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Cause of Mortality and Sarcopenia in Patients with Idiopathic Pulmonary Fibrosis Receiving Anti-Fibrotic Therapy

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Summary at Glance

Skeletal muscle wasting (sarcopenia) without obvious weight loss is commonly found in patients with IPF receiving antifibrotic therapy. Most study patients died of chronic respiratory failure and skeletal muscle loss was associated with worse outcomes in antifibrotic therapy, suggesting that sarcopenia prevention is crucial for patients with IPF.

ABSTRACT

Background and objective: Recent research has highlighted the fundamental role of sarcopenia, characterized by loss of skeletal muscle mass and strength, with a risk of poor outcomes. Anti-Fibrotic Therapy (AFT) preserves lung function by preventing the annual decline in forced vital capacity (FVC) and is associated with improved outcomes in patients with idiopathic pulmonary fibrosis (IPF). However, altered cause of death and prognostic implications of sarcopenia in patients with IPF receiving AFT remain unknown.

Methods: This study comprised two cohorts of patients with IPF receiving AFT, historical cohort of IPF patients without AFT and controls. The cause of mortality was compared with a historical cohort. Sarcopenia was assessed by measuring the cross-sectional area (ESM_{CSA}) and muscle-attenuation (ESM_{MA}) of erector spinae muscles via computed-tomography.

Results: Patients with IPF had smaller ESM_{CSA} and lower ESM_{MA} but similar body mass index (BMI) than controls, suggesting patients with IPF had skeletal muscle loss without any obvious body weight loss. The most common cause of mortality in patients receiving AFT was chronic respiratory failure, accounting for approximately 60%, and decreased proportions of lung cancer were found. Subsequently, low ESM_{CSA} was an independent prognostic factor associated with worse survival rates. Furthermore, combined assessment of ESM_{CSA}, %FVC-predicted, and BMI values provided clear prognostic distinction.

Conclusion: Patients with IPF receiving AFT showed skeletal muscle loss without obvious weight loss. These patients mostly died by chronic respiratory failure, and skeletal muscle wasting has prognostic significance, suggesting that preventing sarcopenia as well as preserving lung function is important for managing these patients. (250 words)

Keywords: Antifibrotic therapy, Idiopathic pulmonary fibrosis, Skeletal muscle loss, Sarcopenia

Running title: Sarcopenia in IPF receiving antifibrotics

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial lung disease (ILD) with unknown etiology [1, 2]. It is characterized by progressive worsening of dyspnea and lung function, resulting in poor prognosis [3, 4]. Two antifibrotic drugs, nintedanib and pirfenidone, have been shown to reduce the decline in forced vital capacity (FVC) [5-8].

Sarcopenia is a progressive and generalised loss of skeletal muscle mass and strengthen, that is associated with adverse outcomes [9-11]. Sarcopenia is commonly found with advanced respiratory disease, and the associated changes in body composition and muscle wasting, as evaluated by computed tomography (CT), have been reported as significant prognostic determinants in patients with and without cancer, including those with nontuberculous mycobacterium and ILD [12-15]. The fundamental role of sarcopenia is its involvement in the pathogenesis of disease progression as well as in therapeutic targets.

Besides its efficacy on the annual rate of decline in FVC, emerging evidence has confirmed that AFT reduces the risks of acute exacerbation (AE) [16], respiratory-related hospitalization [17], and disease progression [18]. However, AFT was administered to only 60% of patients with IPF and certain time lags existed between diagnosis and AFT initiation. Furthermore, sufficient evaluation has not been done to determine disease course and prognostic determinants in patients with IPF based on the characteristics measured at AFT initiation. Moreover, the clinical implications of sarcopenia in AFT remain unassessed. Therefore, this study examined the disease course and prevalence of skeletal muscle loss in patients with IPF receiving AFT by measuring the cross-sectional area (ESM_{CSA}) and muscle-attenuation (ESM_{MA}) of erector spinae muscles, as determined by CT.

METHODS

Study patients

This retrospective study was conducted using two cohorts of patients with IPF who underwent CT at AFT initiation. The two cohorts comprised 106 and 102 consecutive patients with IPF who were administered AFT at the Hamamatsu University School of Medicine and Seirei Hospitals. The diagnosis of IPF was based on the ATS/ERS/JRS/LATA criteria [19]. The study also enrolled 80 consecutive patients with IPF who did not treated with AFT as a historical-cohort, and 72 age- and sex-matched controls. Details were described in the Supplementary Appendix S1.

The study protocol was approved by the Ethical Committee of Hamamatsu University School of Medicine (17-196) and was conducted according to approved guidelines. The need for patient approval and/or informed consent was waived due to the retrospective nature of the study.

CT image analysis

Chest-CT images at the time of AFT initiation were used. Single-slice axial CT images taken at the lower margin of the 12th thoracic vertebra (Th12) were selected to measure ESM_{CSA}. After imaging, ESMs were identified and manually shaded; ESM_{CSA} quantification was based on Hounsfield unit (HU) thresholds (-29–150), and mean ESM_{MA} (HU) levels were assessed using a previously described method [12-14]. Images were analysed using SYNAPSE VINCENT version 3 software (Fujifilm Medical Systems, Tokyo, Japan). Details were described in the Supplementary Appendix S1.

Data collection

Clinical data were obtained from patients' medical records. Laboratory findings and pulmonary function test results obtained at the time of AFT initiation were recorded.

Statistical analysis

Discrete variables were expressed as total (percentages) and continuous variables as median (interquartile range). The Mann-Whitney U test and Fisher's exact test for independence were used to compare continuous and categorical variables, respectively. Overall survival time was measured from the date of AFT initiation. Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model. Cumulative survival probabilities were estimated above and below the cutoff of ESM_{CSA}, body mass index (BMI), and %FVC-predicted using the Kaplan-Meier method and log-rank test. Statistical analyses were performed using GraphPad Prism Version 6 (GraphPad Software, San Diego, USA) and SPSS Statistics (Ver23, IBM Corporation, Armonk, USA). All analyses were two-tailed, and p-values < 0.05 were considered to be statistically significant.

