Neutrophil–lymphocyte ratio in patients with idiopathic pleuroparenchymal fibroelastosis

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ABSTRACT

Background Idiopathic pleuroparenchymal fibroelastosis (iPPFE), a progressive fibrotic disease, is characterised by upper lobe–dominant lung fibrosis involving the pleura and subpleural lung parenchyma. However, no prognostic markers have been established for this condition. Associations between blood leucocyte levels and mortality have been reported in patients with idiopathic pulmonary fibrosis; therefore, we hypothesised that peripheral leucocyte levels are associated with mortality risk in patients with iPPFE.

Methods This retrospective study longitudinally assessed peripheral leucocyte counts at the time of diagnosis and 1 year after diagnosis in two cohorts of 127 patients with iPPFE (69 and 58 patients in Seirei and Hamamatsu cohorts, respectively).

Results A comprehensive assessment of peripheral leucocytes revealed that the neutrophil–lymphocyte ratio (NLR) was associated with mortality in patients with iPPFE after adjusting for age, sex and forced vital capacity in multivariate analyses (adjusted HR, 1.131; 95% CI, 1.032 to 1.227). When the patients were classified based on the median NLR, those with a high NLR had shorter survival than those with a low NLR (median, 32.2 vs 79.8 months; HR, 2.270; 95% CI, 1.416 to 3.696). Interestingly, the results of the NLR classification by median were longitudinally preserved in >70% of patients, and patients with consistently high NLR were at a higher risk of mortality than others (median, 24.8 vs 79.6 months; HR, 3.079; 95% CI, 1.878 to 5.031). Compared with the gender–age–physiology model, a composite model comprising age, sex and NLR successfully classified patients with iPPFE into three groups according to mortality risk.

Conclusion The assessment of peripheral leucocyte counts is easy and might be useful in evaluating disease severity and mortality risk in patients with iPPFE. Our study suggests the importance of focusing on peripheral leucocyte levels in daily practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The prognosis of patients with idiopathic pleuroparenchymal fibroelastosis (iPPFE) is similar to or worse than that of patients with idiopathic pulmonary fibrosis. However, no prognostic markers for iPPFE have been fully identified. Furthermore, no study has evaluated the clinical implications of peripheral leucocyte levels in patients with iPPFE.

WHAT THIS STUDY ADDS

⇒ Higher peripheral neutrophil–lymphocyte ratio (NLR) was associated with mortality in patients with iPPFE. A composite model comprising age, sex and NLR successfully classified patients with iPPFE into three groups according to mortality risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study highlighted the importance of focusing on peripheral leucocyte levels in daily practice. Repeated assessment may particularly help in identifying patients with iPPFE at a high risk of mortality.

INTRODUCTION

Idiopathic pleuroparenchymal fibroelastosis (iPPFE) is a rare type of idiopathic interstitial pneumonia characterised by upper lobe–dominant lung fibrosis involving the pleura and subpleural lung parenchyma. Patients with iPPFE frequently suffer from productive cough, dyspnoea on exertion, body weight loss and severe impairment of forced vital capacity (FVC). Importantly, previous studies have shown that the incidence of acute exacerbation is similar between patients with iPPFE and those with idiopathic pulmonary fibrosis (IPF), with the prognosis of iPPFE being reported to be equivalent to or worse than that of IPF. However, effective treatments for iPPFE have not yet been established.

As leucocytes reflect pathophysiology and immune status, such as inflammation, allergy, malnutrition and immune deficiency, the assessment of peripheral leucocytes (counts and differential) is widely performed in clinical settings for various diseases. Interestingly,
recent studies have shown the clinical implications of peripheral leucocytes in various diseases, including lung cancer and IPF. The neutrophil–lymphocyte ratio (NLR) has been reported to be associated with the survival of patients with non-small cell lung cancer treated with immune checkpoint inhibitors.\(^5\) Peripheral monocyte (Mo) counts were positively correlated with fibrotic lesions on chest CT.\(^6\) Furthermore, peripheral Mo counts and NLR are associated with disease progression and all-cause mortality in patients with IPF.\(^7\)\(^,\)\(^11\)

