups as a whole, only those patients who switched treatments had a statistically significant difference in muscle bulk loss, subgroup analysis offers further insight. The subgroup analysis shows that in patients with a pre-treatment BMI below 30, Nintedanib causes a statistically significant greater loss of PMA. This novel finding offers an important point to consider for clinicians who are deciding between these two treatment options, particularly in those patients who have a below 30 pre-treatment BMI. Although Nintedanib and Pirfenidone have similar efficacy, given the findings of this study, in the absence of contraindications, clinicians should use Pirfenidone over Nintedanib in those with BMI <30 as a first line treatment.

While the reason for the lack of correlation between pulmonary function and morphomic variables is not definite, the authors hypothesize that the antifibrotic agents have differential effects on muscle tissue independent of their impact on pulmonary fibrosis. It is likely that the effect of these drugs on peripheral skeletal muscle is independent of their role in slowing pulmonary disease progression.

Patients with IPF receiving antifibrotic treatment frequently experience weight loss that can be associated with worse outcomes. 10% weight loss is commonly utilised as a crude clinical measurement of prognosis

and prompts consideration for treatment change (21, 22). Morphomic data offers an objective metric in this regard.

Maintaining adequate nutritional status during anti-fibrotic treatment can be difficult with studies showing both Nintedanib and Pirfenidone can cause loss of appetite. Although the amount weight loss and reduction in appetite does not appear to differ between the two treatments, Nintedanib causes significantly more vomiting and diarrhoea compared to Pirfenidone (7). The authors hypothesize, that this difference in side effect profile could explain the increased loss of muscle bulk in the Nintedanib group with a BMI <30 in our cohort.

Sarcopenia is present in approximately 10% of the general healthy population (23), but more than doubles when assessing hospitalised inpatients (24). In IPF, chronic respiratory failure and acute pulmonary exacerbations are the most prominent contributors to mortality. However, as previously discussed, several papers have shown sarcopenia and muscle mass changes to be independent predictors (15, 16, 18). This study adds to the growing literature evidence of muscle loss in IPF, with the pectoralis and erector spinae muscles being affected.

Given the negative consequences of sarcopenia and its association with antifibrotic agents as shown in this study, dietician referral and physiotherapy with resistance training should be offered to all patients commencing on these agents. In addition, consideration should be given to the Mediterranean diet as it has been implicated as a potential protective factor against gastrointestinal side effects (25). The authors suggest regular monitoring of muscle mass, possibly using image analysis software on routine CT scans, as well as BMI measurements to ensure those patients with a significant decline in muscle mass are identified early and treated appropriately.

Indeed, within the authors' institution, dietician referral, physical therapy referral and regular BMI measurements are part of routine practice when commenced on anti-fibrotic treatment.

The findings presented herein raise the question of whether other body tissues are similarly affected by these antifibrotic agents. Hence, future research could focus on measurement of whole body composition to assess the effects of these antifibrotic agents on visceral, parietal and subcutaneous fat and density as well as bone mineral density. With the advent of semi-automated segmentation software such as CoreSlicer, analysis of routine thoracic CTs in this vulnerable patient cohort becomes easy and has the potential to offer important clinical information without subjecting patients to any further tests. Indeed, in the near future, it may be possible to incorporate morphomic analysis into routine clinical practice.

The present study has several limitations. The results were obtained from a single tertiary referral centre by retrospective analysis. The cohort size was modest. There was no untreated group on no antifibrotic treatment as a consequence of the demonstrable efficacy of targeted antifibrotics. There is a subjective element to the morphomic analysis where visual confirmation of correct segmentation is required. Different imaging protocols being included in the study with different intravenous contrast timing and concentration introduced heterogeneity in muscle density assessment. In addition, physical activity levels between patients may differ and engagement with physiotherapy regimens varies between patients. This confounding factor may in turn affect the muscle CSA and densities. Further studies in a larger replication cohort will be required to validate our observations.