RESULTS

Clinical characteristics

The clinical characteristics are summarized in **Table1**. Patients in both cohorts were approximately 70 years of age. The proportions of IPF/UIP was higher in the Hamamatsu-cohort. The AFT initiation occurred more than 2 years after diagnosis in >40% of patients with IPF. Pirfenidone was more commonly used in the Hamamatsu-cohort than in the Seirei-cohort. The majority of patients in both cohorts showed severe-to-moderate restrictive spirometric impairment and decreased lung diffusion capacity for carbon

monoxide (DLCO). Long-term oxygen therapy (LTOT) and immunosuppressant administration were more frequent in patients from the Seirei-cohort than in those from the Hamamatsu-cohort.

Measurements of ESM_{CSA} and ESM_{MA}

The distributions of ESM_{CSA}, ESM_{MA}, and BMI are presented in **Figures1A-1C**. The distributions of ESM_{CSA} and ESM_{MA} were significantly smaller and lower in patients with IPF from the Hamamatsu-cohort than in controls ($p < 0.0001$ and $p = 0.0008$, respectively). However, no difference was found in BMI values.

Patients from the Seirei-cohort, similar to those from the Hamamatsu-cohort, exhibited smaller ESM_{CSA} and decreased ESM_{MA} levels than the controls ($p < 0.0001$ and $p = 0.0039$, respectively), and there was no significant difference in the BMI values. However, no significant differences were found in the values of ESM_{CSA}, ESM_{MA}, and BMI between the two cohorts.

The correlations are presented in **TableS1**.

Prognostic value of ESM_{CSA} in patients with IPF treated with AFT

During the observation period, 59 patients from the Hamamatsu-cohort and 64 from the Seirei-cohort died. The median survival time was 34.0 months and the 5-year survival rate was 19.4%; these values were similar for both cohorts (Supplementary **Figure S1**). The causes of death were also similar between the cohorts. Approximately 60% of patients with IPF died due to chronic respiratory failure, followed by AE in approximately 20%-30% of patients from both cohorts (**Table2**). On the other hand, the incidence of lung cancer (LC) was <10%. Due to unexpected results of prognostic determinants, the cause of mortality was compared between patients treated with or without AFT. Compared with a historical-cohort

of IPF patients who did not treated with AFT (Supplementary **TableS2 and FigureS2**), the frequencies of chronic failure were significantly increased and incidences of LC were decreased (**Table2**).

Receiver operating characteristic curve analysis was performed to evaluate the efficacy of ESM_{CSA}, BMI, and %FVC-predicted values for predicting prognosis. Due to differences in body composition between men and women, separate cut-off values were set for ESM_{CSA} for the two sexes. The identified optimal cut-off values are shown in **TableS3**. The ESM_{MA} values were not significant (data not shown).

For patients from the Hamamatsu-cohort, smaller ESM_{CSA}, lower BMI, and reduced %FVC-predicted values were significantly associated with worse survival (**Figure2A-2C**). Similarly, in the Seirei-cohort and the combined cohorts, patients with IPF with smaller ESM_{CSA}, decreased BMI, and %FVC decline showed significant association with poor prognosis (**Figure2D-2I**).

Univariate and multivariate analyses

In addition to well-known parameters, such as age, %FVC-predicted levels, and %DLCO, univariate analyses revealed significances of muscle wasting and nutrition parameters. Given that age and sex often deviate in accordance with body mass, we performed adjusted multivariate analyses using age and sex (**Table3**). In multivariate analysis-1, ESM_{CSA}, BMI, %FVC-predicted, and %DLCO values were independently associated with mortality in patients with IPF. Similarly, in multivariate analysis-2, when the optimal cut-off values were applied, only ESM_{CSA}, BMI, and %FVC-predicted values were found to be significant factors of mortality.

Clinical utility of assessing body composition changes for prediction of prognosis

As body composition-related parameters and %FVC-predicted values showed relatively high sensitivities of approximately 80%. We hypothesized that the combined use of these parameters would provide a strong indication of the prognosis in practice. Therefore, we further assessed the prognostic utility of the combinations of two of the three parameters based on the above-mentioned optimal cut-off values. Patients were categorized into the following three groups: (1) those in whom both values were above the cut-off; (2) those in whom both values were below the cut-off; and (3) remaining patients. Patients with "lower ESM_{CSA} and lower BMI," "lower ESM_{CSA} and lower %FVC-predicted," and "lower BMI and lower %FVC-predicted" values had the worst prognoses (**Figure3A–C**). In particular, the combined use of ESM_{CSA}, %FVC-predicted, and BMI values successfully distinguished the prognoses.

DISCUSSION

The present study demonstrated that patients with IPF receiving AFT exhibited advanced muscle wasting without obvious weight loss, and mostly died by chronic respiratory failure, up-to 60% of deaths. Prognostic analyses revealed that smaller ESM_{CSA} and lower BMI and %FVC-predicted values at the initiation of AFT were independent prognostic factors associated with worse survival rates, and were enabled better prognostic predictions.

Clinical trials have demonstrated that nintedanib and pirfenidone inhibit the annual rate of decline of FVC in patients with IPF [5-8]. The efficacy of AFT on lung function was consistent in patients with IPF with preserved lung function as well as in those with impairments in lung function [18, 20-22]. Furthermore, the effects were sustained for a long time [23], suggesting that prompt treatment is beneficial for patients with IPF. However, studies have reported that only 50%-60% of patients receive AFT in clinical settings [3, 24, 25]. Similarly, in our cohort, >40% of patients with IPF started AFT more than 2 years after the diagnosis. In addition, 36% of patients were already on LTOT at AFT initiation. These data suggest that administration of antifibrotic drugs was not done early enough. Considering that AFT decreases disease progression by reducing the annual rate of decline of FVC, our data indicate that prompt treatment will improve the prognoses of patients with IPF.

