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Original research article

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Assessment of malnutrition-related risk in patients with idiopathic pleuroparenchymal fibroelastosis

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Take home message

Malnutrition is frequent in patients with idiopathic pleuroparenchymal fibroelastosis and annual decreases in nutritional status are associated with increased mortality, indicating the importance of assessing nutritional status in this patient population.

ABSTRACT

Background: Idiopathic pleuroparenchymal fibroelastosis (iPPFE) is characterised by upper lobe-dominant fibrosis involving the pleura and subpleural lung parenchyma, with advanced cases often complicated by progressive weight loss. Therefore, we hypothesized that nutritional status is associated with mortality in iPPFE.

Methods: This retrospective study assesses nutritional status at the time of diagnosis and one year after diagnosis in 131 patients with iPPFE. Malnutrition-related risk was evaluated using the Geriatric Nutritional Risk Index (GNRI).

Results: Of the 131 patients, 96 (76.3%) were at malnutrition-related risk at the time of diagnosis according to GNRI. Of these, 21 patients (16.0%) were classified as at major malnutrition-related risk (GNRI <82). Patients at major malnutrition-related risk were significantly older and had worse pulmonary function than patients at low (92≤ GNRI <98)- and moderate (82≤ GNRI <92)-malnutrition-related risk. GNRI scores decreased significantly from the time of diagnosis to one year after diagnosis. Patients with lower GNRI (<91.7) had significantly shorter survival than patients with a median GNRI or higher (≥91.8). Patients with declines in annual GNRI scores of 5 or greater had significantly shorter survival than patients with declines in GNRI scores of less than 5. In multivariate analysis, major malnutrition-related risk was significantly associated with increased mortality after adjustment for age, sex and forced vital capacity (hazard-ratio, 1.957). A composite scoring model including age, sex, and major malnutrition-related risk was able to separate mortality risk in iPPFE.

Conclusion: Assessment of nutritional status by GNRI provides useful information for managing patients with iPPFE by predicting mortality risk. (250 words)

Keywords: pleuroparenchymal fibroelastosis, Geriatric Nutritional Risk Index (GNRI), malnutrition-related risk, disease severity, mortality risk

INTRODUCTION

Idiopathic pleuroparenchymal fibroelastosis (iPPFE) is a rare type of interstitial lung disease characterized by fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes [1]. Patients with iPPFE typically present with dry cough and dyspnoea on exertion with decreased forced vital capacity (FVC) [2]. Importantly, the prognosis of patients with iPPFE has been reported to be equal to or worse than that of patients with IPF [3, 4]. Although antifibrotic therapy has been used for patients with iPPFE, and may slow disease progression, its efficacy has not yet been determined [5-8]. Further, there are currently no curative treatments for patients with iPPFE.

The assessment and improvement of nutritional status is important for improving outcomes in a range of diseases. Malnutrition is closely associated with progression of sarcopenia and cachexia, conditions commonly seen in patients with advanced lung disease. Importantly, malnutrition is not just a physical change, but also contributes to disease progression and worsens clinical outcomes. Indeed, the prognostic value of nutritional status has been validated in patients with range clinical conditions including acute ischaemic stroke, heart failure, respiratory failure and malignancies. The majority of patients with iPPFE present with a lean body image and complain of weight loss associated with characteristic physical findings including slender stature and a ‘flattened chest’ [9]. However, few studies have evaluated nutritional status and its association with disease progression and outcomes in patients with iPPFE.

The Geriatric Nutritional Risk Index (GNRI) is a simple nutrition index calculated using serum albumin (Alb), body weight and ideal body weight [10]. The GNRI was originally developed to assess the risks of malnutrition and malnutrition-related mortality and morbidity in hospitalized patients. The utility of GNRI has since been evaluated in a range of clinical conditions, including infectious and neoplastic diseases [11-14], and is now used for

nutritional assessment in a wide range of diseases [15-17]. The GNRI has been validated as a simple indicator of nutritional status that is more comprehensive than body mass index (BMI). However, there have been no reported studies evaluating nutritional status using GNRI and its prognostic significance in patients with iPPFE. Therefore, the present study was conducted to evaluate nutritional status using GNRI in patients with iPPFE and to investigate the association between GNRI scores and mortality.

MATERIALS AND METHODS

Patients

This retrospective study screened 146 consecutive patients with iPPFE who were admitted to Hamamatsu University Hospital, Seirei Hamamatsu Hospital and Seirei Mikatahara Hospital between March 2004 and March 2021. Fifteen patients did not have height and weight data available. Thus, the present study enrolled a total of 131 patients with iPPFE. Patients were censored if they remained alive until 30 June, 2022. The observation period was 36.4 (21.0–67.4) months. The mortality rate was 60.8% during the observation period. The diagnosis of iPPFE was made according to the following criteria [18]: 1) PPFE radiographic pattern on chest CT defined as bilateral subpleural dense consolidation with or without pleural thickening in the upper lobes and less marked or absent lower lobe involvement based on Reddy radiologic criteria [19], with subpleural dense consolidation defined as consolidation below a line 1 cm from the apex of the lung (to exclude the pulmonary apical cap) with a minimum width of 1 cm in contact with pleura [18-22]; 2) radiologic confirmation of disease progression, defined as an increase in upper lobe consolidation with or without pleural thickening and/or a decrease in upper lobe volume on serial radiologic assessments; and 3) exclusion of other lung diseases with identifiable etiologies, such as connective tissue disease-related ILD, chronic hypersensitivity pneumonitis, pulmonary sarcoidosis,

pneumoconiosis and active pulmonary infection. The HRCT patterns of lower lobe ILD were classified according to ATS/ERS/JRS/ALAT IPF guidelines [23].

