Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis

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Summary at a glance

This is the first study to report on a direct comparison of pathologically-proven usual interstitial pneumonia associated with MPO-ANCA (ANCA/UIP) and idiopathic pulmonary fibrosis (IPF). This study shows some radiological and pathological characteristics and better responsiveness to immunosuppressive therapy in ANCA/UIP compared to IPF.

ABSTRACT

Background and objective: Myeloperoxidase anti-neutrophil cytoplasmic antibody **(**MPO-ANCA) is occasionally positive in patients with usual interstitial pneumonia (UIP). However, the differences from idiopathic pulmonary fibrosis (IPF/UIP) have not well documented. We aimed to clarify the clinical, radiological, and pathological features of UIP associated with MPO-ANCA (ANCA/UIP).

Methods: We retrospectively reviewed the medical records of consecutive 12 ANCA/UIP patients not manifesting microscopic polyangitis and 108 IPF/UIP patients with no autoantibodies, both diagnosed by surgical lung biopsy.

Results: There was no significant difference in clinical background, laboratory results, and pulmonary function test between ANCA/UIP patients and IPF/UIP patients except for the percentage of bronchoalveolar lavage neutrophils. HRCT showed subpleural reticulation in both groups. Increased attenuation around honeycombing and cysts was significantly observed in ANCA/UIP. Pathologically, ANCA/UIP had more prominent inflammatory cell infiltration, lymphoid follicles with germinal centers, and cellular bronchiolitis. During the disease course, three of 12 patients (25%) developed microscopic polyangitis. Immunosuppressive treatment tended to be more effective in ANCA/UIP patients, and the survival time in ANCA/UIP patients tended to be longer

than those with IPF/UIP.

Conclusion: ANCA/UIP may be distinguishable from IPF/UIP with combination of HRCT findings of increased attenuation around honeycombing and cysts and some of the characteristic pathological findings. In contrast to IPF/UIP, immunosuppressive treatment could be a therapeutic option for ANCA/UIP

Key words:

MPO-ANCA, usual interstitial pneumonia, idiopathic pulmonary fibrosis,

immunosuppressive treatment

Short Title: Clinical features of UIP with MPO-ANCA

INTRODUCTION

Myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) is occasionally positive in patients with interstitial pneumonia (IP) [1-14]. Usual interstitial pneumonia (UIP) pattern was reportedly a major pattern of fibrosis in the patients with IP associated MPO-ANCA [10]. Recent studies have shown the difficulty in distinguishing UIP associated with MPO-ANCA (ANCA/UIP) from IPF/UIP by HRCT, although some pathological characteristics of ANCA/UIP were reported [11, 15].

We recently reported that UIP associated with primary Sjögren's syndrome had better prognosis and better response to immunosuppressive therapy in comparison with IPF/UIP [16]. 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) statement emphasizes the importance of separating idiopathic pulmonary fibrosis from IP associated with specific systemic conditions such as those related to the collagen vascular diseases. It recommends that the patients with IPF should not be treated with steroids and immunosuppressant agents [17]. If ANCA/UIP is a distinctive form of pulmonary fibrosis, and if treatment response and/or prognosis is distinct, it should be identified from IPF/UIP.

The aim of this study was to compare the clinical, radiological, and pathological

findings of ANCA/UIP with those of IPF/UIP, and to evaluate their prognosis and responses to immunosuppressive therapy.

METHODS

Study subjects

We retrospectively reviewed medical records of consecutive patients who underwent a surgical lung biopsy for the diagnosis of diffuse lung diseases at Kanagawa Cardiovascular and Respiratory center between 2000 and 2012. Of those patients we selected patients pathologically diagnosed with UIP pattern. The diagnosis of UIP was confirmed according to the pathological criteria of the 2002 ATS/ERS consensus classification of IPF [18]. MPO-ANCA was measured at initial presentation or during follow-up. MPA was diagnosed based on the Chapel Hill Consensus Conference nomenclature of systemic vasculitis [19]. Among the patients with ANCA/UIP, we excluded the patients who manifested MPA before surgical lung biopsy. All patients with IPF/UIP included in this study lacked symptoms or signs of collagen vascular diseases with no autoantibodies. Finally, 12 patients with ANCA/UIP and 108 patients with IPF/UIP were included in this study. This study was approved by an Institutional Review Broad of Kanagawa Cardiovascular and Respiratory Center (No 26-38).

