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Can biomarkers predict survival in idiopathic pulmonary fibrosis?

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Abstract:

BACKGROUND AND AIM: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disorder of unknown origin, affecting approximately 3 million individuals globally. Its incidence is increasing, and the median survival following diagnosis is around three years. The aim of this study is to investigate the relationship between Krebs von den Lungen-6 (KL-6), surfactant protein A (SP-A), surfactant protein D (SP-D), matrix metalloproteinase-7 (MMP-7), vascular endothelial growth factor (VEGF), periostin, and pro-B-type natriuretic peptide (pro-BNP) levels and the prognosis of IPF, and to evaluate these markers according to the gender-age-physiology (GAP) index.

METHODS: Forty-seven patients diagnosed with IPF between March 2020 and January 2022 in the Eskisehir Osmangazi University Faculty of Medicine, Chest Diseases Clinic, were included in the study. The patients were followed closely, with radiological and pulmonary function tests every six months. Serum samples were analyzed for KL-6, SP-A, SP-D, MMP-7, VEGF, and periostin levels.

RESULTS: The mean age of patients was 68±7 years. Twelve patients died during the study period. None of the biomarkers showed a significant association with survival in univariate Cox regression analyses. However, GAP Stage 3 was associated with markedly increased mortality compared to Stage 1 (hazard ratio=7.25, p=0.017). Biomarker levels did not differ significantly between GAP stage groups, except for pro-BNP, which was higher in Stage 3 compared to Stage 1 (p=0.021).

CONCLUSIONS: Our results show that serum KL-6, SP-A, SP-D, MMP-7, VEGF, and periostin levels were not predictive of survival in IPF, while pro-BNP levels differed across GAP stages, and GAP Stage 3 was strongly associated with mortality. Although we did not find these biomarkers to be predictive of survival, multicenter studies with larger patient cohorts may provide further insights.

Keywords:

Idiopathic pulmonary fibrosis, biomarkers, survival

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disorder of unknown origin, affecting approximately 3 million individuals globally. Its incidence is increasing, and the median survival following diagnosis is around

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3 years.[1] It is the most common and most severe type of idiopathic interstitial pneumonia.[2] The annual incidence of IPF is estimated to be 2.8–9.3 per 100,000, and this rate is increasing over time.[3,4] The mortality rate has been reported as 13.36 per 100,000.[3]

In IPF, recent studies have revealed potential mechanisms and biomarkers associated with disease progression.[5,6] Krebs von den Lungen-6 (KL-6), primarily expressed by type II alveolar epithelial and bronchial epithelial cells, has been shown to increase markedly in response to regeneration of damaged alveolar epithelium. This elevation in KL-6 levels in the alveolar basement membranes correlates positively with the severity of fibrotic tissue damage in IPF patients.[7,8] Surfactant protein-A (SP-A) and SP-D are members of the collectin family. Plasma SP-A and SP-D levels, which are primarily secreted by alveolar epithelial type II pneumocytes, have been found to increase early after alveolar epithelial disruption.[9,10] Matrix metalloproteinase-7 (MMP-7) is another biomarker secreted by alveolar macrophages and epithelial cells in individuals with IPF. Although it is found in the lung tissue of IPF patients, it is not detected in the lung tissue of healthy individuals.[11] In addition, increased levels of MMP-7 have been reported in bronchoalveolar lavage (BAL) fluid of IPF patients.[12] Vascular endothelial growth factor (VEGF) is a glycoprotein secreted by alveolar epithelial cells that promotes vascular permeability and plays a key role in angiogenesis. Abnormal angiogenesis is thought to be associated with fibrosis in many interstitial lung diseases, and VEGF is being investigated as a potential biomarker.[13] Periostin, a matricellular protein, is found in high concentrations in the lung tissues of patients with IPF and is believed to play a significant role in the fibrotic process. However, its impact on the proliferation of lung fibroblasts remains unclear.[14] In addition, the gender-age-physiology (GAP) index, which was developed based on clinical and physiological parameters, is also used to determine mortality in IPF.[15] The GAP index is simple and convenient to use and has been demonstrated to be reliable for predicting survival in previous studies.[16]

The aim of our study was to determine the relationship between KL-6, SP-A, SP-D, MMP-7, VEGF, periostin, and pro-B-type natriuretic peptide (pro-BNP) levels and the prognosis of IPF, and to evaluate the relationship of these biomarkers with the GAP index. Several studies have investigated changes in KL-6, SP-A, SP-D, MMP-7, VEGF, periostin, and pro-BNP expression in IPF and their association with disease progression. Therefore, this study further deepens the understanding of the roles of biomarkers in IPF, explores their potential clinical applications, and highlights the importance of serum biomarkers in the development of IPF.