The study protocol was approved by the Ethical Committee of Hamamatsu University School of Medicine (22-108) and conducted in accordance with approved guidelines. The requirement for patient approval and/or informed consent was waived due to the retrospective study design.

Data collection

Clinical characteristics at the time of iPPFE diagnosis (age, sex, physical examination, smoking history, blood test results and pulmonary function test results) were retrieved from medical records.

GNRI assessments

GNRI scores were calculated based on data at the time of iPPFE diagnosis and one year after diagnosis as follows: GNRI = [(1.489 × serum albumin (g/L)] + [41.7 × (actual weight / ideal body weight)] [10]. Ideal body weight was calculated from the Lorentz equations (WLo) as follows: For men: height (cm) – 100 – [(height (cm)-150) / 4], For women: height (cm)- 100 – [(height (cm) - 150) / 2.5].

Originally, GNRI was categorized into 4 levels: <82, major malnutrition-related risk; ≥82 to <92, moderate malnutrition-related risk; ≥92 to <98, mild malnutrition-related risk; and ≥98, no malnutrition-related risk. GNRI stages in the present study were defined as at risk (<98 points) and not at risk (≥98 points) based on the total GNRI score.

Gender-age-physiology (GAP) index

The GAP index was calculated on the basis of data at the time of iPPFE diagnosis, as previously described [24]: sex (female, 0 points; male, 1 point), age (≤60 years, 0 points; 61–65 years, 1 point; >65 years, 2 points), FVC (%) (>75%, 0 points; 50 %–75%, 1 point; <50%, 2 points), and % DLCO (>55%, 0 points; 36%–55%, 1 point; ≤35%, 2 points; cannot perform, 3 points). The GAP index was defined based on the total GAP score: Stage I (0–3 points), Stage II (4–5 points), and Stage III (6–8 points).

Composite model comprising gender (G), age (A) and malnutrition-related risk (M)

A composite model was generated to assess mortality risk based on the GAP model with gender (G), age (A), and physiology (P) as variables. The presence of major malnutrition-related risk (M) was used to replace the physiology variable in the GAP index. Thus, a composite model was created using gender (G), age (A) and presence of major malnutrition-related risk (M), as age, male sex, and the presence of major malnutrition-related risk were independently associated with increased mortality. Age greater than 60 years and male sex were both included as a risk factor based on the GAP index. A leave-one-out analysis was performed to avoid overfitting of the variables (**Supplementary Figure 1**). A simple scoring system was developed; 1 point was assigned if the patient's age was greater than 60 years, the patient was male sex, or had major malnutrition-related risk (GNRI < 82). Accordingly, patients were categorized into three groups based on the total point scores: mild (0–1), moderate (2) and severe (3). The model was evaluated using Harrell's concordance index (C-index).

Statistical analysis

Discrete variables are presented as totals (%) and continuous variables are presented as medians with interquartile ranges. The Mann–Whitney U test and the Wilcoxon matched-single ranked test were used to compare unmatched and matched continuous variables, respectively. Fisher's exact test for independence was used to compare categorical variables. Cox proportional hazards regression analysis was used to identify factors associated with mortality. Among the statistically significant covariates identified in univariate analysis, clinically relevant and important variables: age, sex, and FVC (%) were selected for inclusion in the multivariate analysis. Cumulative survival probabilities were estimated using the Kaplan–Meier method and Log–rank test. Overall survival time was measured from the date of iPPFE diagnosis or GNRI assessment at one day after diagnosis. Cut-offs for GNRI score at diagnosis were determined according to the median GNRI score or the presence of major malnutrition-related risk, respectively. Cut-offs for annual changes in GNRI were temporally determined accordingly to the first tertile and clinically meaningful time points. All statistical analyses were conducted using R software (version 4.11) [25]. All hypothesis tests were 2-tailed. P-values of <0.05 were considered statistically significant.

RESULTS

Clinical characteristics

Patient clinical characteristic are shown in **Table 1**. The median age was 66 years old and 84 patients (65.6%) were male. Approximately 70% of patients were never-smokers. Physical examination demonstrated a median BMI of 17.2 kg/m^2 and a median FVC of 64.7%, indicating moderate-to-severe reductions in FVC. Lower lobe ILD on chest CT was observed in 81 patients (61.8%). Median serum total protein (TP) and albumin (Alb) levels were 7.3 mg/dl and 4.0 mg/dl, respectively.

Assessment of malnutrition-related risk according to GNRI

The distribution of GNRI score in patients with iPPFE is shown in **Figure 1**. The median GNRI score was 91.8 (84.1–97.4). Only 31 patients (23.7%) were classified as 'no malnutrition-related risk (GNRI ≥ 98)', with 24.4%, 35.9% and 16.0% of patients classified as 'low malnutrition risk (92 ≤ GNRI < 98)', 'moderate malnutrition risk (82 ≤ GNRI < 92)' and 'major malnutrition risk (GNRI < 82),' respectively.

Patients at major risk of malnutrition were significantly older and had poorer pulmonary function than patients at low or moderate risk of malnutrition (**Supplementary Table 1**).