Although there are currently no established prognostic markers for iPPFE, measurements of the upper lobe volume via three-dimensional-CT, malnutrition-related risk, cross-sectional area (ESM\(_{\text{CSA}}\)) and muscle attenuation (ESM\(_{\text{MA}}\)) of the erector spinae muscles to assess mortality risk in patients with iPPFE have been used as markers.\(^12\)\(^,\)\(^13\)\(^,\)\(^14\) However, CT-derived measurements require specialised software and several minutes to analyse individual CT images even when proficient techniques are employed. Therefore, there is a need to develop simple, cost-effective and reproducible biomarkers for iPPFE. This study aimed to evaluate the associations between peripheral leucocyte levels and mortality risk in patients with iPPFE using data at diagnosis and 1 year after diagnosis.

METHODS

Patients

This retrospective study included 146 patients with iPPFE who were diagnosed at Hamamatsu University School of Medicine (Hamamatsu cohort, n=77) and Seirei Hamamatsu Hospital and Seirei Mikatahara Hospital (Seirei cohort, n=69) between March 2004 and February 2021. Among them, 16 patients who were unavailable for peripheral blood analyses and 3 patients who did not undergo peripheral leucocyte differential analysis at the time of iPPFE diagnosis were excluded. Thus, 127 patients with iPPFE were included in the final analysis. The patients were censored if they remained alive until 31 June 2022.

The diagnosis of iPPFE was made via multidisciplinary discussion at the institutes according to the following criteria\(^1\)\(^,\)\(^5\): (1) PPFE radiographic pattern on chest CT, which was 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 the Reddy et al radiological criteria\(^16\); subpleural dense consolidation was defined as consolidation below 1 cm from the apex of the lung (to exclude the pulmonary apical cap), with a minimum width of 1 cm in contact with the pleura\(^15\)\(^,\)\(^19\); (2) radiological 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 radiological assessments; and (3) exclusion of other lung diseases with identifiable aetiologies, such as connective tissue disease-related interstitial lung disease (ILD), chronic hypersensitivity pneumonitis, pulmonary sarcoidosis, pneumocociosis, organ transplantation, concomitant cancers and active pulmonary infection. None of the patients consumed corticosteroids. The high-resolution CT patterns of lower lobe ILD were classified according to the ATS/ERS/JRS/ALAT IPF guidelines.\(^20\)

The requirement for patient approval and/or informed consent was waived owing to the retrospective nature of the study.

Data collection

The following clinical data of the patients were collected from medical records during iPPFE diagnosis: age, sex, physical examination, pack-year smoking history, laboratory test results and pulmonary function test results. The data regarding counts and levels of peripheral leucocytes, including neutrophils (Neut), lymphocytes (Lym), eosinophils (Eo), Mo and basophils (Baso), were also obtained at the time of iPPFE diagnosis and 1 year after diagnosis, if available. The NLR and Systemic Inflammation Response Index (SIRI) were calculated using the following formulas: Neut/Lym and Mono×Neut/Lym, respectively. No patient had active infection when peripheral leucocytes were evaluated.

The Geriatric Nutritional Risk Index (GNRI) score was calculated based on the data at iPPFE diagnosis as follows: GNRI=((1.489×serum albumin (g/L))+(41.7×(actual weight/ideal body weight))).\(^21\) Ideal weight was calculated using the body mass index (BMI) as follows: ideal weight=22×(height (m))\(^2\).

Flat chest was defined as the reduced ratio of antero-posterior and transverse diameters of the thoracic cage at the level of the sixth thoracic vertebra on chest CT.\(^22\)

Composite model comprising gender (G), age (A) and NLR

A composite model was designed to assess mortality risk based on gender (G), age (A) and NLR. Age over 60 years was considered a risk factor based on the gender–age–physiology (GAP) index.\(^23\) To conduct sensitivity analysis of the composite model, the trends of discrimination performance according to several cut-off values of age and NLR were studied to avoid overfitting the variables. A simple scoring system was developed: 1 point was assigned if the patient was aged >60 years, male or had a median NLR exceeding the cut-off value. Accordingly, the patients were categorised into three groups based on the total points: mild (0–1), moderate (2) and severe (3). The model was evaluated using Harrell’s concordance index (C-index).