Materials and Methods

Study design and participants

This prospective study included 47 patients diagnosed with IPF at the Eskişehir Osmangazi University Faculty of Medicine, Chest Diseases Clinic, between March 2020 and January 2022. All patients, independent of received therapies were followed up regularly, and patients who died during the course of the study were recorded.

Inclusion criteria for the study patient group were as follows:

- Adults aged 18 years or older,
- Newly diagnosed patients,
- Patients who had never been treated,
- Patients without cancer.

The study was approved by the Eskişehir Osmangazi University Faculty of Medicine Ethics Committee (Approval Number: 15, Date: 04.02.2020), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Study variables

The demographic data of the patients at the time of diagnosis, pulmonary function test—the diffusing capacity of the lung for carbon monoxide (PFT-DLCO)—measurements, and high-resolution computed tomography (HRCT) findings were recorded. Patients were staged according to the GAP index. Blood samples were collected into plain tubes, centrifuged at 1500 g for 10 minutes, and serum was separated. Serum samples were stored at -40°C until analysis. KL-6, SP-A, SP-D, MMP-7, VEGF, periostin, and pro-BNP levels were then analyzed in blood samples collected at the time of diagnosis in the Biochemistry Laboratory.

Pro-BNP levels were measured by electrochemiluminescence immunoassay on a cobas e 601 immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). Results were reported as pg/dL. KL-6, SP-A, SP-D, MMP-7, VEGF, and periostin levels were determined by enzyme-linked immunosorbent assay (ELISA).

Statistical analysis

Data analysis was performed with IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp). Summary values of quantitative (numeric) variables were presented as mean±standard deviation and median (Q1-Q3), while summary values of qualitative (categorical) variables were presented as frequency and percentage. The normality of quantitative variables was assessed with the Shapiro-Wilk test, and the homogeneity of variances was assessed with the Levene test. Comparisons of two independent groups with normally distributed data were performed using the independent samples t-test, and comparisons of three groups were made with one-way analysis of variance (ANOVA). When the data exhibited a non-normal distribution, the Mann-Whitney U test was employed for the comparison of two independent groups, while the Kruskal-Wallis test was used for the comparison of three groups. Pairwise comparisons of the groups were made with Bonferroni or Games-Howell tests for significant ANOVA results, while the Dunn test was used for significant Kruskal-Wallis test results. Survival functions of GAP stages were obtained using the Kaplan-Meier method. The log-rank test was used to compare survival functions. The Bonferroni adjustment procedure was applied for pairwise comparisons of survival functions. Univariate Cox regression was applied for biomarkers, age, sex, and GAP stage. Since only one variable showed $p<0.20$, multivariable Cox regression was not conducted. A p value of less than 0.05 was considered significant.

Results

The mean age of the 47 patients included in the study was 68±7 years, and 39 (83%) were male. The median follow-up period for IPF patients was 16 months (range: 1–23). Twelve of these patients died during follow-up. The results of the comparison of basic demographic and clinical characteristics between groups are presented in Table 1. No statistically significant differences were observed between the groups in terms of mean age, sex distribution, smoking status, antifibrotic treatment, or GAP stages ($p>0.05$). When the KL-6, SP-A, SP-D, MMP-7, VEGF, periostin, and pro-BNP levels at the time of diagnosis were evaluated, no significant difference was found between the patients who survived and those who died during follow-up in terms of the survival effect of biomarkers (Table 2). Biomarker levels of patients who survived and died during follow-up are shown in Figure 1.