The present study also examined the prognoses of patients with IPF receiving AFT and found that the most common cause of death was chronic respiratory failure (59.3%), followed by AE (24.4%) and LC (5.7%). Compared with our historical-cohort data, frequencies of LC development and AE (but not significant) were decreased, and proportions of chronic respiratory failure were increased. Interestingly, a study conducted in Hokkaido examined Japanese patients with IPF diagnosed between 2003 and 2007 (i.e., before the establishment of AFT) and found that AE was the most common cause of death (40%) and

that the incidence of LC was twice as high as that in our cohort (11%). On the other hand, chronic respiratory failure accounted for only 24% of deaths [26]. Data from clinical trials (over 52 weeks) have suggested that nintedanib and pirfenidone are effective in reducing the risk of AE [16] and respiratory-related hospitalization [17]. In addition, a retrospective study has reported decreased incidence of LC development in patients with IPF treated with pirfenidone [27]. Consistent with these studies, the present study suggests that decreased incidence of AE and LC development resulted in the observed increased proportion of chronic respiratory failure in patients treated with AFT. Collectively, our results suggest that AFT has potent capabilities to alter the disease course of IPF by inhibiting AE and LC development besides preserving lung function.

Sarcopenia is a progressive and generalised skeletal muscle disorder that involves accelerated loss of muscle mass and functions [9-11]. CT can be used to measure muscle mass loss by measuring the skeletal muscle cross-sectional area, such as ESM_{CSA}, and lipid deposition by measuring skeletal muscle attenuation, such as ESM_{MA} [28, 29]. Body weight loss is a typical feature of advanced respiratory disease, particularly in patients with nontuberculous mycobacterium and pleuroparenchymal fibroelastosis. In these patients, significantly lower BMI and smaller ESM_{CSA} have been reported, but the levels of ESM_{MA} were comparable with those of healthy controls [12, 13], indicating loss of both muscle and fat mass in these patients. On the other hand, this study showed smaller ESM_{CSA} values together with decreased ESM_{MA} levels in patients with IPF at the initiation of AFT. We have also previously shown that patients with IPF exhibited smaller ESM_{CSA} and equivocal ESM_{MA} levels at the time of diagnosis [12]. These data suggest that patients with IPF exhibited skeletal muscle loss with increased lipid deposition rather than loss of fat mass. Importantly, these changes were progressed covertly without any obvious weight loss in the majority of patients with IPF. This emphasizes the need for physicians to be aware of the distinct patterns and

features of sarcopenia in patients with IPF and to not rely solely on observed weight loss before suspecting sarcopenia.

To date, several prognostic factors have been identified in patients with IPF; age, %FVC-predicted, %DLCO levels, distance walked in the 6-minute walk test, pulmonary hypertension, greater extent of fibrosis on chest CT, and the Gender–Age–Physiology (GAP) model [30-34]. However, most studies were conducted using parameters at the time of IPF diagnosis, and little data are available to estimate prognosis at the initiation of AFT. Therefore, the present study used data from the time of AFT initiation to confirm the efficacy of %FVC-predicted values as well as body composition parameters in predicting the prognoses of patients with IPF receiving AFT. Moreover, we found that the combined use of %FVC-predicted and ESM_{CSA} and BMI values yielded better prognostic predictions. Collectively, these results suggest the involvement of body composition changes in the prognosis of patients with IPF and that the disruption of sarcopenia could be a potential therapeutic target.

Indeed, pharmacological and non-pharmacological approach that prevent muscle wasting have been vigorously explored. Though, no specific drugs were approved for sarcopenia, non-pharmacological intervention, resistant-based training (physical activity) was strongly recommended in the international guideline for sarcopenia[35]. However, to achieve the benefits continuously, there were hurdles for keeping compliances. Recently, *Naito et al* reported that multimodal intervention combining home-based low-intensity exercise and nutrition counselling program had shown excellent feasibility and safety in elderly patients with cancer cachexia [36]. Therefore, this multimodal approach might be also adopted to patients with IPF, especially those exhibiting skeletal muscle wasting. Subsequently synergistical benefit together with AFT might be obtained.

The present study has several limitations. First, although we used two cohorts of patients with IPF, this was a retrospective study. Further, longitudinal changes were not examined. Second, comorbidities and lifestyle, such as exercise, that can be attributed to skeletal muscle loss were not assessed in details. Third, although there are several methodologies to evaluate sarcopenic changes, this study used only the measurement of muscle wasting by CT images. Thus, multidimensional assessments are necessary to assess the involvement of body composition changes in the prognosis of patients with IPF in greater detail. Furthermore, although we found alternations in prognostic determinants before and after AFT development in patients with IPF, the number of patients may have been insufficient to derive definite conclusions. Therefore, a further prospective study is required to overcome these limitations.

In conclusion, the present study investigated cause of mortality and prognostic implications of sarcopenia in patients with IPF treated with AFT. Interestingly, we detected skeletal muscle wasting was accompanied without obvious body weight loss, indicating that sarcopenia in patients with IPF proceeded covertly. Importantly, altered cause of mortality were also found: decreased proportions of AE and LC development resulted in increased proportions of chronic respiratory failure. Subsequently, lower ESM_{CSA} levels were an independent prognostic factor associated with poor prognosis in patients with IPF receiving AFT. Furthermore, the combination of ESM_{CSA}, %FVC-predicted and BMI values yielded better prognostic distinctions. These results suggest that assessing sarcopenia is useful for predicting prognosis and that intervention to maintain skeletal muscles could improve the outcomes of patients with IPF.

Data availability statement:

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Author contributions

YS: Conception and design, data collection, data analysis and interpretation, manuscript writing, and final approval of manuscript. YA, KM, HH and KY: Conception and design, data collection, and data analysis. HN, HH, MK, KF, NE, TF, YN, NI and HN: Data collection, data analysis, and supervision. TS: Conception and design, manuscript writing, and administrative support.

Abbreviations:

IPF: idiopathic pulmonary fibrosis

ILDs: interstitial lung diseases

FVC: forced vital capacity

AFT: antifibrotic therapy

ESM_{CSA}: cross-sectional area of erector spinae muscles

ESM_{MA}: mean attenuation of erector spinae muscles

BMI: body mass index

DLCO: diffusing capacity of the lung for carbon monoxide

KL-6: Krebs von den Lungen-6

LTOT: long-term oxygen therapy

AE: acute exacerbation

LC: lung cancer

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FIGURE LEGENDS

Figure 1. Prevalence of changes in body composition in patients with IPF receiving antifibrotic therapy.

