The Gender–Age–Physiology system as a prognostic model in patients with idiopathic pulmonary fibrosis treated with nintedanib: a longitudinal cohort study

Abstract

Introduction: The Gender-Age-Physiology (GAP) system is a tool for predicting prognosis in patients with idiopathic pulmonary fibrosis (IPF). Yet, to date, the GAP system has not been evaluated in patients with IPF who received nintedanib.

Material and methods: This single-center retrospective study included 89 patients with IPF who received nintedanib for at least 3 months. All-cause mortality was set as the end point. Clinical parameters, including the GAP stage, were statistically analyzed for risk factors leading to mortality using the Cox proportional hazard model.

Results: The median follow-up was 16.4 months (range 3.7–37.4 months), during which 23 patients died. Univariate analysis revealed that the GAP stage (hazard ratio [HR] 3.00, 95% confidence interval [CI] 1.52–5.92, p = 0.0014) and PaO₂ (HR 0.95, 95% CI 0.92–0.98, p = 0.0063) were significant prognostic factors. Multivariate analysis revealed that the GAP stage was a significant prognostic factor (HR 2.26, 95% CI 1.07–4.78, p = 0.031). Log-rank analysis revealed that there were no significant differences in “Gender” (p = 0.47) and “Age” (p = 0.18) factors. However, there were significant differences in “Physiology” factors (% of forced vital capacity, p = 0.018; % of diffusing capacity of lung carbon monoxide, p < 0.001). The cumulative incidences of mortality at 1 and 2 years were as follows: GAP I: 5.1% and 6.8%; GAP II: 9.5% and 29.3%; and GAP III: 18.9% and 84.2%.

Conclusions: The GAP system is useful as a prognostic tool in patients with IPF who have been treated with nintedanib.

Key words: diffusing capacity of lung carbon monoxide, forced vital capacity, GAP stage, idiopathic pulmonary fibrosis, nintedanib

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia [1]. IPF exhibits a poor prognosis similar to many types of cancers, with an average survival time of 2–3 years after diagnosis [2–4]. Pulmonary function tests are important in the evaluation of the severity of IPF [1, 4]. In pulmonary function testing, the forced vital capacity (FVC) and the diffusion capacity of lung carbon monoxide (ḊLCO) have been identified as important prognostic factors in patients with IPF [2, 5, 6].

Nintedanib is a tyrosine-kinase inhibitor that targets vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptors [7, 8]. In the most recent international clinical practice guidelines, nintedanib received a conditional recommendation for the treatment of IPF [9]. It should be noted that although nintedanib was useful in patients with severe IPF who did not meet the eligibility criteria for clinical trials of nintedanib (INPULSIS-1/2 trial [10]), we previously reported that the prognosis of these patients was worse [11].

An accurate evaluation of a patient’s clinical severity combined with a theory regarding prognosis are both very important clinical issues in determining appropriate treatment. Several prognostic

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factors for IPF have been reported including male gender [12], elderly age [13], %FVC at baseline [13–15], and %DLCO at baseline [14]. In addition, serum biomarkers (surfactant proteins A and D [16], C-C motif chemokine ligand 18 [15], and matrix metalloproteinase collagen fragments [17]) and gene polymorphisms (MUC5B promoter polymorphism [18]) have been reported as prognostic factors. However, as these biomarkers are difficult to measure in general hospitals, they are not always used as prognostic factors in clinical practice.

The Gender-Age-Physiology (GAP) system has been reported as a simple and useful tool for the prediction of prognosis in patients with IPF in several nationwide IPF registries (e.g., Germany, Australia, and South Korea) [19–22]. However, these registries include many patients who were registered prior to the increased use of antifibrotic drugs. Since 2015, antifibrotic agents (e.g., pirfenidone and nintedanib) have been recommended as treatments for IPF [9].

Recently, the GAP system was evaluated as a prognostic model in patients with IPF treated with pirfenidone [23–25]. However, to date, the GAP system has not been evaluated in patients with IPF who received other recommended antifibrotic agents such as nintedanib. Therefore, in this study, we retrospectively examined whether the GAP system is useful as a prognostic model in patients with IPF who have received nintedanib.