Table 1: Baseline demographics of the study population

Variables	Patients who are alive (n=35)		Patients who died (n=12)		p
	n	%	n	%	
Age	68±8 69 (60–75)		69±6 70 (66–75)		0.76
Gender					
Male	30	85.7	9	75	0.403
Female	5	14.3	3	25	
Smoking					
Non-smoker	8	22.9	3	25	0.908
Smoker	9	25.7	2	16.7	
Ex-smoker	18	51.4	7	58.3	
Antifibrotic treatment					
Yes	29	82.9	11	91.7	0.417
No	6	17.1	1	8.3	
GAP stage					
Stage 1	18	52.9	4	33.3	0.163
Stage 2	14	41.2	5	41.7	
Stage 3	2	5.9	3	25	

Patients with IPF were then grouped according to the GAP index. Mean survival times of GAP stage groups are given in Table 3. When survival functions were compared according to the GAP stages, at least one was found to differ from the others ($p=0.012$). Survival time in Stage 3 was significantly lower than in Stage 1 ($p=0.015$) and Stage 2 ($p=0.036$). Survival functions of GAP stages are shown in Figure 2.

To reveal the relationship between GAP stages and biomarker levels, biomarker levels were compared according to GAP stage groups and are presented in Table 4. There were no significant differences between GAP stage groups in terms of SP-A ($p=0.918$), SP-D ($p=0.729$), periostin ($p=0.724$), KL-6 ($p=0.829$), MMP-7 ($p=0.979$,) and VEGF levels ($p=0.860$). On the other hand, GAP stage groups differed significantly according to pro-BNP levels ($p=0.021$). Pairwise comparison results revealed that pro-BNP values differed between Stage 1 and Stage 3 groups ($p=0.021$), while no significant differences were found between Stage 1 and Stage 2 groups ($p=0.380$) or between Stage 2 and Stage 3 groups ($p=0.241$). The biomarker levels according to the GAP stage groups are shown in Figure 3.

In the univariate Cox regression analyses, none of the investigated biomarkers, demographic variables, or GAP stage (except for Stage 3 vs. Stage 1) were significantly associated with survival (all $p>0.05$). Compared to GAP Stage 1, patients classified as GAP Stage 3 had a markedly elevated mortality risk, with more than a sevenfold higher hazard

Table 2: Biomarker levels of survivors and patients with idiopathic pulmonary fibrosis (IPF)

Biomarker	Patients who are alive (n=35) mean±SD median (Q1-Q3)	Patients who died (n=12) mean±SD median (Q1-Q3)	p
SP-A (ng/mL)	8.3±4.0 7.5 (6.9–8.4)	8.1±3.0 7.5 (6.7–8.0)	0.575
SP-D (ng/mL)	149.5±79.6 130.7 (115.5–155.8)	124.5±46.6 114.1 (100.0–127.9)	0.073
KL-6 (U/mL)	154.3±76.9 136.9 (128.5–162.9)	153.4±67.8 140.5 (115.8–155.5)	0.502
Periostin (pg/mL)	696.0±3258.0 643.0 (590.3–708.9)	707.2±281.0 0.845 633.5 (570.3–717.8)	
VEGF (pg/mL)	118.3±51.3 109.1 (97.9–127.1)	116.9±50.3 102.9 (94.8–117.7)	0.329
MMP-7 (ng/mL)	2.3±0.9 2.2 (1.9–2.5)	2.2±1.2 2.0 (1.7–2.1)	0.143
pro-BNP (pg/mL)	519.8±1211.3 171.0 (70.0–391.0)	1807.7±2692.1 397.0 (86.0–3034.5)	0.098

SP-A: Surfactant protein A, SP-D: Surfactant protein D, MMP-7: Matrix metalloproteinase 7, VEGF: Vascular endothelial growth factor, KL-6: Krebs von den Lungen-6, pro-BNP: Pro-brain natriuretic peptide, SD: Standard deviation

of death (hazard ratio [HR]=7.25; p=0.017). A multivariate Cox model was not established because only a univariate model yielded a result with p<0.20. The results of the univariate Cox regression models are presented in Table 5.

Discussion

In this study, the relationship between KL-6, SP-A, SP-D, MMP-7, VEGF, periostin, and pro-BNP levels and the prognosis of IPF was investigated. GAP stage groups were created and compared with each other according to these biomarker values. Only pro-BNP levels differed between GAP Stage 1 and Stage 3 (p=0.021). The effects of demographic variables, GAP stage, and biomarkers on patient survival were also evaluated. It was observed that patients classified as GAP Stage 3 had a significantly higher risk of mortality. Our findings showed that none of the evaluated biomarkers, including KL-6, SP-A, SP-D, MMP-7, VEGF, and periostin, were significantly related to survival.