The distributions of ESM_{CSA} (A), ESM_{MA} (B), and BMI (C) in patients with IPF from the Hamamatsu and Seirei cohorts and controls; p-values were determined by the Mann–Whitney U test.

Figure 2. Prognostic impact of body composition changes in patients with IPF receiving antifibrotic therapy.

Kaplan–Meier curves of patients with IPF to ESM_{CSA} (A, D, G), BMI (B, E, H), and %FVC-predicted values (C, F, I). p-values were determined by the log-rank test.

Figure 3. Combination analyses of ESM_{CSA}, BMI, and %FVC-predicted values in the prognosis of patients with IPF receiving AFT.

Kaplan–Meier curves of patients with IPF receiving antifibrotic therapy according to ESM_{CSA} and BMI values (A), ESM_{CSA} and %FVC-predicted values (B), and %FVC-predicted and BMI values (C); p-values were determined by the log-rank test.

Table 1. Clinical characteristics of 208 patients with IPF treated with antifibrotic therapy at AFT initiation

	Hamamatsu cohort (n = 106)	Seirei cohort (n = 102)	p-value
Age, year	72.0 [68.0–76.0]	73.0 [66.0–76.0]	0.6469
Sex, male/female	93 (87.7%)/13 (12.2%)	83 (81.4%)/19 (18.6%)	0.2498
cIPF / UIP/IPF	75 (70.8%)/ 31 (29.2%)	90 (88.2%)/ 12 (11.8%)	0.0020
Diagnosis~Antifibrotic	24.5 [3.7–68.4]	12.4 [4.0–40.1]	0.0955
simultaneously	12 (11.3%)	13 (12.7%)	
<6 months	21 (19.8%)	24 (23.5%)	
<1 year	7 (6.6%)	16 (15.7%)	
<2 years	14 (13.2%)	11 (9.8%)	
<3 years	11 (10.4%)	8 (7.8%)	
>3 years	41 (38.7%)	30 (29.4%)	
Pirfenidone/nintedanib	84 (79.8%), 22 (20.8%)	58 (56.9%)/44 (43.1%)	0.0006
Observation period, months	22.1 [13.0–37.0]	23.6 [10.8–36.7]	0.9055
Never smoker	18 (17.0%)	21 (20.6%)	0.5947
Former or current smoker	88 (83.0%)	81 (79.4%)	
Smoking pack-year	30.5 [9.4–53.3]	34.5 [5.0–45.3]	0.4997
Height, cm	162.9 [156.8–166.6]	161.4 [156.0–167.5]	0.5002
Weight, kg	59.8 [53.0–67.3]	58.5 [50.6–66.1]	0.3627
BMI, kg/m^2	23.0 [21.1–25.2]	23.0 [20.8–25.1]	0.6640
ESM_{CSA}, cm^2	34.3 [27.8–40.2]	33.6 [29.4–40.7]	0.8177
ESM_{MA}, HU	38.3 [32.9–43.5]	39.2 [33.1–43.3]	0.7348

Pulmonary Function Test			
FVC, percent predicted	65.3 [54.6–76.8]	68.1 [56.5–79.6]	0.2390
FEV_1/FVC, %	85.3 [79.8–91.1]	86.3 [80.3–92.0]	0.6285
DLCO, %	51.1 [39.7–64.3] (n = 77)	58.5 [45.5–68.5] (n = 89)	0.0190
6-minute walk test			
Distances, m	415 [331-481] (n=87)	410 [322-530] (n=40)	0.9933
Minimum SpO_2<90%	65/87 (74.7%)	30/40 (75.0%)	1.0000
UCG			
TRV ≥ 2.9 m/s	10 (12.8%) (n=78)	12 (21.4%) (n=56)	0.2380
Laboratory			
Hb, g/dl	13.5 [12.3–14.7]	13.7 [13.0–14.8]	0.1321
TP, g/dl	7.5 [7.1–7.8]	7.4 [6.9–7.8]	0.9629
Alb, g/dl	4.0 [3.6–4.2]	3.9 [3.6–4.1]	0.0655
LDH, U/l	243 [205–274]	229 [206–270]	0.4492
KL-6, U/ml	992 [761–1427]	1177 [884–1656]	0.0064
SP-D ng/ml	249 [165–347]	250 [160–389]	0.4887
Treatment			
None	69 (65.1%)	49 (48.0%)	0.0172
LTOT	32 (30.2%)	43 (42.2%)	0.0837
Immunosuppressants	14 (13.2%)	30 (29.4%)	0.0062
History of NAC	2 (1.9%)	0 (0%)	0.4978
History of IVIG	3 (2.8%)	0 (0%)	0.2467

BMI; body mass index, ESM_{CSA}; cross-sectional area of erector spinae muscles, ESM_{MA}; muscle attenuation of erector spinae muscles, FVC; forced vital capacity, $FEV_{1.0}$; forced expiratory volume in 1.0 second, DLCO; diffuse capacity of the lung for carbon monoxide, 6MWT; 6-miniute walk test, Min SpO_2; minimum SpO_2, UCG; ultrasound echocardiogram, TRV; Tricuspid regurgitant jet velocity, KL-6; Krebs von den Lunge-6, SP-D; surfactant protein-D, LTOT; long-term oxygen therapy, NAC; N-acetylcysteine, IVIG; intravenous immunoglobulin

Table 2. Cause of mortality in patients with IPF treated with or without antifibrotic therapy

	AFT (+)			AFT (-)	
	Hamamatsu cohort (n = 59)	Seirei cohort (n = 64)	p-value	Historical cohort (n=53)	AFT (+) *vs* AFT (-) p-value
Chronic respiratory failure	37 (62.7%)	36 (56.3%)	0.5817	22 (41.5%)	0.0331
Acute exacerbation	16 (27.1%)	14 (21.9%)	0.5341	17 (32.1%)	0.3533
Lung cancer	2 (3.4%)	5 (7.8%)	0.4422	10 (18.7%)	0.0110
Infection	2 (3.4%)	3 (4.7%)	1.0000	1 (1.9%)	0.6697
Others	2 (3.4%)	6 (9.4%)	0.2760	3 (5.7%)	1.000

Table 3. Prediction of mortality in patients with IPF treated with antifibrotic therapy by univariate and multivariate Cox-proportion analyses