Materials and methods

This single-center, retrospective study was performed in accordance with the amended Declaration of Helsinki. The research protocol was approved by the Human Ethics Committee of Chiba University Hospital (approval number: 3481). We obtained informed consent with an option to opt out.

Patients

Overall, 142 consecutive patients received nintedanib in the Chiba University Hospital between November 2015 and December 2018. Patients who did not have IPF (n = 31), patients with lung cancer at the start of nintedanib (n = 8), and patients who received nintedanib for acute exacerbations (n = 3) were excluded. Of the remaining 100 patients, 11 patients were excluded because they discontinued treatment within 3 months of starting therapy with nintedanib. Ultimately, 89 patients with IPF were enrolled (Figure 1).

GAP system

The GAP score was calculated according to the report by Ley et al. [19]: gender (female, 0 points; male, 1 point), age (≤ 60 years, 0 points; 61–65 years, 1 point; > 65, 2 points), %FVC (≥ 75%, 0 points; 50–75, 1 point; < 50, 2 points), and %DLCO (≥ 55%, 0; 36–55, 1 point; ≤ 35, 2 points; cannot obtain DLCO, 3 points). The GAP stage was determined based on the total GAP score: stage I (0–3 points), stage II (4–5 points), and stage III (6–8 points).

JRS severity staging system

The JRS severity staging system consists of the combination of two known prognostic variables which are resting arterial partial pressure of oxygen (PaO₂) and peripheral capillary oxygen saturation (SpO₂) in the 6-minute walk test (6MWT).

![Figure 1. Study flow chart. In total, 124 patients received nintedanib in our hospital between November 2015 and December 2018. Patients who did not have IPF (n = 26), with lung cancer at the start of nintedanib treatment (n = 6), and who received nintedanib for acute exacerbation stage (n = 3) were excluded. Of the remaining 92 patients, 12 were excluded because they discontinued treatment within 3 months of nintedanib administration. Ultimately, 82 patients with IPF were enrolled (GAP stage I, n = 20; GAP stage II, n = 45; GAP stage III, n = 17). GAP — Gender-Age-Physiology stage; IPF — idiopathic pulmonary fibrosis.](image-url)
The present severity staging system for IPF defines PaO₂ ≥ 80 Torr at rest as stage I, 70–79 Torr as stage II, 60–69 Torr as stage III, and < 60 Torr as stage IV. If the SpO₂ at the end of 6MWT is < 90%, then the severity should be increased by one stage for patients with stage II or III.

**Statistical analysis**

The clinical data regarding continuous variables are expressed as the mean ± standard deviation. The categorical variables are given as percentages. The Cox proportional hazard model analysis was used to identify significant factors for predicting patient mortality. Kaplan-Meier survival curves and log-rank tests were used to compare patient survival according to GAP stages. The level of significance (p value (p) < 0.05) was adopted as statistically significant. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28] and the graphical user interface for R (R version 3.2.0, The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

The baseline characteristics of the included patients (GAP I, n = 22; GAP II, n = 48; GAP III, n = 19) are shown in Table 1. The median duration of follow-up time, which started following 3 months of treatment, was 16.4 months (range 3.7–37.4 months). Twenty-three deaths (25%) were observed during the follow-up time (GAP I, n = 2 [9%]; GAP II, n = 11 [22%]; GAP III, n = 10 [52%]). The causes of death are shown in Table 2. Ten patients died of chronic pulmonary failure and eight patients died due to an acute exacerbation of disease.

The log-rank test result revealed a significant difference in mortality among the three groups (GAP I, II, and III; p = 0.0013; Figure 2). The cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.1 % and 6.8 %; GAP II, 9.5 % and 29.3 %; and GAP III, 18.9 % and 84.2 %.

The survival curves drawn for each of the four factors comprising the GAP system (gender, age, %FVC, and %DLCO) are shown in Figures 3–6. There were no significant differences between male and female patients (p = 0.47; Figure 3), or among the three age groups (p = 0.18; Figure 4). There was a significant difference among the three groups in %FVC (p = 0.018; Figure 5) and %DLCO (p < 0.001; Figure 6).