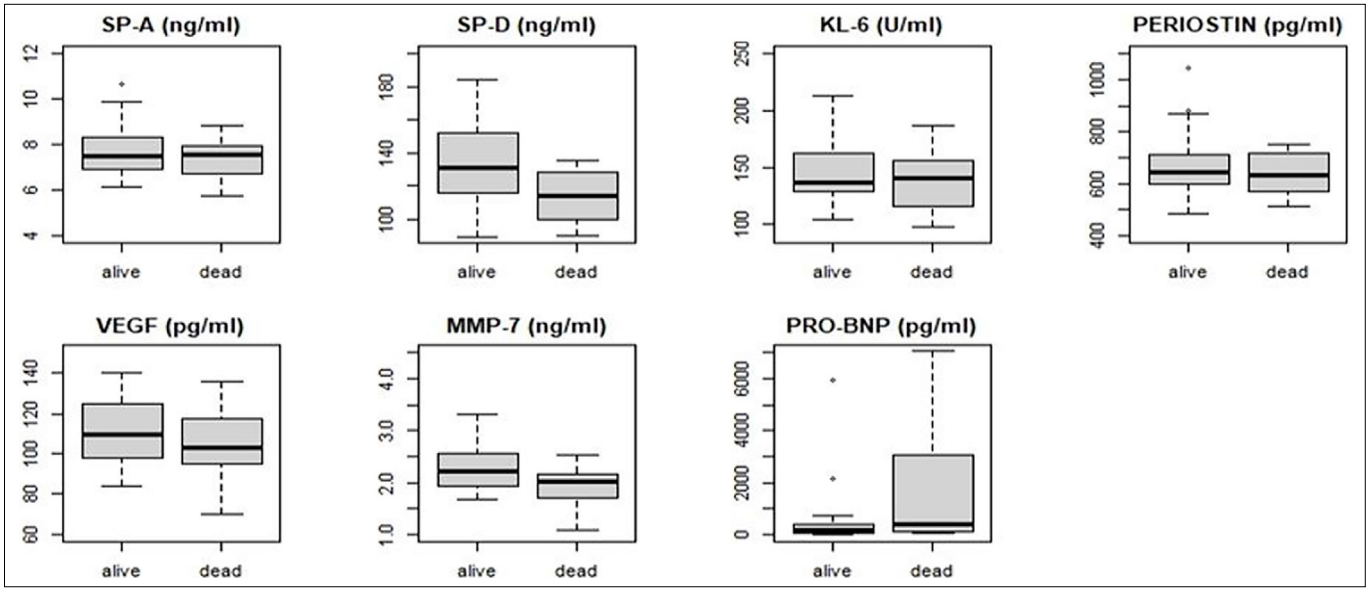

Figure 1: Biomarker levels of patients with IPF who survived and died during follow-up

SP-A: Surfactant protein A, SP-D: Surfactant protein D, MMP-7: Matrix metalloproteinase 7, VEGF, Vascular endothelial growth factor, KL-6: Krebs von den Lungen-6, Pro-BNP: Pro-brain natriuretic peptide, IPF: Idiopathic pulmonary fibrosis

Table 3: Mean survival times according to the gender–age–physiology (GAP) stages

GAP stage (n)	Life expectancy (months) Mean±SD
1 (22)	20.6±1.5
2 (20)	19.8±1.3
3 (5)	11.3±1.3