Statistical analyses

Categorical variables were expressed as total (%), and continuous variables were presented as medians with IQR. The Mann-Whitney U test and Wilcoxon signed-rank 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 in univariate analysis, age, sex and FVC (%) were selected in multivariate analysis as clinically relevant and important variables. Among the leucocyte variables that were statistically significant in univariate analyses, Neut (%), Lym (%), Neut count, Lym count, Lym/Eo ratio, Lym/Mono ratio, SIRI and NLR were selected as covariates in multivariate analyses based on the risk ratio obtained via univariate analyses. Subsequently, these covariates were assessed along with age, sex and FVC (%) using multivariate analyses. The median values of NLR in the Seirei cohort (exploratory cohort) at iPPFE diagnosis and 1 year after diagnosis were determined as cut-off points. Subsequently, the same values were used as cut-off points in the Hamamatsu cohort (validation cohort) and Combined cohort. Cumulative survival probabilities were estimated above and below the median of NLR using the Kaplan-Meier method and Wilcoxon signed-rank test. Overall survival was estimated from the date of iPPFE diagnosis. All statistical analyses were conducted using R software (V.4.1.1). All hypothesis tests were two-tailed, and a p value of <0.05 was considered to indicate statistical significance.

**Patient and public involvement**

Given the retrospective design of this study, patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

**RESULTS**

**Clinical characteristics**

The clinical characteristics of patients with iPPFE are presented in [table 1](#). Most patients were aged approximately 70 years, and >60% of them were men. The median observation period was approximately 3 years. The patients had low BMI (median, 17.0 kg/m²), moderate-to-severe impairments in FVC and high residual volume/total lung capacity ratio. Furthermore, chest CT revealed lower lobe ILD in 60% of patients. The comparison of the Seirei and Hamamatsu cohorts is shown in online supplemental table 1. Patients in the Seirei cohort had lower lobe ILD than those in the Hamamatsu cohort.

**Assessment of peripheral leucocyte levels and their association with mortality**

The results of peripheral leucocyte assessment at iPPFE diagnosis are presented in online supplemental table 2. The median levels of Neut, Lym, Eo, Mono and Baso were 65.5%, 23.5%, 2.9%, 5.7% and 0.5%, respectively. The distributions of Neut, Lym and NLR were similar regardless of the presence of lower lobe ILD on chest CT. To examine the correlation between peripheral leucocyte levels and survival, Cox regression analyses were conducted (online supplemental table 3). Among various covariates, Neut (%), Lym (%), Neut counts, Lym counts, NLR, Lym/Eo ratio, Lym/Mono ratio and SIRI showed a significant difference in univariate analyses. Multivariate analyses revealed that only NLR was associated with mortality risk after adjusting for age, sex and FVC (%) (HR, 1.131 (1.032 to 1.227), p=0.005) ([table 2](#)).

**Table 1** Clinical characteristics of patients with iPPFE

<table>
<thead>
<tr>
<th>Patients with iPPFE (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Sex, male/female</td>
</tr>
<tr>
<td>Observation period, months</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Smoking, never/former pack-year</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Flat chest</td>
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<tr>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>FVC, %</td>
</tr>
<tr>
<td>FEV₁, %</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
</tr>
<tr>
<td>DLCO, %</td>
</tr>
<tr>
<td>RV/TLC, %</td>
</tr>
<tr>
<td>CT images</td>
</tr>
<tr>
<td>Presence of lower lobe ILD, yes</td>
</tr>
<tr>
<td>HRCT pattern (UIP, probable, indeterminate, alternative diagnosis)</td>
</tr>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
</tr>
<tr>
<td>KL-6, U/mL</td>
</tr>
<tr>
<td>SP-D, ng/mL</td>
</tr>
<tr>
<td>LDH, IU/L</td>
</tr>
<tr>
<td>TP, g/mL</td>
</tr>
<tr>
<td>Alb, g/mL</td>
</tr>
<tr>
<td>GNRI score</td>
</tr>
<tr>
<td>Antifibrotic therapy</td>
</tr>
<tr>
<td>(Pirfenidone, nintedanib)</td>
</tr>
</tbody>
</table>

