의학석사 학위논문

Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis

한국인 특발성폐섬유화증 환자에서 GAP 점수의 유용성 검증

2014 년 2 월

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의학과 내과학 전공

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A thesis of the Degree of Master of Science in Medicine

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February 2014

The Department of Medicine,

Seoul National University

College of Medicine

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Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis

by
Kim Eun Sun

A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Internal Medicine) at Seoul National University College of Medicine

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Approved by Thesis Committee:

Professor Young Whan Kim Chairman
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한국인 특발성폐섬유화증 환자에서 GAP 점수의 유용성 검증

지도 교수 이 상 민

이 논문을 의학석사 학위논문으로 제출함

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김은선

김은선의 의학석사 학위논문을 인준함

2013년 12월

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ABSTRACT

Introduction: The GAP model has been validated in independent cohorts in western countries. However, no study has assessed whether the risk of mortality predicted by GAP model matches the observed mortality in different populations. We evaluated the clinical course of IPF and validated the GAP model in Korean IPF patients.

Methods: We included 268 patients who had been diagnosed with IPF according to established clinical and histologic criteria in Seoul National University Hospital between 2005 and 2009. For each patient, demographics, and lung physiologic parameters such as percent predicted functional vital capacity (FVC), percent predicted carbon monoxide diffusing capacity (DLco) at the diagnosis of IPF were evaluated. The occurrence of respiratory hospitalization, acute exacerbation of IPF, mechanical ventilator care, and death were also evaluated. Finally, we validated the GAP model using discrimination and calibration to predict the risk of death in Korean IPF patients.

Results: The study population consisted of 181 men and 87 women, with a mean age of 65.9 year (SD = 9.6). Mean baseline of percent predicted FVC was 77.8 (SD = 18.8) and percent predicted DLco was 65.9 (SD = 21.7). 54 (20.1%) patients underwent surgical lung biopsy to confirm the diagnosis, and 10 (3.7%) were diagnosed with lung cancer. 157 (58.6%) deaths occurred

during the follow-up period, and median time to death was 4.64 years. Observed cumulative mortality at 1, 2, and 3 years were 10.4%, 20.9%, and 31.0%, respectively and cumulative mortality incidence differed substantially among GAP stages ($p < 0.001$). The GAP model produced estimates of 1-year mortality risk consistent with observed data (c-statistics: GAP calculator 0.74 and GAP index and staging system 0.72, $p < 0.29$). However, Calibration (c-statistics: GAP calculator 0.68 and GAP index and staging system 0.69) and discrimination ($p < 0.001$) of GAP model were compromised with under-prediction of 3-year risk of death.

Conclusions: The GAP model did not predict the 3-year risk of death accurately in Korean IPF patients. Further external validation or modification of the GAP model is needed before using it in a clinical setting in Korea.

Keywords: Idiopathic pulmonary fibrosis, GAP model, mortality
Student number: 2012-21681

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LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

IPF - Idiopathic Pulmonary Fibrosis

GAP - Gender, Age, and 2 Physiology variables

(FVC and DL_{co})

FVC - Forced Vital Capacity

FEV1 - Forced Expiratory Volume in 1 second

DL_{co} - Diffusing capacity from carbon monoxide

PFT - Pulmonary Function Test

DM – Diabetes Mellitus

HTN – Hypertension

TB – Tuberculosis

CLD – Chronic Liver Disease

CKD – Chronic Kidney Disease

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). IPF is the most common of the idiopathic pulmonary pneumonias and carries the worst prognosis, with median survival ranging from 2.5 to 3.5 years, and, to date, no proven effective therapies are available for the treatment of IPF beyond lung transplantation (1-6). Although IPF has an overall poor prognosis, the clinical course of individual patients varies from slow progression to acute decompensation and death. Physicians caring for IPF patients are frequently required to make complex and difficult decisions regarding whether or not to start, intensify, or stop treatment; or when to recommend referral of the patient for lung transplantation. These decisions would be made easier if accurate and objective measurements of patient's current clinical status and risk of progression to death were available. To date, several clinical prediction models have been developed for patients with IPF (7-9). However, they have not been widely adopted in clinical practice because they lack formal external validation and use some variables that are not routinely measured in current clinical practice. Recently, a new GAP model has been developed using four simple variables including gender (G), age (A), and 2 lung physiology variables (P) (forced vital capacity, FVC and carbon monoxide diffusing capacity, DLco). The GAP model is the first prediction model in IPF based on