SD: Standard deviation

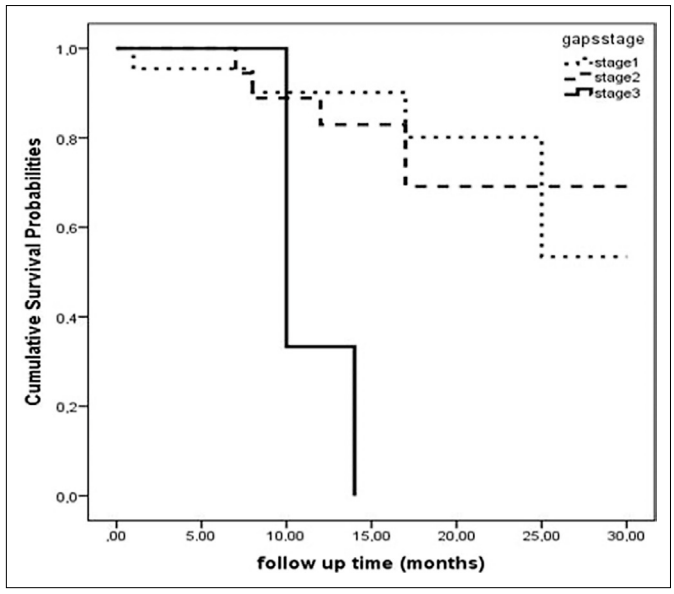

Figure 2: Survival functions of GAP stages
GAP: Gender-age-physiology

Studies have been carried out on biomarkers to determine disease prognosis in IPF, but there are still no accepted, sensitive, and specific biochemical tests or biomarkers. In the study conducted by d'Alessandro et al.,[17] serum KL-6 concentrations were shown to identify patients with fibrotic disease, and high baseline KL-6 levels were found to be significantly associated with worse survival. Barlo et al.[18] compared the median SP-D values of 72 IPF patients and 305 healthy controls and found that surfactant protein-D serum levels were significantly higher in patients than in controls ($p<0.0001$). The median survival time was 13 months in patients with high levels (>460 ng/mL) and 67 months in the group with low levels (<460 ng/mL). Richards et al.[19] reported a relationship between MMP-7 levels and mortality and disease progression in 241 patients with IPF. Their findings indicated that high MMP-7 concentrations were predictive of reduced overall survival, transplant-free survival, and progression-free survival. In a study conducted by Song et al.[20] with 118 IPF patients, two-year follow-up results of MMP-7 and SP-A levels were compared, and one-year survival was found to be 59% in patients with high levels of both biomarkers and 83.3% in patients with low levels. In a study by Tzouvelekis et al.[21] including 97 IPF patients and 41 healthy controls, the cut-off threshold of 12.1 ng/mL of plasma MMP-7 was used as a dichotomous variable and clearly differentiated high- from low-risk mortality groups, as assessed by significant associations with both all-cause mortality and transplant-free survival. The all-cause mortality rate was 41% (20 deaths) in the high MMP-7 group and 2% (one death) in the low MMP-7 group. In a study conducted by Ando et al.[22] in 41 patients with IPF, it was determined that patients with serum VEGF levels above the average had a tendency toward worse

Table 4: Comparison of biomarker levels according to the gender–age–physiology (GAP) stages

Biomarker	Stage 1 mean±SD median (Q1-Q3)	Stage 2 mean±SD median (Q1-Q3)	Stage 3 mean±SD median (Q1-Q3)	p
SP-A (ng/mL)	8.9±5.3	7.8±1.3	7.4±1.0	0.918
	7.5 (6.9–9.2)	7.5 (6.9–8.1)	7.6 (6.9–7.6)	
SP-D (ng/mL)	158.3±99.2	131.5±38.7	121.8±19.9	0.729
	132.1 (107.2–166.5)	123.0 (107.5–146.3)	124.6 (112.4–135.1)	
Periostin (pg/mL)	757.5±444.3	661.9±87.4	615.3±85.9	0.724
	637.9 (610.3–742.6)	655.6 (590.3–708.9)	635.4 (556.6–641.5)	
KL-6 (U/mL)	166.6±95.9	141.2±25.5	153.5±27.6	0.829
	137.5 (127.7–176.5)	146.0 (127.3–157.7)	142.1 (132.0–178.3)	
MMP-7 (ng/mL)	2.4±1.4	2.2±0.5	2.2±0.4	0.979
	2.1 (1.8–2.4)	2.1 (1.9–2.5)	2.2 (2.1–2.4)	
VEGF (pg/mL)	129.3±71.0	108.4±16.9	109.6±16.4	0.860
	110.1 (96.1–127.9)	108.7 (97.9–118.2)	102.8 (97.9–113.2)	
pro-BNP (pg/mL)	831.8±1935.5	735.6±1444.5	2218.2±3233.8	**0.021**
	91.5 (34.5–293.5)	203.0 (102.0–564.0)	706.0 (536.5–3900.0)	

SP-A: Surfactant protein A, SP-D: Surfactant protein D, MMP-7: Matrix metalloproteinase 7, VEGF: Vascular endothelial growth factor, KL-6: Krebs von den Lungen-6, pro-BNP: Pro-brain natriuretic peptide, SD: Standard deviation