Clinical analysis

The clinical information extracted from the medical records included laboratory results, pulmonary function test results, and analysis of bronchoalveolar lavage (BAL) fluid obtained before surgical lung biopsy. If any immunosuppressive therapy was initiated during the clinical course, we compared their clinical status and changes in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) before (0-3 months) and 6 (6-10) months after treatment initiation. Categorical variables indicative of the type of change (worsened, stable, or improved) were defined by combining significant changes in pulmonary function (changes in FVC $\geq$ 10% and/or changes in DLCO $\geq$ 15%) with acute exacerbation events, or death related to respiratory disorders. We defined “worsened” as a significant decrease in pulmonary function or experiencing at least one of the abovementioned events, we defined “improved” as a significant increase in pulmonary function and not experiencing any of these events. All other cases were regarded as “stable.”

Patients who began immunosuppressive therapy at the time of an acute exacerbation or development of MPA were excluded from the response analysis because our focus was the chronic phase treatment. We used the standard definition of acute exacerbation [20]. If another immunosuppressive drug included later in the clinical course, the response analysis only applied to the first treatment regimen.

Radiological analysis

Before surgical lung biopsy, chest high-resolution CT (HRCT) scans were performed for each patient during holding at full inspiration; 1.0- or 2.0-mm thick sections were collected throughout the lungs, all images were randomized and independently reviewed by one experienced radiologist (T.I.) and one experienced pulmonologist (T.B.) blinded to clinical and pathological information.

The HRCT scans were analyzed for the following characteristics: honeycombing, ground glass opacity, consolidation, reticulation, localization of attenuation in conjunction with honeycombing and cyst, traction bronchiectasis, bronchial wall thickening, pulmonary artery dilation, enlarged mediastinal lymph nodes, and pleural thickening. Those features to be examined were selected as referring the previous studies or from our experience [16, 21-24]. Disagreements between the radiologist and the pulmonologist after the first assessment were resolved by discussion.

Pathological analysis

Histological sections of surgical lung biopsy specimens were stained with hematoxylin-eosin and elastica van Gieson. We randomly selected 30 slides from 108 slides diagnosed with IPF/UIP. In total, forty two slides were randomized and independently reviewed by two experienced lung pathologists (T.T. and K.O.) who had no access to the clinical and radiological findings.

The following pathological features were semiquantitatively graded as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe): interstitial inflammation, plasma cell inflammation, interstitial fibrosis, smooth muscle hyperplasia, lymphoid follicles with germinal centers, organizing pneumonia (intra-alveolar polypoid organization), fibroblastic foci, microscopic honeycombing, emphysema, cysts, cellular bronchiolitis, bronchiolar fibrosis, vascular medial thickening, perivascular collagen deposition, and pleuritis. Those features were selected as referring the previous studies [16]. Any disagreements between the two pathologists were discussed until a consensus was reached.

Statistical analysis

Data are presented as mean ± standard deviation, unless otherwise stated. Fisher's exact test or Mann-Whitney U test was used for the comparisons between groups as appropriate. Survival time from initial consultation was analyzed by Kaplan-Meier method and the log-rank test with the end points being death or the last contact. A p-value of less than 0.05 was considered significant.

RESULTS

Clinical and laboratory findings of ANCA/UIP in comparison with IPF/UIP

The clinical characteristics of the 12 patients with ANCA/UIP were compared with those of the 108 IPF/UIP patients and are summarized in Table 1. Clinical background, symptoms at initial consultation, pulmonary function test were not significantly different between the two groups. Significant difference was observed only in the percentage of BAL neutrophils ($p=0.02$). All patients with ANCA/UIP lacked extrapulmonary symptoms or signs, having no autoantibodies other than MPO-ANCA.

Radiological and Pathological findings

In radiological analysis, the presence/absence of honeycombing, ground glass opacity, consolidation and distribution of reticular abnormality were not different between both two groups. Regarding localization of attenuation in conjunction with cyst, increased attenuation around honeycombing and cysts was noted in ANCA/UIP group. The presence/absence of each features on HRCT are described in Table 2.