Association between nutritional status and survival

We next assessed survival according to malnutrition-related risk defined by GNRI. Patients with a lower median GNRI (<91.8) had significantly shorter survival than patients with a median GNRI or higher (≥91.8; **Figure 2A**). No significant difference in survival was observed between patients at no risk of malnutrition and those at low risk of malnutrition. However, patients at low risk of malnutrition had significantly longer survival than patients at moderate and major risk of malnutrition (**Figure 2B**). Patients at major risk of malnutrition risk had significantly shorter survival compared to other groups (**Figure 2C**).

Univariate and multivariate analysis of GNRI for mortality

We determined whether malnutrition-related risk defined by GNRI and GNRI score were associated with mortality. Univariate analysis demonstrated that age, sex, FVC, serum albumin, presence of lower lobe ILD, lower GNRI score, and presence of major malnutrition-related risk were significantly associated with increased mortality. BMI was not

associated with mortality (**Table 2**). Multivariate analysis revealed that the presence of major malnutrition-related risk was significantly associated with increased mortality independent of age, sex and FVC (**Table 2**). GNRI score did not remain significant in multivariate analysis. DLCO was evaluated in 84 patients with iPPFE. When GNRI was evaluated together with age, sex, FVC, and DLCO by multivariate analyses, the values of GNRI and DLCO were not significant (**Supplementary Table 2**).

Longitudinal assessment of malnutrition-related risks in patients with iPPFE

Next, we examined the association between mortality and annual changes in nutritional status as assessed by GNRI. Among 131 patients, 109 patients had nutritional assessments both at the time of diagnosis and one year later. GNRI scores decreased significantly from the time of diagnosis to one year after diagnosis (91.5 vs. 89.7, respectively, P = 0.002**; Figure 3A**), with 32 patients (29.4%) found to have a marked decrease in GNRI score (decrease of 5 or more). Patients whose GNRI scores declined by 5 or more had significantly short survival than patients whose GNRI scores declined by less than 5 (**Figure 3B**).

Mortality risk according to age, sex and presence of major malnutrition-related risk in patients with iPPFE.

The GAP model has been widely used and validated as a mortality risk assessment for IPF patients. Therefore, we first attempted to apply the GAP model to assess mortality risk in iPPFE patients. As shown in **Figure 4A**, the GAP model showed poor performance in discriminating mortality. In particular, stage II (moderate) and stage III (severe) survival curves were reversed, with patients with stage II found to worse survival than patients with stage III.

We next attempted to develop a composite model for assessing mortality risk using major malnutrition-related risk together with age and sex as age, sex and the presence of major malnutrition-related risk were independently associated with increased mortality. In line with the GAP index, 1 point was assigned for age >60 years, male sex and presence of major malnutrition-related risk. Patients were categorized into three groups based on total point scores: mild (0–1), moderate (2) and severe (3). Our composite model demonstrated good prognostic separation (median survival times: mild, 24.8; moderate, 38.8; and severe, 98.5 months; C-index, 0.719; **Figure 4B**).

DISCUSSION

The present study assessed nutritional status using the GNRI and evaluated its clinical significance in patients with iPPFE. We found that more than 75% of patients with iPPFE were considered to be at malnutrition-related risk (GNRI < 92) at the time of diagnosis, with major malnutrition-related risk (GNRI < 82) identified in 16.0% of patients. Nutritional status assessed by GNRI significantly decreased one year after diagnosis. Importantly, patients with lower GNRI scores had significantly shorter survival compared to patients with higher GNRI scores. In addition, major malnutrition-related risk was significantly associated with increased mortality in multivariate analysis independent of age, sex and FVC. Moreover, annual decline in nutritional status assessed by GNRI was significantly associated with shorter survival and higher mortality. A simple composite model with age, sex and major malnutrition-related risk yielded good prognostic separation in iPPFE patients. Collectively, these results suggest that the majority of patients with iPPFE have poor nutritional status based on GNRI score and that assessment of nutritional status by GNRI has utility in predicting outcomes in iPPFE patients.

The GNRI, consisting of BMI and serum albumin levels, is a valid tool for assessing malnutrition-related morbidity [10] and mortality in patients with various clinical conditions including acute ischaemic stroke, heart failure, respiratory failure and malignancies [13-17]. However, there have been no studies using GNRI to assess the nutritional status of patients with iPPFE who often have lower BMI and slender body types. The present study is the first to evaluate GNRI in patients with iPPFE. Several comprehensive nutrition scoring systems have been developed to assess nutritional status. However, these scoring systems are typically complex requiring multiple items to be calculated. In contrast, the GNRI is a simple nutrition scoring system requiring only BMI and serum albumin levels, both of which are routinely and easily measured in clinical practice. The present study clearly demonstrated that three-quarters of patients with iPPFE had malnutrition risk according to GNRI, with nutritional status significantly deteriorating at one year after diagnosis. Taken together, these observations indicate that the majority of patients with iPPFE are malnourished at the time of diagnosis and that their nutritional status worsens over time. Indeed, nutritional status, indeterminate efficacy, and a high prevalence of gastrointestinal disorders due to antifibrotic therapy might have had an effect on the small number of patients treated with antifibrotic therapy in this study.