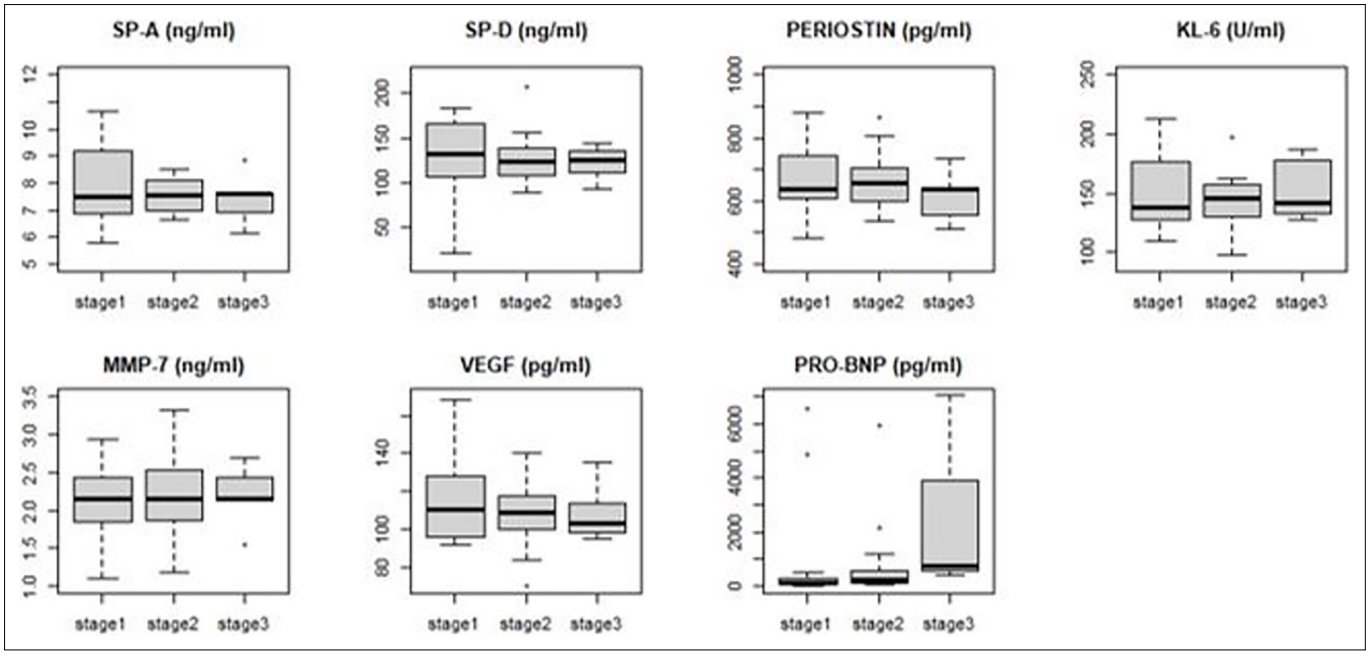

Figure 3: Biomarker levels according to the GAP stages

SP-A: Surfactant protein A, SP-D: Surfactant protein D, MMP-7: Matrix metalloproteinase 7, VEGF, Vascular endothelial growth factor, KL-6: Krebs von den Lungen-6, Pro-BNP: Pro-brain natriuretic peptide, GAP: Gender-age-physiology

survival compared to those with serum VEGF levels below the average (five-year survival rates were 42.9% and 80%, respectively). Shimizu et al.[23] evaluated periostin levels by comparing IPF patients with a healthy control group. The serum M-PN (monomeric periostin) level of the group with acute exacerbation (n=37) was found to be significantly higher than the control group (n=5) (p=0.02), but there was no significant difference in those with stable IPF (n=11) (p=1.00). A cut-off value of -2.7 ng/mL (85.7% sensitivity; 75% specificity) for M-PN change at three months was used to predict survival using receiver operating characteristic (ROC) analysis. The patients were then divided into two groups: decreased group (n=13, <-2.7 ng/mL) and increased group (n=11, ≥-2.7 ng/mL). Three-month survival was significantly better in the decreased group (92.3%) compared to the increased group (36.3%) (p=0.002). Compared with previous studies involving larger patient cohorts, our study, which included a smaller number of participants, did not observe a significant association between the studied biomarkers and survival (Table 5).