The pathological scores are summarized in Table 3. Patchy and paraseptal distribution of fibrosis was common in both groups. A variety of significant differences were noted between the two groups. Interstitial inflammation, plasma cell infiltration, lymphoid follicles with germinal centers, cysts, cellular bronchiolitis were significantly more

prominent in ANCA/UIP group. No patients showed evidence of capillaritis or vasculitis in ANCA/UIP group.

Typical HRCT and pathological images of a patient with ANCA/UIP and IPF/UIP are shown in Fig 1. Increased attenuation around honeycombing and cysts in HRCT well corresponded to the pathological findings.

Clinical course and treatment response

The median follow-up period was 72 months (range, 14-195 months) for ANCA/UIP patients and 56 months (range, 4-168 months) for IPF/UIP patients. A total of 5 patients with ANCA/UIP and 53 patients with IPF/UIP died between follow-up visits, and none of the patients underwent lung transplantation.

Survival analysis in patients with ANCA/UIP in comparison with patients with IPF/UIP is shown in Fig 2. The median survival time in the ANCA/UIP group was 132 months, and 84 months in the IPF/UIP group. The survival time in patients with ANCA/UIP tended to be longer than that of IPF/UIP ($p=0.22$).

The detailed clinical course is summarized in Table 4. In ANCA/UIP group, 11 of 12 patients had positive MPO-ANCA titers at initial presentation and positive conversion occurred in one patient. There was no difference in the frequency of acute exacerbation between two groups. In ANCA/UIP group, three patients (25%) developed MPA during follow-up.

Immunosuppressive therapy was initiated during the chronic phase in 6 of 12 patients with ANCA/UIP and in 25 of 108 patients with IPF/UIP, as they were diagnosed with progressive and/or symptomatic disease by clinicians. In ANCA/UIP group, five of six patients (83%) experienced significant improvement, and none of the patients worsened. In contrast, 11 of 25 (44%) patients with IPF/UIP worsened. Immunosuppressive treatment tended to be more effective in ANCA /UIP.

DISCUSSION

This is the first study to report on a direct comparison of pathologically-proven ANCA/UIP and IPF/UIP. We identified several characteristic features of ANCA/UIP.

ANCA/UIP group had higher percentage of neutrophils in BAL fluid, and analysis of HRCT scans identified increased attenuation around honeycombing and cysts as a key characteristics of ANCA/UIP. ANCA/UIP had more prominent inflammatory cell infiltration, lymphoid follicles with germinal centers, and cellular bronchiolitis upon pathological analysis in comparison with IPF/UIP. Immunosuppressive treatment tended to be more beneficial in ANCA/UIP patients and the survival time tended to be longer than that of IPF/UIP. The difference in the responsiveness to immunosuppressive treatment may be explained by the differences in HRCT and

pathological findings between ANCA/UIP and IPF/UIP.

In the present study, we found no significant difference in clinical background, laboratory results and pulmonary function test between ANCA/UIP and IPF/UIP. This was consistent with the results of previously published reports [9, 11, 25]. However, a significant difference was observed in the percentage of neutrophils in BAL fluid. This result was discrepant from the previous study reporting no significant difference in BAL fluid analysis [9, 25]. It is reasonable to consider the higher percentage of neutrophils reflects the chronic neutrophilic inflammation, resulting in neutrophil destruction to induce the production of MPO-ANCA.

During the disease course, three of 12 ANCA/UIP patients (25%) developed MPA. In these three patients developing MPA, two patients died of MPA. One patient who died of MPA was initially treated with corticosteroid and immunosuppressive agent and developed MPA after cessation of immunosuppressive agent. Another developed MPA during follow-up period before initiating treatment. MPA was a fatal complication in ANCA/UIP patients. On the contrary, no patients on immunosuppressant developed MPA. This result is consistent with previous studies [11, 26]. It is possible that immunosuppressive therapy could reduce the risk of developing MPA.