competing-risks analysis, and it is the only predictor model that have been externally validated in a distinct cohort of patients with IPF (10). However, it has a limitation that both the derivation and validation cohorts were drawn from western countries only.

The number of incidental and prevalent IPF cases varied greatly in the presented studies (prevalence from 0.5 to 27.9 cases per 100,000) (11-13). The prevalence of IPF has been estimated between 14 and 63 cases per 100,000 persons based on a USA analysis of healthcare claims data with variation depending on the case definitions used in this analysis (14). In the Europe, a range of sources estimate an prevalence of 1.25 to 23.4 cases per 100,000 (13). Few studies of IPF incidence or prevalence were available in geographic regions other than the USA or Europe. However, there were some differences in the epidemiology of IPF between Asian and western countries. For example, a large population-based study conducted in Taiwan revealed that the incidence and prevalence (0.5 – 6.4 per 100,000 and 0.5 – 1.4 per 100,000, respectively) were found to be relatively lower in Asian than in western countries (15). Another study from Japan did not directly report the prevalence of IPF, although the data was used to calculate approximate estimates. The estimate of overall IPF prevalence was of 2.95 per 100,000 which was lower than those reported in the western counties(16). Furthermore, there have been several studies about racial and ethnic disparities of IPF (17-21). In this study, we hypothesized that the GAP model would not predict the risk of death accurately in the Korean IPF patients.

MATERIALS AND METHODS

1. Study design and patients

Patients diagnosed with IPF between 2005 and 2009 at Seoul National University hospital (SNUH), a university-affiliated tertiary care hospital in Korea, were included. The diagnosis of IPF was made by the ward pulmonolgists based on medical history, available pulmonary function test (PFT), high-resolution CT (HRCT), and/or surgical lung biopsy following the established criteria (1, 6, 22-24). Briefly, eligible patients were required to have a HRCT scan showing features consistent with defined criteria for a definite diagnosis of IPF. Surgical lung biopsy was required to confirm a diagnosis of probable IPF, regardless of the degree of certainty associated with the clinical and radiographic diagnoses. However, when the radiographic and histopathologic patterns are discordant, diagnosis of IPF was accomplished with a multidisciplinary discussion among experienced clinical experts in the field of interstitial lung diseases. Patients were excluded from the study if there was no available PFT at diagnosis, or if there was clinical evidence of a connective tissue disease, lung cancer or lung metastasis from other malignancy, an occupational or environmental exposure that may result in interstitial lung disease (ILD), or a history of ingestion of a drug or an agent known to cause pulmonary fibrosis (Figure 1). The study was approved by Institutional Review Board and Ethics Committee of SNUH (IRB No. H-1304-018-477) and conducted in compliance with the declaration of Helsinki.