Importantly, the present study demonstrated that poor nutritional status defined by GNRI was associated with mortality risk in patients with iPPFE. Indeed, patients with a lower median GNRI (< 91.8) had significantly poorer survival than patients with a median GNRI or higher (≥ 91.8). In addition, multivariate Cox-regression hazard analysis identified major malnutrition-related risk as a significant prognostic factor independent of age, sex and FVC. However, neither major malnutrition-related risk nor GNRI score were significant when evaluated with age, FVC, and DLCO. This can be attributed to the limited number of patients evaluated for DLCO in the present study. Although BMI is also thought to partially represent

nutritional status, BMI was not a significant prognostic factor even in univariate Cox-regression hazard analysis in our cohort of patients with iPPFE. Our results are consistent with previous studies that examined the association between BMI and mortality risk by Cox-regression hazard analyses in patients with iPPFE [26-28]. The reason for this discrepancy in the prognostic value between GNRI and BMI may be that GNRI is more comprehensive than BMI in assessing nutritional status in iPPFE, and the prevalence of BMI in this study was distributed in a narrow range and as low as BMI 17.2 kg/m^2 [14.9-18.5].

In addition, we found that longitudinal changes in nutritional status assessed by GNRI was associated with mortality risk in iPPFE patients. Patients with a greater decline in GNRI had a significantly poorer prognosis than patients who did not, suggesting that trends in GNRI are also important in predicting the prognosis of patients with iPPFE. Collectively, these observations suggest that GNRI at the time of diagnosis and the trend in GNRI over time are significant prognostic factors in patients with iPPFE. Malnutrition in iPPFE patients represents a multifactorial problem reflecting the complex interplay of systematic inflammation leading to cachexia, worsening nutritional status from poor intake and reduced exercise tolerance due to sarcopenia and dyspnoea. Indeed, our previous study reported that muscle wasting is frequently observed and body composition change evaluated by elector spine muscle attenuation on CT is associated with mortality in patients with iPPFE [26]. In line with our results, interestingly, body-weight loss was strongly correlated with FVC decline in patients with iPPFE and IPF [29, 30]. These results suggest an underlying mechanism between the pathogenesis of lung fibrosis and deterioration of nutritional status. Additionally, a short-term efficacy of pulmonary rehabilitation in terms of exercise capacity was also reported in patients with iPPFE [31]. Therefore, it is of great interest to determine whether direct interventions to improve nutritional status using a nutrition support team,

supplements, or anamorelin, a ghrelin receptor agonist, can improve clinical outcomes in patients with iPPFE.

To date, several prognostic factors including lower FVC [27, 28, 32, 33], presence of lower lobe ILD [28] and history of pneumothorax [34] have been reported in patients with iPPFE [34]. Recently, we also identified upper lobe lung volume measured using 3D-CT and standardised with predicted FVC as a significant prognostic factor in patients with iPPFE [32]. However, the significance of these reported prognostic factors is not fully consistent between previous studies. When predicting the prognosis of patients with a complex disease such as iPPFE, the use of a single modality may be insufficient. Instead, a composite model that includes multiple measurements would be preferable. In this regard, we attempted to develop a composite model using age, gender and presence of major malnutrition-related risk, all of which were found to independent poor prognostic factors in the present study. We found that our composite model had good prognostic discrimination in patients with iPPFE (C-index, 0.719). In contrast, the GAP model performed relatively poorly in discriminating iPPFE prognosis, which is consistent with the results of our previous study. Indeed, survival curves for GAP stage II and GAP stage III were completely inverted in the present study. Recently, we reported a separate composite model using age, sex and standardized upper lobe lung volumes measured by 3D-CT [32]. This 3D-CT model achieved good prognostic separation with a higher C-index (0.762) in patients with iPPFE. However, the use of a 3D-CT composite model is time-consuming and costly, and has the additional weakness of radiation exposure. In contrast, the present composite model is simple and less time-consuming with no radiation exposure. Taken together, our simple composite model using age, sex and presence of major malnutrition-related risk defined by GNRI represents a useful tool for assessing mortality risk in patients with iPPFE during routine clinical practice.

The present study had several limitations. First, this was a retrospective cohort study and the number of patients were relatively small as iPPFE is a rare type of ILD. Additionally, all of the patients were Asian. In particular, the BMI of Asian patients tends to be lower than those of other ethnicities. Therefore, prospective international validation studies involving a larger number of patients are required to confirm the results of the present study. Second, although this study assessed annual changes in nutritional status among patients with iPPFE, the observation period was relatively short. Therefore, future longer-term studies are required fully assess changes in nutritional status over time among patients with iPPFE. Third, the present study assessed nutrition status using GNRI only; however, there are several methods of evaluating nutritional status.

In conclusion, the results of the present study demonstrate that patients with iPPFE frequently have poor and progressively worsening malnutrition as assessed by GNIR. Importantly, nutritional status and annual change in GNIR were significantly associated with increased risk of mortality. Our composite scoring model, including age, sex and presence of major malnutrition-related risk as defined by GNRI, achieved good prognostic separation in patients with iPPFE, indicating that this model has utility in predicting mortality. Collectively, these results indicate that assessment of nutritional status by GNRI provides useful information for managing iPPFE by estimating mortality risk in clinical practice.

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Author contributions

YS: Conception and design, data collection, data analysis and interpretation, manuscript writing, and final approval of the manuscript. AF: data collection, KM: statistical analysis, MKono, HHasegawa, DH, KY and SI: Conception and design, data collection, and data analysis. YI, HY, HHozumi, MKarayama, KF, NE, TF, NI and HN: Data collection, data analysis, and supervision. TS: Conception and design, manuscript writing, and administrative support.

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

FIGURE LEGENDS

Figure 1. Distribution of GNRI scores and malnutrition-related risk in patients with iPPFE at diagnosis.

Distribution of GNRI scores and malnutrition-related risk in patients with iPPFE at the time of diagnosis. iPPFE, idiopathic pleuroparenchymal fibroelastosis; GNRI, Geriatric Nutritional Risk Index.