Data are expressed as median (IQR). Alb, albumin; BMI, body mass index; DLCO, diffuse capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GNRI, Geriatric Nutritional Risk Index; ILD, interstitial lung disease; iPPFE, idiopathic pleuroparenchymal fibroelastosis; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; RV/TLC, residual volume divided by the total lung capacity; SP-D, surfactant protein-D; TP, total protein; UIP, usual interstitial pneumonia.

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Other sets of multivariate analyses are presented in online supplemental table 4.

**Association between NLR and survival in patients with iPPFE**

We next assessed survival according to NLR. The distributions of NLR in the Seirei (exploratory cohort), Hamamatsu (validation cohort) and Combined cohorts were similar (median 2.775 (1.665–4.280), 2.620 (1.835–3.890), 2.775 (1.790–4.020), respectively). Subsequently, the median NLR of the Seirei cohort (cut-off 2.775) was applied to the Hamamatsu and Combined cohorts. The clinical characteristics of patients with iPPFE having high (>2.775) or low (<2.775) median NLR are presented in online supplemental table 5. Patients with high NLR were associated with older age, lower BMI, decreased albumin and impaired spirometry compared with those with low NLR. Patients with high NLR showed lower GNRI score than those with low NLR, and NLR was negatively associated with GNRI score (online supplemental figure 1). Furthermore, patients with high median NLR (>2.775) in the Seirei cohort had significantly shorter survival than those with low median NLR (<2.775) (median, 34.8 vs 89.4 months; HR, 2.703; 95% CI, 1.358 to 5.658; figure 1A). Using the same cut-off value, we obtained similar findings in the Hamamatsu (median, 32.2 vs 79.8 months; HR, 1.940; 95% CI, 1.007 to 3.931; figure 1B) and Combined (median, 32.2 vs 79.8 months; HR, 2.270; 95% CI, 1.416 to 3.696; figure 1C) cohorts.

**Longitudinal changes in the NLR of patients with iPPFE**

We examined the longitudinal changes in the counts and levels of peripheral leucocytes at the time of iPPFE diagnosis and 1 year after diagnosis (online supplemental table 1). Overall, no significant differences were observed in leucocyte counts and levels between diagnosis and 1 year after diagnosis; the levels and absolute counts of Neut tended to increase, whereas those of Lym tended to decrease. Similar to NLR at iPPFE diagnosis, the distributions of NLR at 1 year after iPPFE diagnosis in Seirei, Hamamatsu and Combined cohorts were similar (median 3.000 (1.858–5.097), 2.878 (1.798–4.395) and 3.000 (1.816–4.728), respectively). The median NLR in the Combined cohort increased from 2.775 to 3.000 (figure 2A). Interestingly, 40 of 55 (72.7%) patients with low median NLR at diagnosis (<2.775) still had low median NLR at 1 year after diagnosis (<3.000). Similarly, 40 of 55 (72.7%) patients with high median NLR at diagnosis (>2.775) still had high median NLR after 1 year (>3.000) (figure 2B).

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**Table 2 Multivariate Cox proportional hazards analysis for mortality in patients with iPPFE**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.064</td>
<td>1.033 to 1.098</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, male</td>
<td>6.197</td>
<td>3.254 to 12.537</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC, %</td>
<td>0.966</td>
<td>0.952 to 0.980</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neut/Lym ratio</td>
<td>1.131</td>
<td>1.032 to 1.227</td>
<td>0.005</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; iPPFE, idiopathic pleuroparenchymal fibroelastosis; Lym, lymphocytes; Neut, neutrophils.
Further, another set of survival analyses was conducted based on NLR classification based on median value obtained in the Combined cohort (figure 2B). Interestingly, patients with iPPFE who consistently had high NLR showed worse outcomes than those who did not (HR, 3.079; 95% CI, 1.878 to 5.031; figure 2C).