The log-rank test result also revealed a significant difference in the survival of patients who were not admitted for hospital care among the

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**Table 1. Baseline characteristics of 89 included patients**

|                        | Total (n = 89) | GAP I (n = 22) | GAP II (n = 48) | GAP III (n = 19) |
|------------------------|---------------|---------------|----------------|-----------------|
| Age                    | 71.3 ± 6.2    | 70.3 ± 5.4    | 71.6 ± 7.0    | 71.5 ± 4.6     |
| Male, n (%)            | 68 (76%)      | 15 (68%)      | 39 (81%)      | 14 (73%)       |
| Smoker, n (%)          | 68 (76%)      | 15 (68%)      | 38 (79%)      | 15 (78%)       |
| BMI (kg/m²)            | 23.8 ± 4.0    | 23.9 ± 4.0    | 23.9 ± 4.1    | 23.4 ± 3.7     |
| Severity staging system in JRS (I/II/III/IV) | 29 / 4 / 26 / 30 | 13 / 1 / 5 / 3 | 14 / 2 / 17 / 15 | 2 / 1 / 4 / 12 |
| UIP pattern in HRCT    | 66 (74%)      | 13 (59%)      | 37 (77%)      | 16 (84%)       |
| Pre-treatment with PFD | 32 (35%)      | 4 (18%)       | 15 (31%)      | 13 (68%)       |
| Long-term home oxygen therapy | 23 (25%) | 3 (13%) | 9 (18%) | 11 (57%) |
| PaO₂ (mm Hg)           | 73 ± 13       | 81 ± 13       | 73 ± 12       | 63 ± 11        |
| Minimum SpO₂ by 6MWT (%) | 80 ± 9       | 83 ± 10       | 80 ± 7        | 75 ± 12        |
| KL-6 (U/mL)            | 1421 ± 1114   | 1252 ± 953    | 1323 ± 1106   | 1889 ± 1242    |
| FVC (mL)               | 2172 ± 802    | 2735 ± 833    | 2129 ± 706    | 1601 ± 544     |
| %FVC (%)               | 67 ± 19       | 86 ± 17       | 64 ± 14       | 50 ± 11        |
| %DLCO (%)              | 56 ± 21       | 71 ± 9        | 54 ± 22       | 32 ± 7         |
| Follow-up duration, median [range] (month) | 16.4 [3.7–37.4] | 16.5 [4.5–33.9] | 18.1 [3.7–37.4] | 12.5 [4.0–36.0] |
| Death, n (%)           | 23 (25%)      | 2 (9%)        | 11 (22%)      | 10 (52%)       |

6MWT — 6 minutes walk test; BMI — body mass index; DLCO — diffusing capacity of the lungs for carbon monoxide; FVC — forced vital capacity; GAP — Gender Age-Physiology; HRCT — high-resolution computed tomography; JRS — Japan respiratory society; KL-6 — Krebs von den Lungen-6; PFD — pirfenidone; UIP — usual interstitial pneumonia
Figure 2. Survival curves of GAP stages I, II, and III. The log-rank test result reveals a significant difference in mortality among the three groups (GAP I, II, and III) (*p = 0.0013*). GAP — Gender-Age-Physiology stage.

Figure 3. Survival curves between male and female patients. The log-rank test result reveals no significant difference between male and female patients (*p = 0.40*).

Figure 4. Survival curves of the three age groups. The log-rank test result reveals no significant difference among the three age groups (*p = 0.14*). Y.o. — years old.

Figure 5. Survival curves of the three groups of %FVC. The log-rank test result reveals a significant difference among the three groups of %FVC (*p = 0.015*). %FVC — percentage of forced vital capacity.

| Table 2. Cause of death |
|------------------------|
| **Total (n = 89)**     |
| **GAP I (n = 22)**     |
| **GAP II (n = 48)**    |
| **GAP III (n = 19)**   |
| Death, n (%)           | 23 (25%) | 2 (9%) | 11 (22%) | 10 (52%) |
| Chronic pulmonary failure | 10      | 0      | 6        | 4        |
| Acute exacerbation     | 8       | 0      | 4        | 4        |
| Lung cancer            | 2       | 1      | 1        | 0        |
| Pneumonia              | 3       | 1      | 0        | 2        |