We found that ANCA/UIP and IPF/UIP showed different pathologic features, despite having the same basic UIP pattern; ANCA/UIP had more prominent inflammatory cell

infiltration, lymphoid follicles with germinal centers, and cellular bronchiolitis compared with IPF/UIP. Inflammatory cell infiltration and lymphoid follicles with germinal centers are reportedly common pathological features of collagen vascular diseases and lung-dominant collagen vascular diseases in previous studies [27-29]. Recent study reported that lymphoid follicles with germinal centers and small airway disease were characteristic features of patients with IP associated with MPO-ANCA [15]. Our present study supported their findings.

On the other hand, other studies have shown the difficulty in distinguishing ANCA/UIP from IPF/UIP by HRCT [11, 25]. We presented the radiological findings of increased attenuation around honeycombing and cysts as a feature of ANCA/UIP. The pathological features of ANCA/UIP such as inflammatory cell infiltration and lymphoid follicles with germinal centers well correspond to the presence of increased attenuation around cysts in HRCT. These features may be associated with the better response to immunosuppressive therapy in ANCA/UIP patients.

It is not clear whether ANCA/UIP should be treated by immunosuppressive drugs. Recent statement for IPF declared that the patients with IPF should not be treated with steroids or immunosuppressant agents [17]. PANTHER-IPF study provided evidence against the use of a combination of prednisone, azathioprine, and *N*-acetylcysteine in IPF patients [30]. Our study supports the use of immunosuppressive drugs for the treatment of ANCA/UIP. ANCA/UIP probably have more prominent inflammation

than IPF/UIP, which implies that ANCA/UIP has more lesions capable of responding to immunosuppressive therapy. Immunosuppressive treatment could be a therapeutic option for ANCA/UIP.

This study had several limitations. This study was single-center retrospective study. The number of patients with ANCA/UIP was small. The small sample size makes it difficult to draw any firm conclusions. Since this study focused on patients who underwent a surgical lung biopsy, there is a possibility of selection bias. In addition, the radiological and pathological features found in this study may not be specific for ANCA/UIP and may possibly apply to other collagen vascular disease related UIP, although it is beyond our scope to argue that.

In conclusion, features of pathological and radiological findings in ANCA/UIP presented in this study may help distinguishing the disease from IPF/UIP, and may explain the good response to and support the indication of immunosuppressive therapy.

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Table 1 Clinical characteristics in patients with usual interstitial pneumonia associated with MPO-ANCA and idiopathic pulmonary fibrosis

Characteristics	ANCA/UIP	IPF/UIP	P-value
Patients	12	108	
Age median (range)	65.2 (48-74)	65.6（37-78）	0.98
Male	8	82	1.00
Smoking history (n)			
Never	6	28	0.09
Former/Current (pack year)	6 (15±18)	80 (31±29)	
Initial symptoms (n)			
Dyspnea on exertion	2	49	0.06
Cough	8	65	0.76
Fever	0	3	1.00
Bloody sputum	0	1	0.19
Weight loss	0	1	0.19
Pulmonary function			
FVC % pred.	92.9±17.3	83.0±16.5	0.08
FEV1/FVC (%)	79.6±8.6	81.0±6.6	0.85
DL_{CO} % pred.	81.7±30.2	81.2±21.6	0.69
Serological test			
LDH (U/l)	227±38.9	232±40.4	0.63
KL-6 (IU/ml)	1218±624	1208±771	0.66

SP-D (ng/ml)	205±127	263±173	0.46
CRP (mg/dl)	0.85±1.56	0.48±1.31	0.12
PaO_2 (Torr)	81.0±11.6	80.7±9.3	0.74
$PaCO_2$ (Torr)	43.1±3.4	41.7±3.5	0.17
Brochoalveolar lavage fluid			
Total cells ($\times 10^4$/ml)	25.3±13.4	27.7±32.1	0.45
Lymphocytes (%)	15.2±11.2	15.3±15.7	0.54
Neutrophils (%)	9.05±7.92	3.52±6.21	0.02

Data are presented as median (range) in number of patients or mean ± standard deviation in values.