**Clinical utility of NLR for assessing mortality risk**

The GAP index, a composite simple scoring system, is useful in predicting mortality in patients with IPF and other types of ILD. Therefore, we first attempted to apply the GAP index in patients with iPPFE. As presented in figure 3A, the GAP model (available n=97) exhibited poor performance in discriminating iPPFE-associated mortality risk (median survival time, 98.5 vs 27.0 vs 31.9 months; C-index, 0.696). Notably, the survival curves for stage II (moderate) and stage III (severe) were reversed.

Next, we attempted to evaluate mortality risk in patients with iPPFE using age, sex and NLR. In line with the GAP index, 1 point was assigned for age >60 years, male sex and NLR ≥2.775. The median value of NLR was used as the cut-off point. The trends of discrimination performance according to age and NLR are presented in online supplemental figure 3. The patients were categorised into three groups based on the total points: mild (0–1), moderate (2) and severe (3). This model successfully classified the patients with iPPFE into three groups based on survival times (median survival times: mild, 98.5; moderate, 47.8; and severe, 21.3 months; C-index, 0.737; figure 3B). The subset analyses according to each cohort were also shown in online supplemental figure 4, and consistent results were obtained.

**DISCUSSION**

This study longitudinally evaluated the prognostic implications of peripheral leucocytes in patients with iPPFE. Interestingly, increased Neut and lymphocytopenia (both counts and differential) were associated with high mortality risk, and NLR was most strongly associated with mortality after adjusting for age, sex and FVC. When the median value was used as the cut-off value, patients with higher NLR had significantly shorter survival than those with lower NLR. A composite model comprising age, sex and NLR categorised the patients into three groups according to mortality risk. Thus, peripheral leucocyte assessment can provide clinically useful information for managing patients with iPPFE.

To the best of our knowledge, this is the first study to examine the possible association between peripheral leucocytes and the prognosis of iPPFE. This study revealed that increased Neut counts, decreased Lym counts and increased NLR were associated with mortality in patients with iPPFE. Conversely, Mo counts were not significantly associated with mortality. Three previous studies analysing five cohorts of patients with IPF revealed that patients with IPF having high Mo counts (≥0.95×10⁹ cell/L) were at a high risk of all-cause mortality. Meanwhile,
Achaiah et al reported that Mo counts were not associated with disease progression or all-cause mortality in patients with IPF; however, they found that increased Neut counts, decreased Lym counts and increased NLR were risk factors for mortality and disease progression. These differences could be explained by the difference in study populations; the proportion of patients with Mo counts of ≥0.95x10^9 cell/L varied by 2.4%–18.9% among the cohorts in previous studies; however, none of the patients had Mo counts of ≥0.95x10^9 cell/L in this study. Furthermore, these differences may be attributed to the differences in the pathophysiology of iPPFE and IPF.

The present study showed that high NLR in patients with iPPFE was associated with low BMI and decreased serum albumin levels. With regards to immune-nutrition, malnutrition is a well-known cause of lymphocytopenia. Recently, we reported that 73.3% of patients with iPPFE showed malnutrition-related risks at the time of diagnosis according to the GNRI that consists of BMI and serum albumin levels. Conversely, a previous study showed that BMI of patients with IPF was greater than that of patients with iPPFE (median BMI: 23.1 kg/m^2 vs 17.2 kg/m^2). Malnutrition-related risks were observed in 38% of patients with IPF receiving antifibrotic therapy according to the GNRI. Indeed, significant negative correlations were found in the NLR and GNRI of patients with iPPFE (online supplemental figure 1). Thus, higher NLR may be partly associated with nutritional disorder in patients with iPPFE.