CONCLUSION

The findings in this study suggest that in patients suffering from idiopathic pulmonary fibrosis, the choice of antifibrotic agent may influence the rate of muscle bulk loss over time. Nintedanib was found to have a statistically significant greater loss of pectoralis muscle bulk in comparison to Pirfenidone in patients who had a pre-treatment BMI of below 30. This finding suggests Pirfenidone should be used over Nintedanib in the treatment of IPF in patients with a BMI <30. However, further studies with larger samples sizes are required to strengthen our findings.

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TABLES

Table 1: Comparison of baseline demographics between treatment groups.

	Pirfenidone Median (n=46)	**Nintedanib Median (n=22)**	**Pirfenidone-Nintedanib Median (n=16)**	***p* - value**
Gender (Male)	80%	73%	81%	0.77
BMI (kg/m^2)	27 (25 – 29)	29 (26 – 32)	28 (25 – 32)	0.21
Smoking status (Former)	70%	64%	75%	0.55
Imaging Interval (Months)	17.5 (11 – 28)	13.5 (10 – 23)	18.5 (11 – 37)	0.39
Index FVC (L)	2.78 (2.43 – 3.15)	2.51 (1.77 – 2.96)	2.69 (2.4 – 3.14)	0.33
Index D_LCO (mmol/kPa/min)	11.94 (9.5 – 14.53)	14.26 (11.69 – 17.21)	12.36 (9.08 – 13.81)	0.13

BMI Body mass index, *D_LCO* Diffusing capacity for carbon monoxide, *FVC* Forced vital capacity, *kg/m^2* Kilogram per metre squared, *mmol/kPa/min* Millimole per kilopascal per minute, *n* Number of patients.

Table 2: Comparison of median change (Δ) in pulmonary function and morphomics between treatment groups over the duration of the study (T0 to T1)

	Pirfenidone (n=46)	**Nintedanib (n=22)**	**Pirfenidone-Nintedanib (n=16)**	***p*-value**
Pulmonary Function Tests				
Δ FVC (L)	-0.14 (0.341)	-0.06 (0.263)	-0.04 (0.233)	**0.02**
Δ D_LCO (mmol/kPa/min)	-1.90 (3.45)	-0.93 (2.52)	-0.45 (1.82)	**0.05**
Morphomics				
Δ Pectoralis Muscle Area (cm^2)	-1.1 (9.31)	-6.47 (11.7)	-4.49 (4.75)	**0.0017**
Δ Pectoralis Muscle Density (HU)	-1.03 (8.71)	-5.08 (13.1)	-0.28 (10.02)	0.124
Δ Erector Spinae Muscle Area (cm^2)	-0.36 (5.33)	-2.43 (8.08)	-5.3 (5.56)	**0.008**
Δ Erector Spinae Muscle Density (HU)	0.90 (6.75)	-1.24 (12.0)	1.48 (11.4)	0.247

Boldface indicates statistical significance. Values are displayed as the median difference followed by the standard deviation in brackets. Δ Change in parameter, *cm^2* Centimetre squared, *D_LCO* Diffusing capacity for carbon monoxide, *FVC* Forced vital capacity, *HU* Hounsfield unit, *L* Litres, *mmol/kPa/min* Millimole per kilopascal per minute, *n* Number of patients, *T0* Initial time point, *T1* Follow-up time point.

FIGURE LEGENDS

Figure 1:

Title: Example of pulmonary fibrosis and segmentation of pectoralis and erector spinae musculature for morphomic analysis.

Description: Non contrast CT thorax demonstrating pulmonary fibrosis in coronal (A) and axial (B) planes in lung windows and in the same patient, demonstrating the ability of the analytic morphomic software CoreSlicer in segmenting the pectoralis musculature (C) (red) and erector spinae musculature (D) (red) in axial soft tissue windows. Excellent interrater reliability was noted with values >0.9 for all morphomic variables.

Figure 2.

Title: Box and whisker plot showing change in CSA of PM and ESM for each treatment group.

Description: Evident trend between treatment groups is the greater the decrease in pulmonary function the greater the relative preservation of muscle *CSA* Cross sectional area. Box plots represent median change in parameter with whiskers representing quartiles and circles representing individual data points.