Figure 2. Association of malnutrition-related risk and mortality in patients with iPPFE.

(**A**) Kaplan–Meier curves of patients with iPPFE according to GNRI scores above and below the median. (**B**) Malnutrition-related risk stratified according to GNRI score. (**C**) Present or absence of major malnutrition-related risk determined by GNRI score. P-values were determined by the Log–rank test. iPPFE, idiopathic pleuroparenchymal fibroelastosis; GNRI, Geriatric Nutritional Risk Index.

Figure 3. Annual changes in nutritional status and association with mortality in patients with iPPFE.

(**A**) Annual changes in GNRI score in patients with iPPFE at the time of diagnosis and at one year after diagnosis. (**B**) Kaplan–Meier curves of patients with iPPFE according to annual changes in GNRI score. P-values were determined by the Log–rank test. iPPFE, idiopathic pleuroparenchymal fibroelastosis; GNRI, Geriatric Nutritional Risk Index.

Figure 4. Kaplan–Meier curves of patients with iPPFE based on age, sex and major malnutrition-related risk.

(**A**) Kaplan–Meier curves of patients with iPPFE according to GAP index. (**B**) Kaplan–Meier curves of patients with iPPFE and age, sex and presence of malnutrition-related risk determined by GNRI. P-values were determined by the Log–rank test. iPPFE, idiopathic pleuroparenchymal fibroelastosis; GNRI, Geriatric Nutritional Risk Index; GAP, gender-age-physiology model.

Supplementary Figure 1. Trends in the discrimination performance according to age and standardized upper lobe-volume.

Trends in the discrimination performance (C-index) by age, sex, and standardized upper lobe volume for mortality. The C-index values at each age are shown. The box plots indicate the C-index distributions acquired using leave-one-out analysis, and the dotted line represents the maximum and minimum values at each point.

Table 1. Clinical characteristics of patients with iPPFE

	iPPFE patients (n=131)
Age, yr	66 [63-76]
Sex, male/female	86 (65.6%) / 45 (34.4%)
Observation period, months	36.4 [20.9-69.3]
Mortality	77 (58.8%)
Smoking never / former	84 (64.1%) / 47 (35.9%)
pack-year	0 [0-10]
BMI, kg/㎡	17.2 [14.8-18.6]
Flat chest	33 (25.2%)
Pulmonary Function Test	
FVC, %-predicted	64.7 [48.2-80.4]
FEV_1, %-predicted	77.9 [60.9-95.5]
FEV_1/FVC, %	95.7 [89.4-100]
DLCO, %	91.2 [71.3-112.9] (n=84)
RV/TLC, %	48.3 [42.5-56.9] (n=82)
CT images	
Presence of lower lobe ILD, yes	81 (61.8%)
UIP pattern (definite, probable, indeterminate, alternative)	14, 35, 25, 7

Laboratory	
PaO_2, Torr	80.2 [71.4-87.9] (n=98)
$PaCO_2$, Torr	46.5 [41.3-50.9] (n=98)
KL-6, U/ml	436 [331-609] (n=128)
SP-D, ng/ml	172 [118-252] (n=126)
LDH, IU/l	193 [173-215]
TP, g/ml	7.3 [7.1-7.7]
Alb, g/ml	4.0 [3.7-4.3]
Antifibrotic therapy	
(Pirfenidone, Nintedanib)	12 (12, 0)

Data are presented as mean ± standard deviation or number (%)

iPPFE, idiopathic pleuroparenchymal fibroelastosis; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; DLCO, diffuse capacity of the lung for carbon monoxide; RV/TLC, residual volume divided by total lung capacity; CT, chest tomography; ILD. interstitial lung disease; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D; LDH, lactate dehydrogenase.

Table 2. Univariate and Multivariate Cox-proportion analysis for mortality in patients with iPPFE

Predictor	HR	95% CI	p-value	Predictor	HR	95% CI	p-value
Univariate analysis				**Multivariate analysis 1**			
Age, yr	1.060	1.034 – 1.087	<0.001	Age, yr	1.049	1.019 – 1.080	0.001
Sex, male	2.251	1.357 – 3.906	0.003	Sex, male	4.496	2.502 – 8.532	<0.001
BMI, kg/m^2	0.964	0.886 – 1.048	0.395	FVC, %-predicted	0.970	0.958 – 0.982	<0.001
Flat chest	0.933	0.576 – 1.564	0.784	Major malnutrition-related risk: GNRI <82	1.957	1.024 – 4.000	0.039
FVC, %-predicted	0.973	0.962 – 0.984	<0.001	**Multivariate analysis 2**			
$FEV_{1.0}$, %-predicted	0.981	0.972 – 0.991	<0.001	Age, yr	1.047	1.018 – 1.079	0.002
$FEV_{1.0}$ / FVC, %	1.093	1.045 – 1.148	<0.001	Sex, male	4.414	2.469 – 8.334	<0.001
DLCO, %	0.983	0.973 – 0.992	<0.001	FVC, %-predicted	0.971	0.958 – 0.983	<0.001
RV/TLC, %	1.069	1.036 – 1.104	<0.001	GNRI, continuous variables	0.979	0.950 – 1.011	0.183
KL-6, U/ml	1.001	1.000 – 1.001	<0.001				
SP-D, U/ml	1.001	1.000 – 1.002	0.005				
TP, mg/dl	0.866	0.590 – 1.270	0.462				
Alb, mg/dl	0.353	0.217 – 0.582	<0.001				
LDH, IU/	1.009	1.004– 1.015	<0.001				
Lower lobe ILD	3.169	1.879 – 5.641	<0.001				
GNRI, continuous variables	0.951	0.927 – 0.976	<0.001				
GNRI, per malnutrition-related risk	1.518	1.185 – 1.960	0.001				
Major malnutrition-related risk: GNRI <82	2.892	1.544 – 5.129	<0.001				

iPPFE, idiopathic pleuroparenchymal fibroelastosis; BMI, body mass index; FVC, forced vital capacity; DLCO, diffuse capacity of the lung for carbon monoxide; RV/TLC, residual volume divided by total lung capacity; KL-6, Krebs von den Lunge-6; ILD, interstitial lung disease