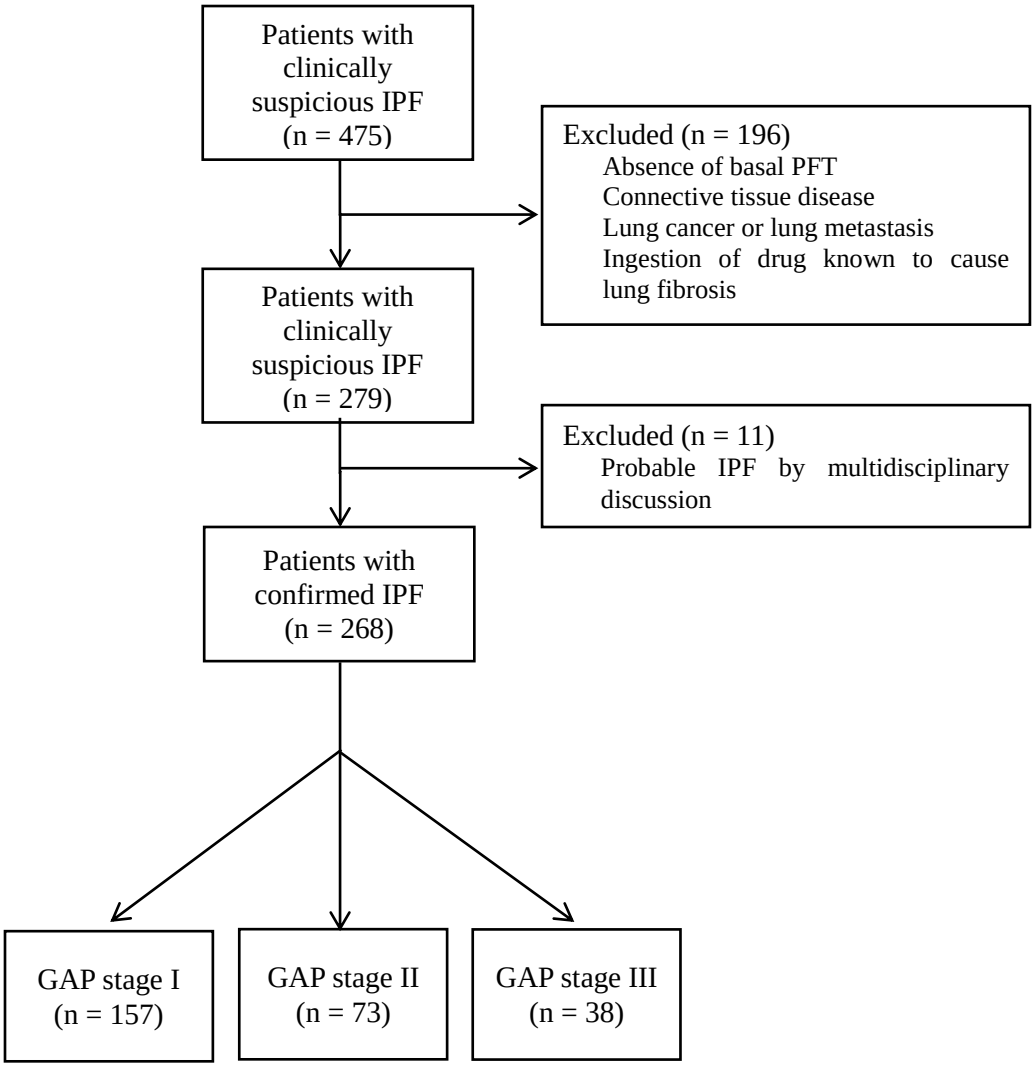


Figure1. Flow chart of patient enrollment into the study

2. Clinical Assessment and Outcome

We assessed patients' demographic characteristics including smoking status and clinical characteristics. Information on respiratory hospitalization, acute exacerbation of IPF, mechanical ventilator care and death were also

evaluated by medical chart review and interview. Acute exacerbation of IPF was defined by the onset of rapid deterioration (within days to a few weeks) in symptoms, lung function, and radiographic appearance (bilateral ground-glass opacities and consolidation superimposed on a reticular pattern on HRCT) in the absence of infection, heart failure, pulmonary embolism, or other identifiable cause (25-27). Vital status was ascertained through a record linkage with the Korea mortality registry for the years between January 2005 and July 2013. The cause of death was obtained by review of the hospital discharge information when available. Additional institutional ethical approval for the linkage was obtained. Both of the GAP calculator and GAP index & staging system were applied to each patient to obtain the GAP index, stage, and predicted 1-, 2-, and 3-year mortality. Finally we compared the observed risk of all-cause mortality with the mortality risk predicted by the GAP model.