ANCA: anti-neutrophil cytoplasmic antibody

IPF: idiopathic pulmonary fibrosis

UIP: usual interstitial pneumonia

FVC: forced vital capacity

FEV1: forced expiatory volume in 1 second

DL_{CO}: diffusing capacity of lung for carbon monoxide

LDH: lactate dehydrogenase

KL-6: Krebs von den Lugen-6

SP-D: surfactant protein-D

CRP: C-reactive protein

PaO_2: arterial oxygen tension

$PaCO_2$: arterial carbon dioxide tension

Table 2. Comparison of HRCT findings between usual interstitial pneumonia associated with MPO-ANCA and idiopathic pulmonary fibrosis

HRCT findings, Yes/No	ANCA/UIP	IPF /UIP	p-value
Honeycombing	9/3	57/51	0.22
Reticulation	12/0	108/0	1.00
Distribution：Subpleural / bronchovascular /diffuse	9/3/0	88/12/8	0.17
Traction bronchiectasis	12/0	108/0	1.00
Bronchial thickening	0/12	8/100	1.00
Increased attenuation around honeycombing and cysts	5/7	8/100	<0.01
Pulmonary artery dilation	0/12	6/102	1.00
Enlarged mediastinal lymph nodes	1/11	15/93	1.00
Pleural thickening	0/12	3/105	1.00
Ground glass attenuation	3/9	27/81	1.00
Consolidation	0/12	2/106	1.00
Micronodules	1/11	21/87	0.69
Emphysema	4/8	29/79	0.73

Data are presented as number of patients. All p-values were evaluated by comparing between ANCA/UIP and IPF/UIP using Fisher’s exact test.

HRCT: high resolution CT

ANCA: anti-neutrophil cytoplasmic antibody

UIP: usual interstitial pneumonia

IPF: idiopathic pulmonary fibrosis

Table 3. Comparison of pathological features between usual interstitial pneumonia associated with MPO-ANCA and idiopathic pulmonary fibrosis

Pathological features, Grade 0/1/2/3	ANCA /UIP	IPF/UIP	p-value
Interstitial inflammation	0/0/5/7	0/22/6/2	<0.01
Plasma cell infiltration	0/1/5/6	2/23/4/1	<0.01
Interstitial fibrosis	0/0/7/5	0/6/10/14	0.71
Smooth muscle hyperplasia	0/5/6/1	0/10/16/4	0.55
Lymphoid follicle with germinal center	2/5/4/1	28/2/0/0	<0.01
Organizing pneumonia	6/4/2/0	14/13/3/0	0.97
Fibroblastic foci	1/7/3/1	4/12/12/2	0.69
Microscopic honeycombing	5/3/2/2	7/15/6/2	0.74
Emphysema	9/3/0/0	11/16/2/1	0.02
Cyst	1/6/2/3	15/12/3/0	0.01
Cellular bronchiolitis	0/5/5/2	10/19/0/1	<0.01
Bronchiolar fibrosis	11/0/1/0	23/7/0/0	0.33
Vascular medial thickening	6/6/0/0	17/9/4/0	1.00
Perivascular collagen deposition	10/2/0/0	28/2/0/0	0.78
Pleuritis	11/1/0/0	26/4/0/0	0.65

Data are presented as number of patients. All p-values were evaluated by comparing between ANCA/UIP and IPF/UIP using Mann-Whitney's U-test. The higher grade means more severe change in pathological assessment.

ANCA: anti-neutrophil cytoplasmic antibody

UIP: usual interstitial pneumonia

IPF: idiopathic pulmonary fibrosis

Table 4. Comparison of clinical course and treatment between usual interstitial pneumonia associated with MPO-ANCA and idiopathic pulmonary fibrosis

	ANCA/UIP	IPF/UIP	p-value
Occurrence			
MPA	3	0	-
Acute exacerbation	1	30	0.17
Treatment response in six-month period			
Improved / stable / worsened	5/1/0	2/12/11	0.057
Causes of death	(n=5)	(n=53)	
Acute exacerbation	1	17	-
MPA	2	0	-
Chronic respiratory failure	2	23	-
Respiratory tract infection	0	2	-
Lung cancer	0	2	-
Others	0	9	-

Data are presented as number of patients.

MPA: microscopic polyangitis

ANCA: anti-neutrophil cytoplasmic antibody

UIP: usual interstitial pneumonia

IPF: idiopathic pulmonary fibrosis

FIGURE LEGENDS

Figure 1. Typical HRCT images and histopathology of a patient with ANCA/UIP (a.b) and a patient with IPF/UIP (c.d)

a. Subpleural reticulation (i.e., honeycombing, cysts, and traction bronchiectasis), increased attenuation around honeycombing and cysts is noted.

b. Panoramic view of a lower lobe in a patient with ANCA/UIP.