SuppleTable 1. Clinical characteristics of patients with iPPFE

	No malnutrition-related risk (n=31)	Low malnutrition-related risk (n=32)	Moderate malnutrition-related risk (n=47)	Major malnutrition-related risk GNRI < 82 (n=21)	p-values
Age, yr	65 [58-70]	68 [59-74]	71 [64-75]	76 [71-81]	<0.001
Sex, male/female	21 (67.7%) / 10 (32.3%)	18 (56.3%) / 14 (43.8%)	32 (68.1%) / 15 (31.9%)	15 (71.4%) / 6 (28.6%)	0.626
Observation period, months	47.2 [21.2-77.2]	53.8 [21.6-68.9]	35.3 [20.4-76.9]	26.5 [8.4-32.5]	0.020
Mortality	17 (54.8%)	12 (37.5%)	33 (70.2%)	15 (71.4%)	0.018
Smoking never / former pack-year	19 (61.3%) / 12 (38.7%) 0 [0-14]	27 (84.4%) / 5 (15.6%) 0 [0-0]	23 (48.9%) / 24 (51.1%) 2.7 [0-22.3]	15 (71.4%) / 6 (28.6%) 0 [0-8.8]	0.012
BMI, kg/㎡	19.3 [17.9-21.4]	17.3 [15.9-18.5]	16.0 [14.5-17.9]	14.1 [13.1-16.1]	<0.001
Flat chest	8 (25.8%)	4 (12.5%)	13 (27.7%)	8 (38.1%)	0.191
Pulmonary Function Test					
FVC, %-predicted	73.9 [66.3-88.8]	74.7 [54.8-89.7]	53.9 [44.7-67.8]	48.7 [39.6-65.9]	<0.001
FEV_1, %-predicted	88.1 [77.0-99.6]	86.5 [72.7-107.0]	64.1 [55.7-89.6]	63.3 [49.8-77.0]	<0.001
FEV_1/FVC, %	93.6 [85.5-97.0]	94.9 [88.5-100.0]	97.0 [91.6-100]	98.3 [95.4-100]	0.049
DLCO, %	96.1 [69.2-115.4] (n=18)	89.9 [81.9-122.3] (n=19)	80.4 [68.0-107.2] (n=35)	94.3 [77.9-110.6] (n=12)	0.315
RV/TLC, %	41.8 [37.1-43.9] (n=17)	46.6 [41.3-52.8] (n=19)	50.8 [45.3-59.5] (n=35)	59.3 [49.4-68.2] (n=11)	<0.001
CT images					
Presence of lower lobe ILD, yes	18 (58.1%)	18 (56.3%)	29 (61.7%)	16 (76.2%)	0.486
UIP pattern (definite, possible, indeterminate,	4, 9, 5, 0	2, 9, 5, 2	5, 9, 10, 5	3, 8, 5, 0	0.563

alternative)

Laboratory					
PaO_2, Torr	78.6 [70.2-83.0] (n=19)	85.2 [75.9.-89.0] (n=21)	76.0 [70.6-87.6] (n=37)	82.1 [70.8-88.7] (n=21)	0.611
$PaCO_2$, Torr	47.5 [42.1-54.2] (n=19)	45.7 [39.5-48.7] (n=21)	46.8 [42.1-54.3] (n=37)	45.2 [39.7-50.8] (n=21)	0.464
KL-6, U/ml	400 [331-722] (n=31)	410 [290-492] (n=31)	476 [358-581] (n=46)	409 [331-669] (n=20)	0.348
SP-D, ng/ml	202 [136-278] (n=31)	166 [123-250] (n=31)	165 [110-240] (n=45)	169 [116-252] (n=19)	0.791
LDH, IU/l	199 [183-226]	190 [164-216]	188 [168-205]	201 [182-222]	0.192
TP, g/ml	7.5 [7.2-7.9]	7.5 [7.1-7.8]	7.3 [7.1-7.7]	7.1 [6.4-7.4]	0.010
Alb, g/ml	4.4 [4.2-4.5]	4.2 [4.1-4.4]	3.8 [3.6-4.1]	3.3 [3.0-3.6]	<0.001
Antifibrotic therapy					
(Pirfenidone, Nintedanib)	6 (6, 0)	0 (0, 0)	4 (4, 0)	2 (2, 0)	0.060

Data are presented as mean ± standard deviation or number (%)

iPPFE, idiopathic pleuroparenchymal fibroelastosis; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; DLCO, diffuse capacity of the lung for carbon monoxide; RV/TLC, residual volume divided by total lung capacity; CT, chest tomography; ILD. interstitial lung disease; KL-6, Krebs von den Lunge-6; SP-D, surfactant protein-D; LDH, lactate dehydrogenase.