Predictor	HR	95% CI	p-value		HR	95% CI	p-value
Univariate analysis				**Multivariate analysis 1**			
Age, year	1.029	1.001–1.058	0.0431	Age, year	0.988	0.958–1.022	0.4607
Gender, male	1.126	0.685–1.980	0.6593	Gender, male	1.891	1.020–3.803	0.0557
Pirfenidone	1.049	0.693–1.633	0.8260	BMI, kg/m^2	0.920	0.847–0.996	0.0440
Period: Diagnosis-administration	1.002	0.997–1.006	0.4907	ESM_{CSA}, cm^2	0.957	0.930–0.986	0.0037
BMI, kg/m^2	0.896	0.846–0.948	0.0002	FVC, percent predicted	0.984	0.970–0.998	0.0282
ESM_{CSA}, cm^2	0.962	0.944–0.981	0.0001	DLCO, %	0.983	0.967–0.997	0.0225
ESM_{MA}, (HU)	1.000	0.981–1.019	0.9387				
FVC, percent predicted	0.969	0.958–0.981	<0.0001				
FEV_1/FVC, %	1.056	1.031–1.082	<0.0001	**Multivariate analysis 2**			
DLCO, %	0.970	0.956–0.984	<0.0001	Age, year	1.005	0.976–1.037	0.7252
Alb, g/dl	0.545	0.368–0.824	0.0031	Gender, male	1.505	0.902–2.685	0.1396
KL-6, U/ml	1.000	1.000–1.000	0.0027	BMI, <24.1 kg/m^2	1.673	1.063–2.709	0.0307
SP-D, ng/ml	1.001	1.000–1.002	0.0565	ESM_{CSA}, <39.2/29.6 cm^2	1.899	1.141–3.249	0.0159
BMI, <24.1 kg/m^2	2.431	1.623–3.754	<0.0001	FVC percent predicted, <75.5%	2.379	1.507–3.911	0.0003
ESM_{CSA}, < 39.2/29.6 cm^2	2.879	1.878–4.583	<0.0001				
FVC percent predicted, <75.5%	2.754	1.778–4.450	<0.0001				

BMI; body mass index, ESM_{CSA}; cross-sectional area of erector spinae muscles, ESM_{MA}; muscle attenuation of erector spinae muscles, FVC; forced vital capacity, $FEV_{1.0}$; forced expiratory volume in 1.0 second, DLCO; diffuse capacity of the lung for carbon monoxide,

Figure1

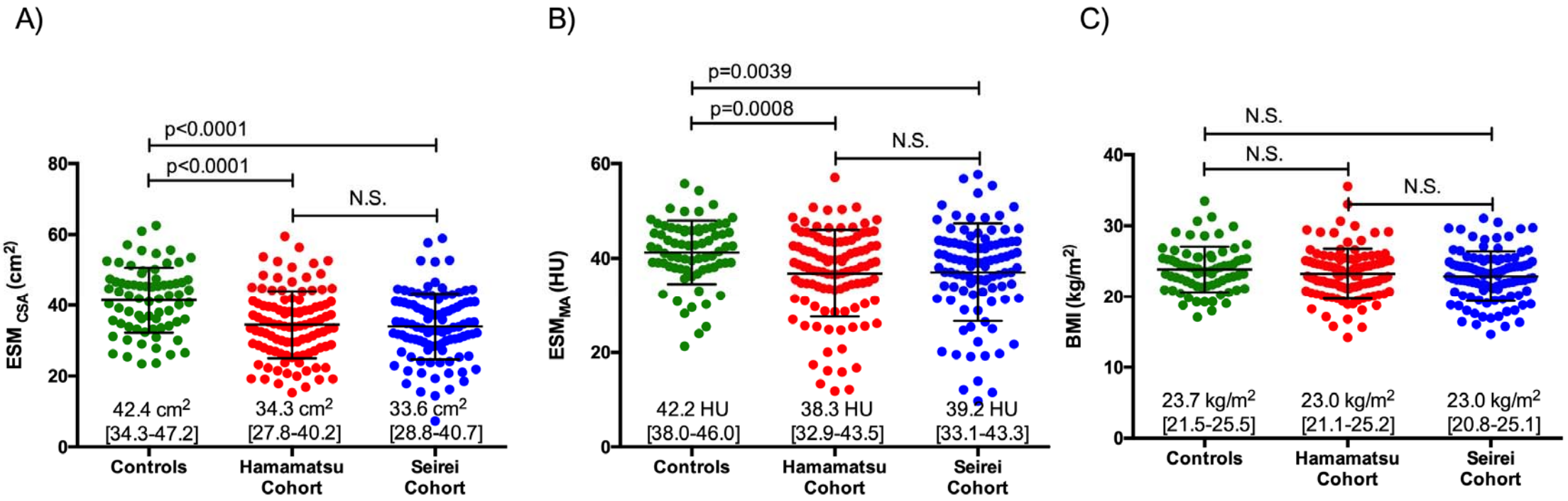

A)
p<0.0001
p<0.0001
N.S.
ESM CSA (cm2)
80
60
40
20
0
42.4 cm2
[34.3-47.2]
34.3 cm2
[27.8-40.2]
33.6 cm2
[28.8-40.7]
Controls
Hamamatsu Cohort
Seirei Cohort
B)
p=0.0039
p=0.0008
N.S.
ESMMA (HU)
60
40
20
0
42.2 HU
[38.0-46.0]
38.3 HU
[32.9-43.5]
39.2 HU
[33.1-43.3]
Controls
Hamamatsu Cohort
Seirei Cohort
C)
N.S.
N.S.
N.S.
BMI (kg/m2)
40
30
20
10
0
23.7 kg/m2
[21.5-25.5]
23.0 kg/m2
[21.1-25.2]
23.0 kg/m2
[20.8-25.1]
Controls
Hamamatsu Cohort
Seirei Cohort