The pathophysiologies of IPF and iPPFE have not been fully elucidated. The distinct pathological features of iPPFE include intra-alveolar fibrosis and elastosis with visceral pleural fibrosis, which differ from those of usual interstitial pneumonia (UIP)/IPF. However, substantial patients with iPPFE had lower lobe ILD, suggesting possibly shared underlying mechanisms between iPPFE and IPF. The current conceptual model of lung fibrosis is characterised by recurrent epithelial injury and subsequent aberrant repair along with exaggerated inflammatory and fibrotic responses, leading to extracellular matrix deposition and fibrotic tissue remodelling, which in turn can result in fibrosis formation. Immune cells and certain genetic backgrounds may be involved in this process. Previous studies have demonstrated that immune cells, including Neut, Lym and Mo, play pivotal roles in the pathogenesis of lung fibrosis. In addition, previous clinical data have shown that increased Neut levels in bronchiolar alveolar lavages are associated with worse outcomes in patients with IPF. Although these studies examined the association between fibrosis and pulmonary microenvironments, including immune cells, it remains unclear whether changes in peripheral leucocyte levels reflect the pathophysiology of pulmonary fibrosis. Further studies are warranted to elucidate these findings.

Next, this study evaluated peripheral leucocyte levels both at diagnosis and 1 year after diagnosis and revealed that high NLR was longitudinally associated with poor outcome in patients with iPPFE. In our cohorts, the
results of NLR classifications by median value were preserved in >70% of patients between diagnosis and 1 year after diagnosis. This finding was supported by a previous study conducted by Scott et al, who showed that patients with IPF and high Mo counts (≥0.95×10^9 cell/L) maintained their high counts throughout the course of the disease. Similarly, the expression profiles of peripheral blood genes that were associated with outcomes in IPF (mortality and transplant-free survival) tended to remain conserved over time. This study also demonstrated that patients who repeatedly had high NLR were at a higher risk of mortality than others. Collectively, these results indicated the advantages of peripheral leucocyte assessment, including simplicity, low invasiveness, cost-effectiveness and repeatability. Repeated evaluations may be useful in increasing the certainty of identifying patients with iPPFE at a higher risk of mortality.

This study has several limitations. First, this was a retrospective cohort study, and the number of patients was relatively small because iPPFE is a rare type of ILD. Although this study showed that NLR classifications by median value were longitudinally preserved in >70% of patients, the NLR of other patients varied. Thus, NLR can potentially be changed in some degrees. Similarly, NLR may be influenced by comorbidity and therapeutic interventions. Third, the role of NLR in the pathogenesis of iPPFE and pulmonary fibrosis remains unclear. To confirm our observations and elucidate the association between peripheral leucocyte levels and the pathophysiology of iPPFE, further prospective validation studies are warranted.

In conclusion, this study longitudinally evaluated the association between peripheral leucocyte levels and mortality risk in patients with iPPFE. Among peripheral leucocyte variables, increased Neut and decreased Lym counts were associated with poor survival, and increased NLR was most associated with mortality risk in patients with iPPFE both at diagnosis and 1 year after diagnosis. Importantly, longitudinal and repeated assessments are potentially useful in identifying patients with iPPFE at a high risk of mortality. Our composite model consisting of NLR, age and sex successfully classified the patients with iPPFE based on prognosis. These results suggest the clinical utility of peripheral leucocyte assessment in managing patients with iPPFE.

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Contributors YS: Conceptualisation, data curation, formal analysis, project administration, resources, writing—original draft, funding acquisition and final approval of the manuscript. MKo, HHa, DH, KY and SI: Conceptualisation, data curation, formal analysis, resources and writing—review and editing. YI, HHo, DK, KY and SI: Data curation, formal analysis, resources and writing—review and editing. TF, YT, NH, TF and NI: Data curation, formal analysis, resources and writing—review and editing. YS is the guarantor for this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Ethical Committee of Hamamatsu University School of Medicine (22-108), and the study was conducted in accordance with approved guidelines.

Provenance and peer review Not commissioned; externally peer reviewed.

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

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