Supplementary Table 2. Age, sex, FVC, and DLCO adjusted multivariate Cox-proportion analysis for mortality in patients with iPPFE

Predictor	HR	95% CI	p-value
Multivariate analysis 3			
Age, yr	1.076	1.031–1.127	0.001
Sex, male	3.364	1.589–7.904	0.003
FVC, %-predicted	0.948	0.927–0.969	<0.001
DLCO, %	0.992	0.983–1.001	0.095
Major malnutrition-related risk: GNRI <82	1.283	0.551–2.726	0.536
Multivariate analysis 4			
Age, yr	1.074	1.027–1.125	0.002
Sex, male	3.550	1.646–8.479	0.002
FVC, %-predicted	0.950	0.927–0.972	<0.001
DLCO, %	0.992	0.983–1.001	0.094
GNRI, continuous variables	0.982	0.936–1.031	0.459

iPPFE, idiopathic pleuroparenchymal fibroelastosis; FVC, forced vital capacity; DLCO, diffuse capacity of the lung for carbon monoxide

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Figure 1

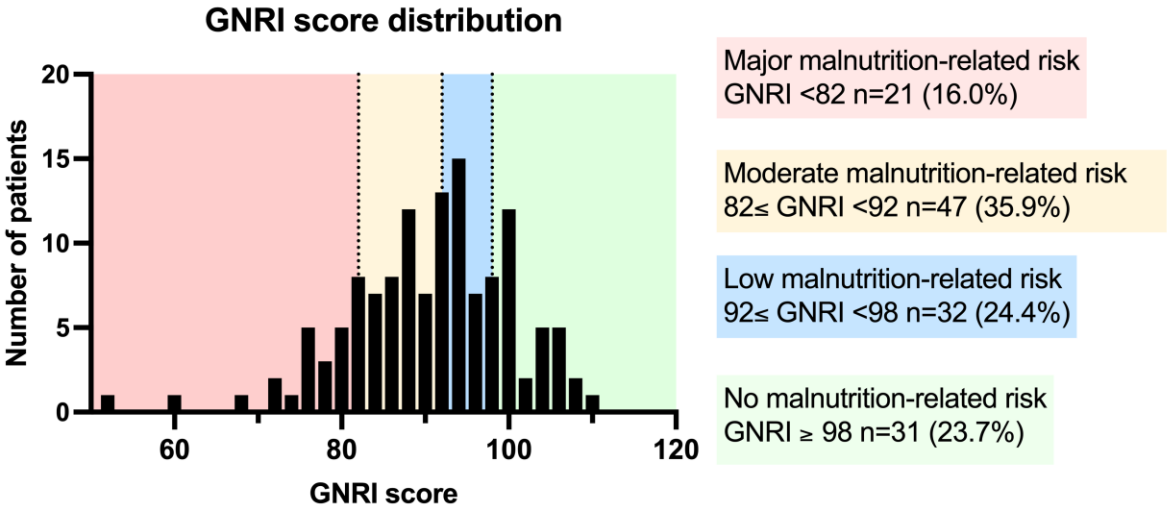
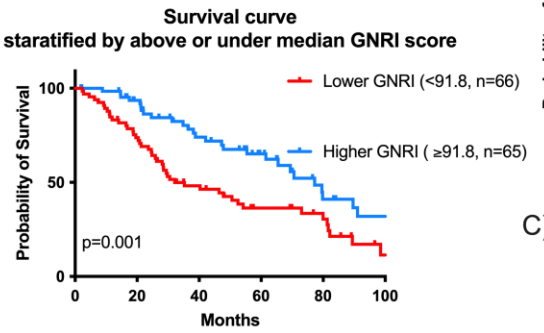
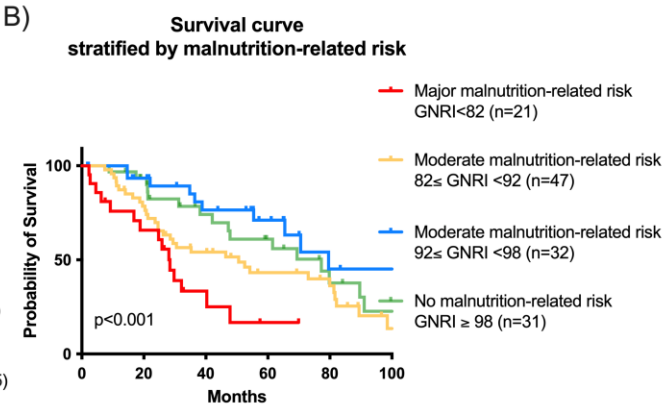

GNRI score distribution
Number of patients
20
15
10
5
0
60
80
100
120
GNRI score
Major malnutrition-related risk
GNRI <82 n=21 (16.0%)
Moderate malnutrition-related risk
82≤ GNRI <92 n=47 (35.9%)
Low malnutrition-related risk
92≤ GNRI <98 n=32 (24.4%)
No malnutrition-related risk
GNRI ≥ 98 n=31 (23.7%)

Figure 2

A)


Survival curve
staratified by above or under median GNRI score
Lower GNRI (<91.8, n=66)
Higher GNRI (≥91.8, n=65)
Probability of Survival
100
50
0
p=0.001
0
20
40
60
80
100
Months

B)