GAP — Gender-Age-Physiology
Univariate analysis revealed that the GAP stage [hazard ratio (HR) 3.00, 95% confidence interval (CI) 1.52–5.92, p = 0.0014], PaO₂ (HR 0.95, 95% CI 0.92–0.98, p = 0.0063), and long-term home oxygen therapy (HR 2.72, 95% CI 1.17–6.28, p = 0.018) were significant risk factors (Table 3). Additionally, the %FVC (HR 0.96, 95% CI 0.93–0.98, p = 0.0042) and the %DLCO (HR 0.93, 95% CI 0.90–0.97, p < 0.001), which constitute the GAP stage, were demonstrated as significant risk factors. Multivariate analysis with the GAP stage, PaO₂, and body mass index (BMI), which had low p-values in the univariate analysis, showed that the GAP stage (HR 2.26, 95% CI 1.07–4.78, p = 0.031) and BMI (HR 0.89, 95% CI 0.80–0.99, p = 0.048) were significant prognostic factors (Table 3).

**Discussion**

To the best of our knowledge, this is the first study to demonstrate that the GAP system, which is a prognostic model for patients with IPF, also has prognostic value in patients with IPF that had been treated with the antifibrotic agent nintedanib (Figure 2). In Japan, the JRS severity system is a classification system based on PaO₂ and the lowest Spo₂ in the 6MWT. In the present study, we found that while PaO₂ was a significant prognostic factor in univariate analysis, the JRS severity system was not (Table 3). Moreover, multivariate analysis revealed that the GAP system and BMI were also significant prognostic factors. The GAP system has been reported as a simple and useful tool for the prediction of prognosis in patients with IPF [19]. However, the use of the GAP system as a prognostic model was proposed before the widespread use of antifibrotic drugs for IPF treatment. Therefore, it was potentially less useful in the context of antifibrotic drug treatment. Recently, the GAP system has been validated as a prognostic model for patients with IPF receiving the antifibrotic drug pirfenidone [23–25]. Our current results confirm these findings and suggest that the GAP system is also an appropriate prognostic model for patients with IPF receiving the antifibrotic drug nintedanib.

In this study, %FVC was the strongest prognostic factor among the four items evaluated in the GAP system. The effects of age and gender were weaker than those of %FVC and %DLCO (Figures 3–6). We found no significant differences in sex (HR 0.72, 95% CI 0.29–1.76, p = 0.47) in the univariate analysis, although male patients tended to have a better prognosis (Figure 3). In the original report of the GAP system by Ley et al. [19], sex had a lower impact on prognosis compared with other factors. Although mortality due to IPF was initially reported to be higher in men [12], a recent study by Song et al. [29] found that among 380 patients with IPF, survival time was nearly equivalent between male (46.6 months) and female (45.0 months) patients (Chi-squared test result reveals a significant difference among the three groups of %DLCO (p < 0.001). %DLCO, diffusing capacity of lung carbon monoxide.
Table 3. Univariate and multivariate analysis of survival

|                                | Univariate analysis |                   |            | Multivariate analysis |                   |            |
|--------------------------------|---------------------|-------------------|-----------|-----------------------|-------------------|-----------|
|                                | HR                  | 95% CI            | p-value   | HR                    | 95% CI            | p-value   |
| Age                            | 0.98                | 0.93–1.04         | 0.63      |                       |                   |           |
| Male                           | 0.72                | 0.29–1.76         | 0.47      |                       |                   |           |
| Smoker                         | 0.96                | 0.35–2.60         | 0.94      |                       |                   |           |
| BMI                            | 0.90                | 0.82–1.00         | 0.056     | 0.89                  | 0.80–0.99         | 0.048     |
| Severity staging system in JRS | 1.37                | 0.95–1.99         | 0.091     |                       |                   |           |
| GAP stage                      | 3.00                | 1.52–5.92         | 0.0014    | 2.26                  | 1.07–4.78         | 0.031     |
| UIP pattern in HRCT            | 2.30                | 0.68–7.77         | 0.17      |                       |                   |           |
| Pre-treatment with PFD         | 1.47                | 0.88–2.45         | 0.13      |                       |                   |           |
| Long-term home oxygen therapy  | 2.50                | 1.10–5.68         | 0.027     |                       |                   |           |
| \(\text{PaO}_2\)                | 0.95                | 0.92–0.98         | 0.0063    | 0.97                  | 0.93–1.00         | 0.11      |
| Minimum \(\text{SpO}_2\) by 6MWT| 0.96                | 0.93–1.00         | 0.061     |                       |                   |           |
| KL-6                           | 1.00                | 0.99–1.00         | 0.91      |                       |                   |           |
| FVC                            | 0.50                | 0.27–0.90         | 0.022     |                       |                   |           |
| \%FVC                          | 0.96                | 0.93–0.98         | 0.0042    |                       |                   |           |
| \%DLCO                         | 0.95                | 0.92–0.98         | 0.0023    |                       |                   |           |