Patchy distribution of perilobular fibrosis, lymphoid follicles with germinal centers and microcystic change are noted. (HE, x 1.25) Moderate interstitial inflammatory cells and fibroblastic foci (arrow) are observed. (HE, x 4)

c. HRCT images of a patient with IPF/UIP.

d. Panoramic view of a lower lobe in a patient with IPF/UIP (HE, x 1.25)

Less marked interstitial inflammatory cells. (HE, x 4)

ANCA: anti-neutrophil cytoplasmic antibody

IPF: idiopathic pulmonary fibrosis

UIP: usual interstitial pneumonia

Figure 2. Kaplan-Meier distribution of survival time in patients with ANCA/UIP vs. those with IPF/UIP

ANCA: anti-neutrophil cytoplasmic antibody

IPF: idiopathic pulmonary fibrosis

UIP: usual interstitial pneumonia

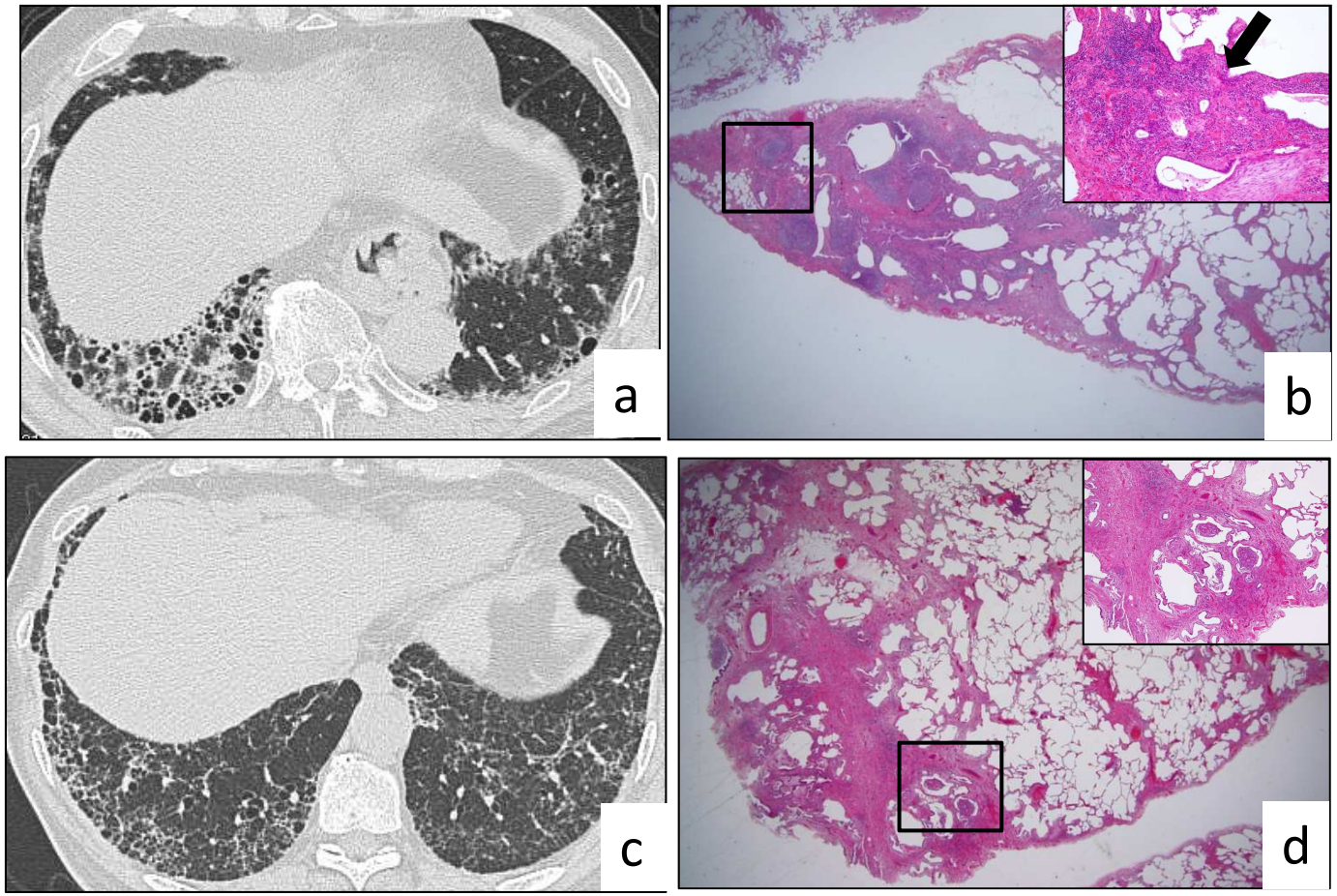

Fig. 1

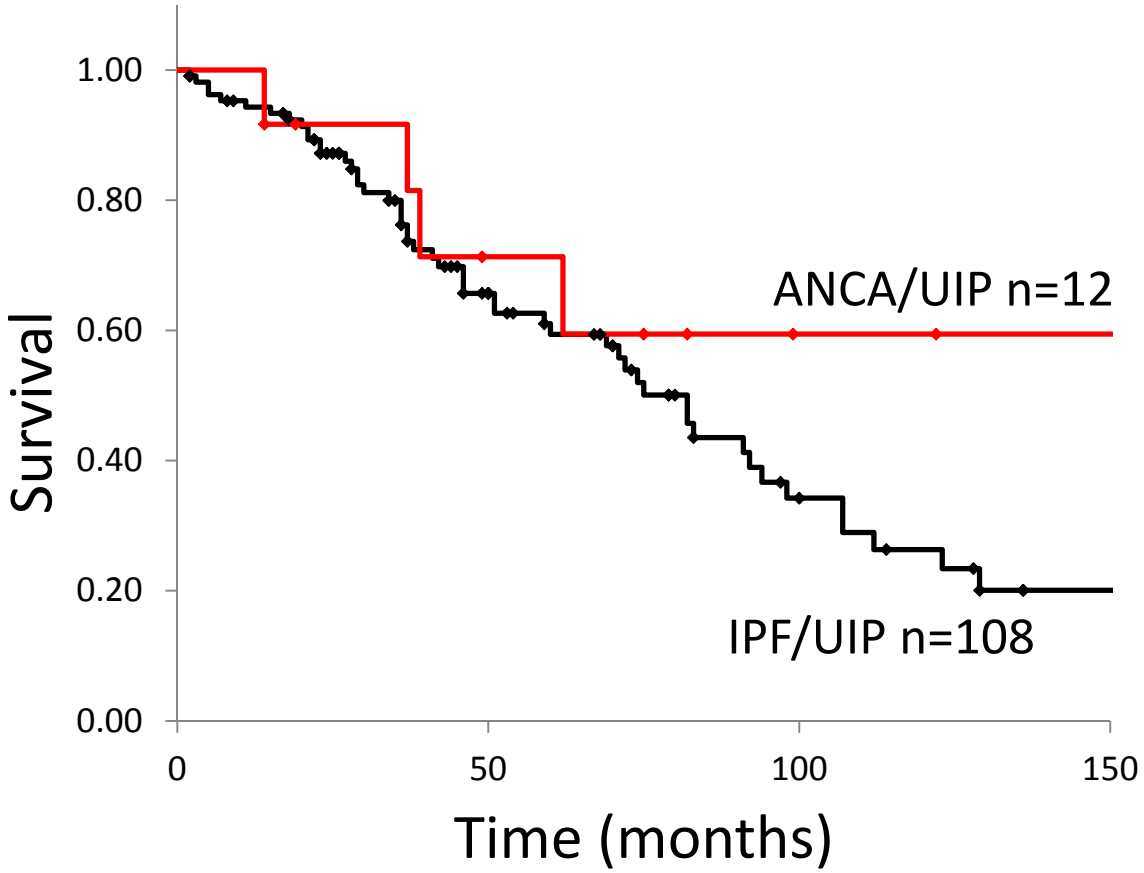

Fig 2. Survival curve