Survival curve
stratified by malnutrition-related risk
Major malnutrition-related risk
GNRI<82 (n=21)
Moderate malnutrition-related risk
82≤ GNRI <92 (n=47)
Moderate malnutrition-related risk
92≤ GNRI <98 (n=32)
No malnutrition-related risk
GNRI ≥ 98 (n=31)
Probability of Survival
100
50
0
p<0.001
0
20
40
60
80
100
Months

C)

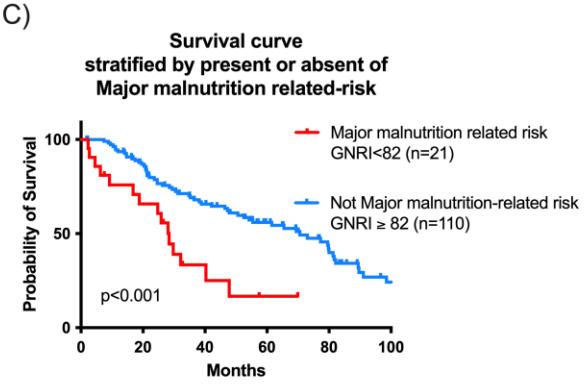
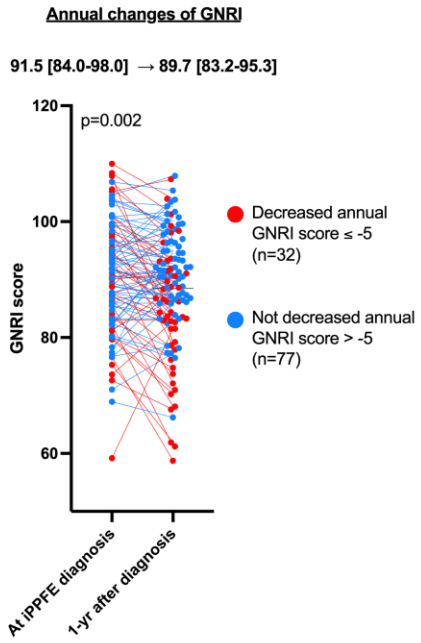

Survival curve
stratified by present or absent of
Major malnutrition related-risk
Major malnutrition related risk
GNRI<82 (n=21)
Not Major malnutrition-related risk
GNRI ≥ 82 (n=110)
Probability of Survival
100
50
0
p<0.001
0
20
40
60
80
100
Months

Figure 3

A)


Annual changes of GNRI
91.5 [84.0-98.0] → 89.7 [83.2-95.3]
p=0.002
GNRI score
120
100
80
60
At IPPFE diagnosis
1-yr after diagnosis
Decreased annual GNRI score ≤ -5 (n=32)
Not decreased annual GNRI score > -5 (n=77)

B)

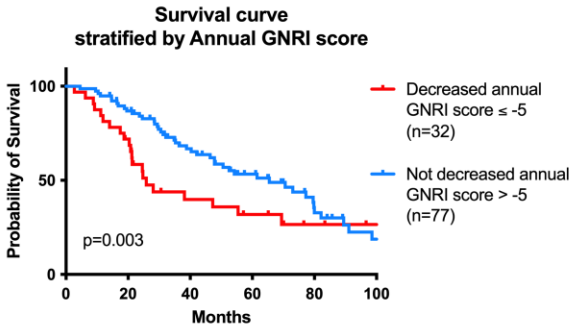
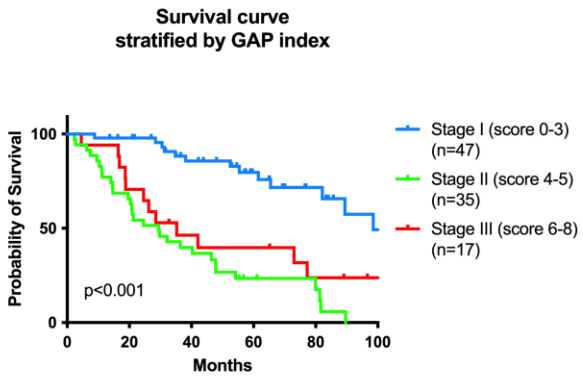
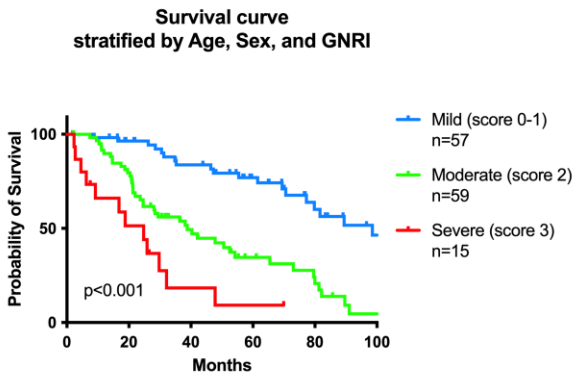

Survival curve
stratified by Annual GNRI score
Probability of Survival
100
50
0
p=0.003
0
20
40
60
80
100
Months
Decreased annual GNRI score ≤ -5 (n=32)
Not decreased annual GNRI score > -5 (n=77)

Figure 4

A)


Survival curve
stratified by GAP index
Probability of Survival
100
50
0
0
20
40
60
80
100
Months
p<0.001
Stage I (score 0-3)
(n=47)
Stage II (score 4-5)
(n=35)
Stage III (score 6-8)
(n=17)

B)


Survival curve
stratified by Age, Sex, and GNRI
Probability of Survival
100
50
0
0
20
40
60
80
100
Months
p<0.001
Mild (score 0-1)
n=57
Moderate (score 2)
n=59
Severe (score 3)
n=15

Supplementary Figure 1