Figure2

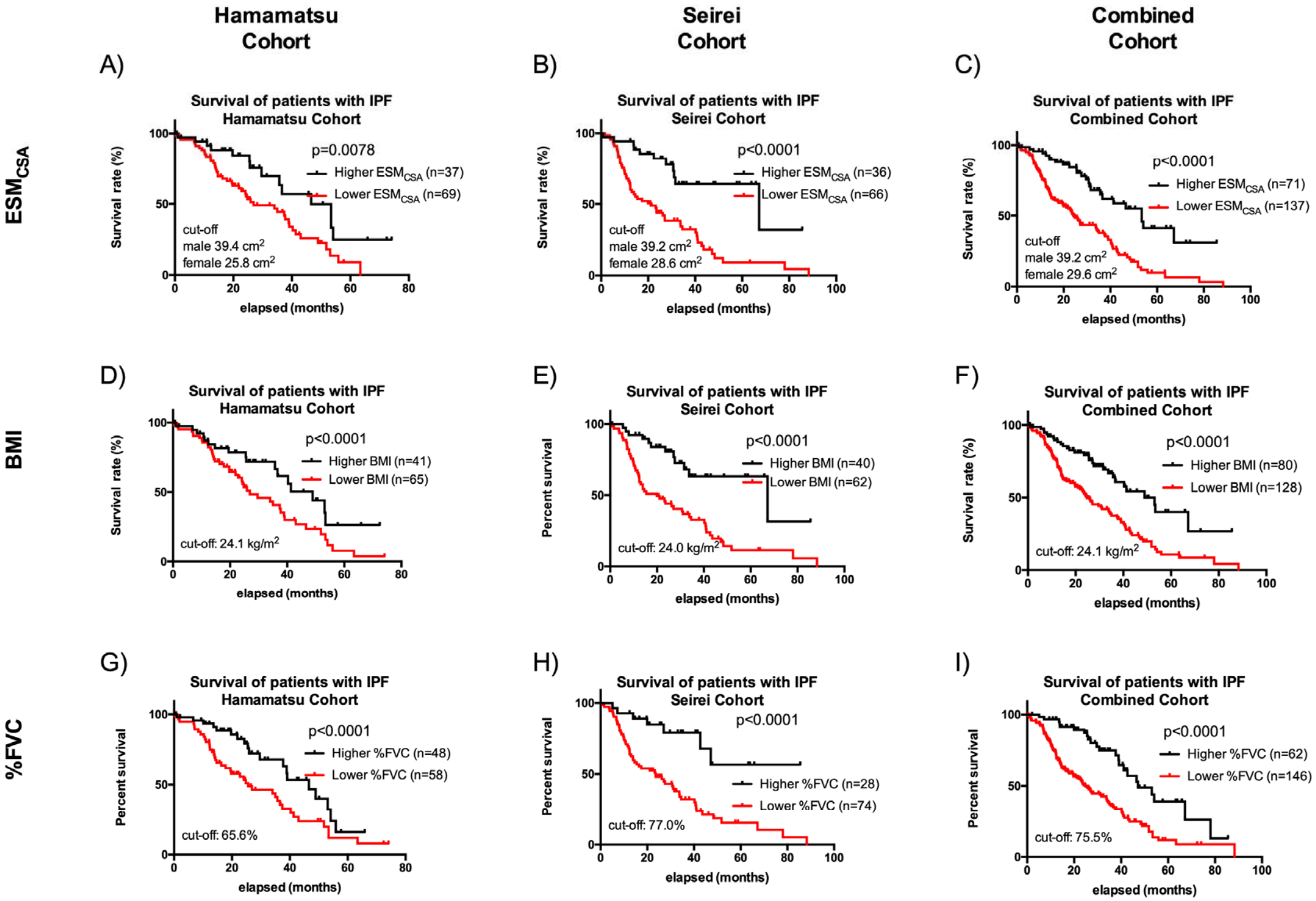
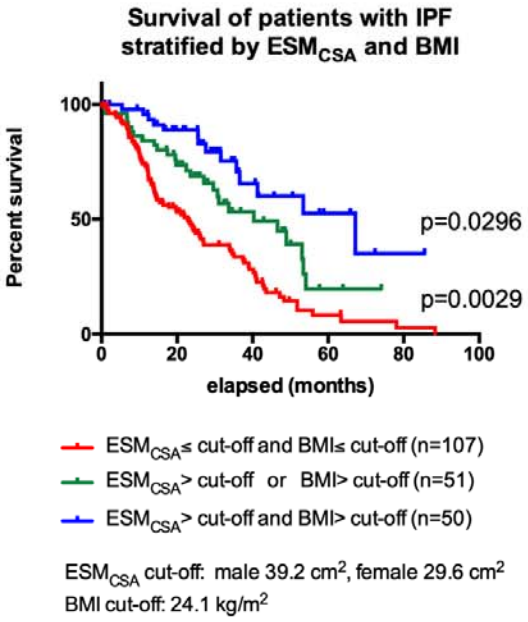
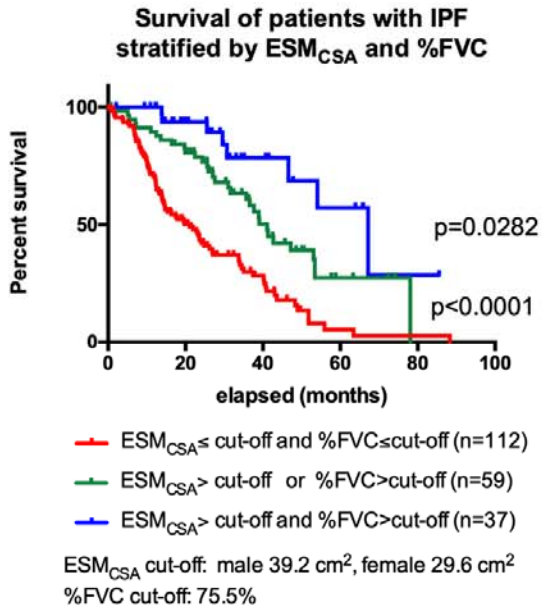