In the study performed by Song et al.[24] in 131 patients with IPF, serum pro-BNP levels and echocardiographic findings were compared. Pulmonary hypertension was found in 25% of the patients, and serum pro-BNP levels were high in 14.5%. The one-year mortality rate was 70.5% in patients with high pro-BNP levels, while it was 23.7% in patients with normal pro-BNP levels. The relationship between high pro-BNP levels and mortality is well established.[25,26] Although pro-BNP does not play a role in the pathogenesis of IPF, it is thought that elevated pro-BNP levels can be used as a prognostic biomarker. In our study, when survival times were compared according to GAP stage, it was found that the prognosis of patients in the Stage 3 group was worse than in the other groups. There was no statistically significant difference between Stages 1

Table 5: Results of univariate Cox regression models

Variables	HR	95% CI	p
SP-A	0.995	0.865–1.146	0.949
KL-6	1.001	0.995–1.008	0.688
SP-D	0.997	0.987–1.007	0.588
Periostin	1	0.999–1.002	0.851
VEGF	1.001	0.991–1.011	0.913
MMP-7	1.015	0.583–1.768	0.958
Age	1.027	0.944–1.117	0.535
Gender	1.82	0.491–6.743	0.37
GAP stage*			
Stage 2	21.152	0.308–4.306	0.833
Stage 3	7.252	1.432–36.726	**0.017**

*: Reference category: Stage 1. HR: Hazard ratio, CI: Confidence interval, SP-A: Surfactant protein A, SP-D: Surfactant protein D, MMP-7: Matrix metalloproteinase 7, VEGF: Vascular endothelial growth factor, KL-6: Krebs von den Lungen-6

and 2 (p=1.000). Pro-BNP levels of patients in the Stage 3 IPF group, classified according to GAP stage, were significantly higher than those in Stage 1 (p=0.021), but there was no statistically significant difference between Stages 1 and 2 or between Stages 2 and 3 (p=0.380 and p=0.241, respectively).

In a study conducted by Lee et al.,[27] 1,262 patients diagnosed with IPF were evaluated according to GAP staging. Of these, 760 patients were grouped as Stage I, 455 as Stage II, and 47 as Stage III, and then patients were further separated according to their GAP index. Study results showed that higher GAP scores and GAP stages were associated with worse prognosis. Survival time in Group 3 was lower than in Groups 1 and 2 (p=0.043 and p=0.039, respectively) and higher than in Groups 4, 5, and 6. (p=0.043, p=0.032, and p=0.003, respectively). In our study, when survival times were compared according to GAP stage, the prognosis of patients in the Stage 3 group was again found to be worse than in the other groups.

While the pro-BNP levels of patients in Stage 3 were found to be significantly higher than those in Stage 1 (p=0.021), there was no statistically significant difference between Stage 1 and Stage 2, or between Stage 2 and Stage 3 (p=0.380 and p=0.241, respectively). When biomarker levels were compared according to GAP stages, no significant differences were found for SP-A, SP-D, periostin, KL-6, MMP-7, or VEGF (p=0.918, p=0.729, p=0.724, p=0.829, p=0.979, and p=0.860, respectively).

Our study has several limitations. It was a single-center study with a relatively small patient cohort, and only 12 deaths were observed during follow-up, which limited the statistical power of our analyses. While we did not find serum KL-6, SP-A, SP-D, MMP-7, VEGF, pro-BNP, or periostin levels to be predictive of survival, larger multicenter studies with more events are needed to validate these findings and further explore the potential prognostic relevance of these biomarkers.

Conclusion

Our study findings indicate that these biomarkers were not significantly predictive of survival in patients with IPF, whereas GAP Stage 3 showed a clear association with mortality. Future multicenter studies with larger patient cohorts may help clarify these relationships.

Ethics Committee Approval

The study was approved by the Eskisehir Osmangazi University Faculty of Medicine Non-interventional Clinical Research Ethics Committee (No: 15, Date: 04/02/2020).

Informed Consent

Written informed consent was obtained from all patients who participated in this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

No AI technologies were utilized.

Author Contributions

Concept – A.K., F.A., H.Y.; Design – A.K., F.A.; Supervision – A.K., F.A.; Resource – A.K., F.A., İ.Ö.A.; Materials – F.A., H.Y.; Data Collection and/or Processing – A.K., F.A., İ.Ö.A., H.Y.; Analysis and/or Interpretation – İ.Ö.A., H.Ö.; Literature Review – A.K., F.A.; Writing – A.K., F.A., H.Ö.; Critical Review – A.K., F.A., H.Y., H.Ö.

Peer-review

Externally peer-reviewed.

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