6MWT — 6 minutes walk test; BMI — body mass index; CI — confidence interval; \(\text{DLCO}\) — diffusing capacity of the lungs for carbon monoxide; FVC — forced vital capacity; GAP — Gender-Age-Physiology; HR — hazard ratio; HRCT — high-resolution computed tomography; JRS — Japan Respiratory Society; KL-6 — Krebs von den Lungen-6; UIP — usual interstitial pneumonia; PFD — pirfenidone

These findings are consistent with the outcome of our study and together suggest that the administration of nintedanib does not affect the relationship between gender and prognosis.

In the present study, elderly people (> 65 years) did not have a worse prognosis than young people (≤ 60 years). While Song et al. [29] reported that younger patients (< 50 years) tended to have a good prognosis compared to that of elderly patients (> 75 years), the difference was not significant (Kolmogorov-Smirnov test, \(p = 0.268\)). One potential reason for this difference is due to nintedanib’s high frequency of side effects (e.g., diarrhea, anorexia, liver injury) [10]. Elderly patients with a poor general condition might not have received nintedanib due to their attending physician’s preferences. This may have affected the assessment of differences in prognosis by age.

In this study, the cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.1% and 6.8%; GAP II, 9.5% and 29.3%; and GAP III, 18.9% and 84.2%, respectively. These results are similar to those reported by Harari et al. [25] in their study of patients who received pirfenidone (GAP I, 8.4% and 17.2%; GAP II, 17.6% and 34.2%; and GAP III 28.3% and 51.2%, respectively) thus indicating the validity of the present study. Together, these findings also suggest that the therapeutic effects obtained by nintedanib and pirfenidone might be similar.

Notably, our results showed that patients with GAP stage III have an extremely poor prognosis. Therefore, it is desirable to start treatment of these patients immediately. However, our results indicate that for patients with IPF with GAP stage I/II, it is also important to start early treatment with antifibrotic drugs. In the original report of the GAP system by Ley et al., [19] the cumulative incidences of mortality at 1 and 2 years were as follows: GAP I, 5.6% and 10.9%; GAP II, 16.2% and 29.9%; and GAP III 39.2% and 62.8%. Although obtaining a direct comparison between the studies is difficult due to differences in patient background, the overall mortality rate in the present study tended to be better than that reported by Ley et al. [19]. However, it should be noted that the 2-year mortality rate for GAP III patients was higher in the present study. The long-term effects of nintedanib in patients with advanced IPF are unknown and should be clarified in further studies.

Our study revealed that the GAP system is not only a prognostic model, but also an appropriate predictive model of survival in non-admitted pa-
tients with IPF who were receiving the antifibrotic drug nintedanib (Figure 7).

This study had some limitations. Firstly, the study had a retrospective, single-center design with a small sample size. Secondy, the median follow-up duration was short. Therefore, in the future, it will be necessary to demonstrate the usefulness of the GAP system in patients receiving antifibrotic drugs in a large-scale, nationwide, prospective study.

Conclusions

The GAP stage is useful as a prognostic tool in patients with IPF who have been treated with nintedanib. The physiological parameters of the GAP system (%FVC and %DLco) are of particular importance with regard to patient prognosis.

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Authors’ contributions

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Competing interests

MA, KT s, and KT a report receipt of personal fees from Boehringer Ingelheim Japan.

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