Hamamatsu Cohort
Seirei Cohort
Combined Cohort
ESMCSA
BMI
%FVC
A)
B)
C)
D)
E)
F)
G)
H)
I)
Survival of patients with IPF
Hamamatsu Cohort
Survival of patients with IPF
Seirei Cohort
Survival of patients with IPF
Combined Cohort
Survival rate (%)
Percent survival
elapsed (months)
p=0.0078
Higher ESMCSA (n=37)
Lower ESMCSA (n=69)
cut-off
male 39.4 cm2
female 25.8 cm2
p<0.0001
Higher ESMCSA (n=36)
Lower ESMCSA (n=66)
cut-off
male 39.2 cm2
female 28.6 cm2
p<0.0001
Higher ESMCSA (n=71)
Lower ESMCSA (n=137)
cut-off
male 39.2 cm2
female 29.6 cm2
p<0.0001
Higher BMI (n=41)
Lower BMI (n=65)
cut-off: 24.1 kg/m2
p<0.0001
Higher BMI (n=40)
Lower BMI (n=62)
cut-off: 24.0 kg/m2
p<0.0001
Higher BMI (n=80)
Lower BMI (n=128)
cut-off: 24.1 kg/m2
p<0.0001
Higher %FVC (n=48)
Lower %FVC (n=58)
cut-off: 65.6%
p<0.0001
Higher %FVC (n=28)
Lower %FVC (n=74)
cut-off: 77.0%
p<0.0001
Higher %FVC (n=62)
Lower %FVC (n=146)
cut-off: 75.5%

Figure3

A)


Survival of patients with IPF
stratified by ESMCSA and BMI
Percent survival
100
50
0
0
20
40
60
80
100
elapsed (months)
p=0.0296
p=0.0029
ESMCSA≤ cut-off and BMI≤ cut-off (n=107)
ESMCSA> cut-off or BMI> cut-off (n=51)
ESMCSA> cut-off and BMI> cut-off (n=50)
ESMCSA cut-off: male 39.2 cm2, female 29.6 cm2
BMI cut-off: 24.1 kg/m2

B)


Survival of patients with IPF
stratified by ESMCSA and %FVC
Percent survival
100
50
0
0
20
40
60
80
100
elapsed (months)
p=0.0282
p<0.0001
ESMCSA≤ cut-off and %FVC≤cut-off (n=112)
ESMCSA> cut-off or %FVC>cut-off (n=59)
ESMCSA> cut-off and %FVC>cut-off (n=37)
ESMCSA cut-off: male 39.2 cm2, female 29.6 cm2
%FVC cut-off: 75.5%

C)

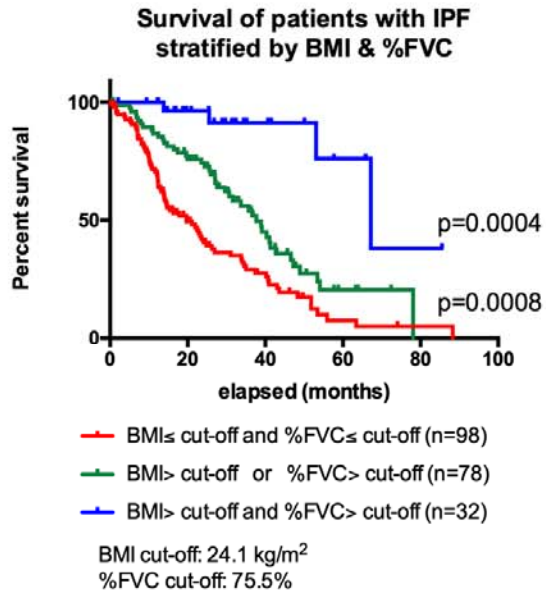
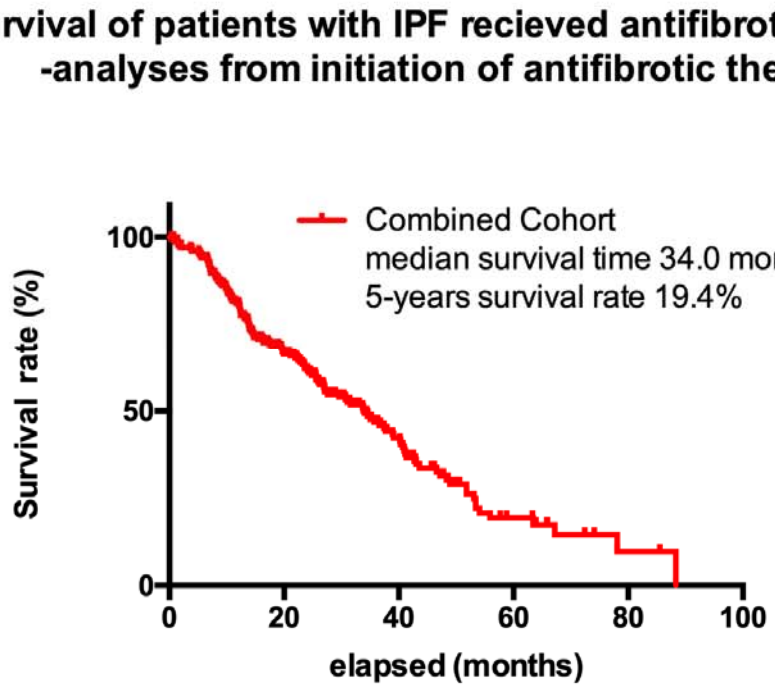

Survival of patients with IPF
stratified by BMI & %FVC
Percent survival
100
50
0
0
20
40
60
80
100
elapsed (months)
p=0.0004
p=0.0008
BMI≤ cut-off and %FVC≤ cut-off (n=98)
BMI> cut-off or %FVC> cut-off (n=78)
BMI> cut-off and %FVC> cut-off (n=32)
BMI cut-off: 24.1 kg/m2
%FVC cut-off: 75.5%

Figure S1

A)


Survival of patients with IPF recieved antifibrotic therapy
-analyses from initiation of antifibrotic therapy-
Combined Cohort
median survival time 34.0 months
5-years survival rate 19.4%
Survival rate (%)
100
50
0
0
20
40
60
80
100
elapsed (months)

B)

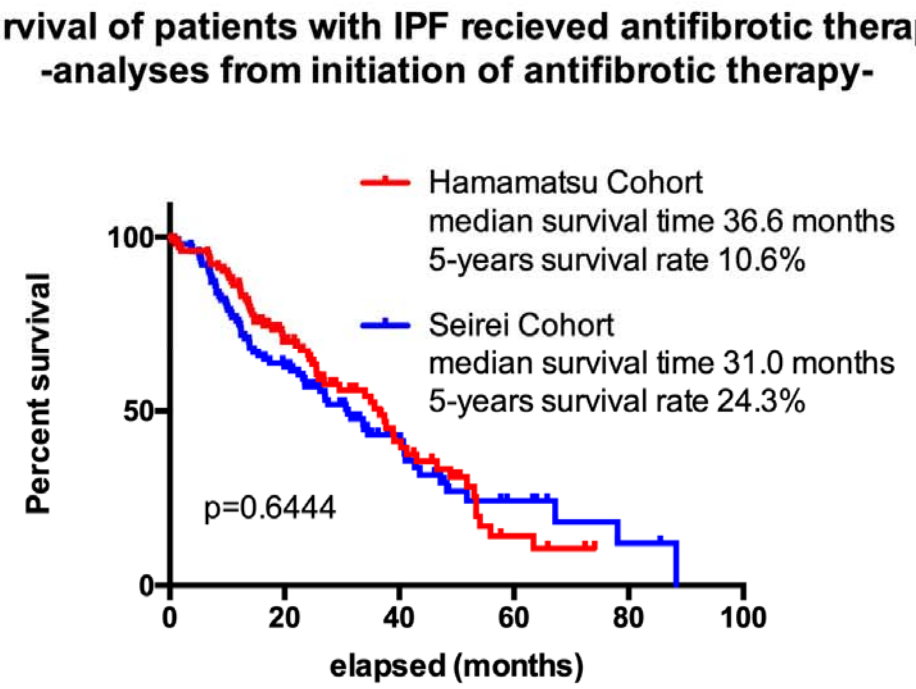
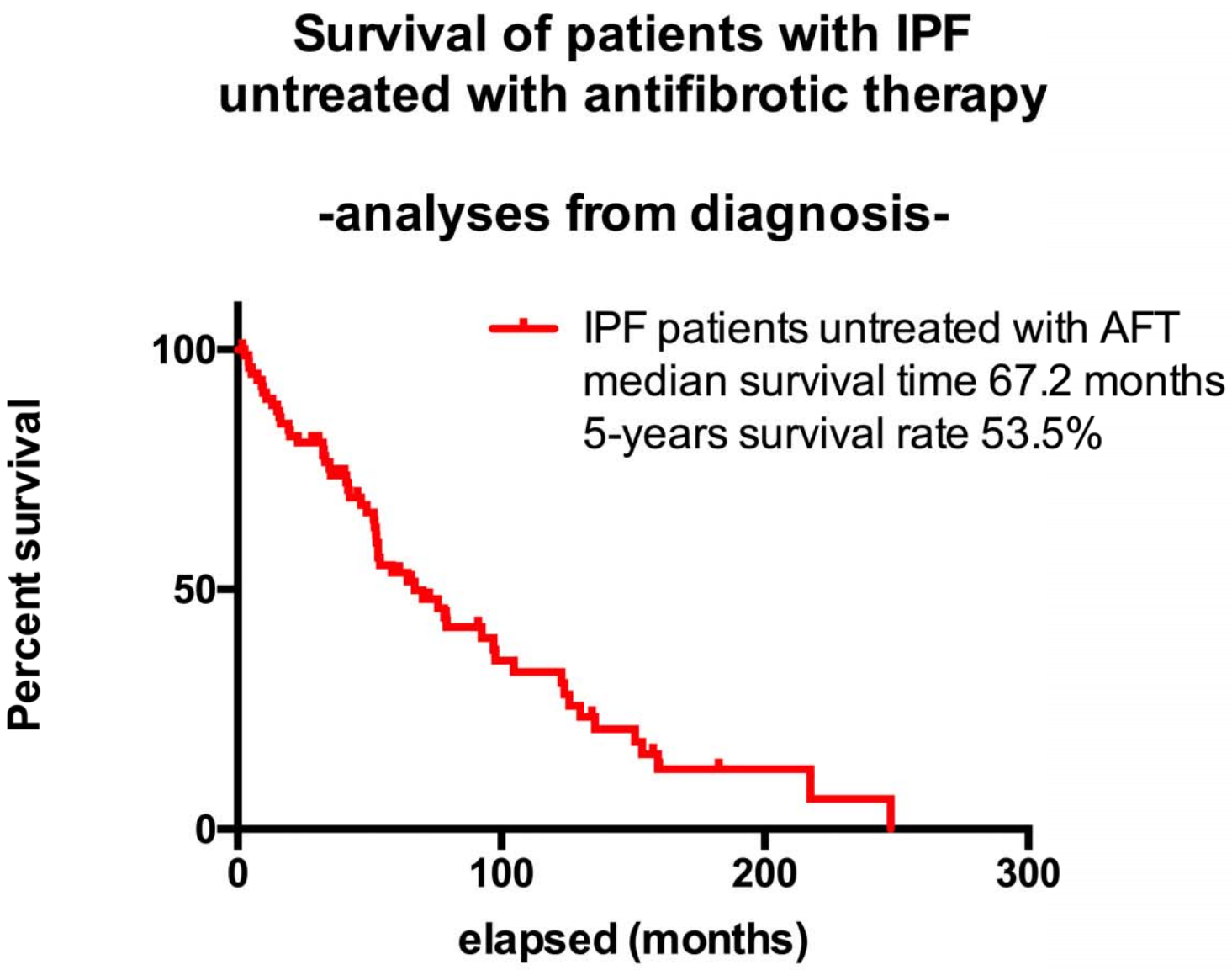

Survival of patients with IPF recieved antifibrotic therapy
-analyses from initiation of antifibrotic therapy-
Hamamatsu Cohort
median survival time 36.6 months
5-years survival rate 10.6%
Seirei Cohort
median survival time 31.0 months
5-years survival rate 24.3%
p=0.6444
Percent survival
100
50
0
0
20
40
60
80
100
elapsed (months)

Figure S2


Survival of patients with IPF
untreated with antifibrotic therapy
-analyses from diagnosis-
IPF patients untreated with AFT
median survival time 67.2 months
5-years survival rate 53.5%
Percent survival
100
50
0
0
100
200
300
elapsed (months)