3. Statistical analysis

Descriptive data were expressed as mean (standard deviation, SD), unless otherwise specified. Student's t-test was used to compare continuous variables, and chi-square or Fisher's exact tests were used to compare categorical variables. Survival curves were estimated using the Kaplan-Meier method, and differences in survival time between the three GAP stage groups were calculated by the log-rank test. On the basis of the reported Cox proportional hazard, we calculated 1-, 2-, and 3-year risk for all-cause mortality for all

patients, and compared the risk of death predicted by the GAP model with the observed mortality, with use of calibration plots and goodness-of-fit statistics (Hosmer-Lemeshow test). Finally, we calculated the c-statistic for the GAP model as a measure of discrimination. Unless otherwise noted, all tests were two-sided and performed at the 0.05 significance level. Analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and the Medical Research Collaborating Center (MRCC) of SNUH reviewed the statistical analyses.

RESULTS

1. Patient characteristics

The characteristics of the 268 patients with IPF registered in the study are summarized in Table 1. Mean age was 65.9 year (SD = 9.6), 181 (67.5%) patients were male, and 151 (56.3%) had a positive smoking history. Patients were designated as current smokers if they had smoked cigarettes regularly within previous three months (n = 35), ex-smokers if they had not smoked cigarettes in the previous three months but had smoked in the past (n = 116), and never smokers (n = 117). Surgical lung biopsy was performed for IPF in 54 (20.1%) patients. 2 patients had family history of IPF, and they had at least two affected first or second-degree relatives. Mean baseline percent predicted FVC was 77.8 (SD = 18.8), percent predicted FEV1 89.8 (SD = 21.5), and percent predicted DLco was 65.9 (SD = 21.7). There were 157 (58.6%) patients with GAP stage I, 73 (27.2%) with GAP stage II, and 38 (14.2%) with GAP stage III, based on GAP risk assessment system.

Characteristic	Total (n = 268)	GAP stage I (n = 157)	GAP stage II (n = 73)	GAP stage III (n = 38)	p-value
Age, y	65.9 (9.6)	63.9 (9.6)	67.1 (8.7)	71.5 (8.6)	<0.001
Male sex	181 (67.5)	100 (63.7)	50 (68.5)	31 (81.6)	0.105
Smoking					0.102
Never	117 (43.7)	76 (48.4)	30 (41.1)	11 (28.9)	

Ex-smoker	116 (43.3)	58 (36.9)	36 (49.3)	22 (57.9)	
Current-smoker	35 (13.0)	23 (14.7)	7 (9.6)	5 (13.2)	
Smoking PY	16.8 (22.8)	14.8 (21.7)	20.0 (26.2)	18.8 (22.8)	0.291
DM	47 (17.5)	25 (15.9)	14 (19.2)	8 (21.0)	0.690
HTN	57 (21.3)	39 (24.8)	13 (17.8)	5 (13.2)	0.201
TB	41 (15.3)	19 (12.1)	15 (20.5)	7 (18.4)	0.215
CLD	11 (4.1)	6 (3.8)	5 (6.8)	0 (0.0)	0.217
CKD	10 (3.7)	7 (4.5)	2 (2.7)	1 (2.6)	0.756
Malignancy	25 (9.3)	16 (10.2)	4 (5.5)	5 (13.2)	0.354
Biopsy-proven	54 (20.1)	34 (21.7)	14 (19.2)	6 (15.8)	0.700
FVC (% pred.)	77.8 (18.8)	85.5 (15.8)	68.9 (15.8)	63.3 (19.9)	<0.001
FEV1 (% pred.)	89.8 (21.5)	96.2 (20.6)	82.8 (17.9)	77.1 (22.1)	<0.001
DLCO (% pred.)	65.9 (21.7)	72.4 (20.3)	53.1 (16.3)	34.7 (8.8)	<0.001

Table1. Demographic Characteristics of Study patients

2. Clinical Assessment

The mean number of admission and acute exacerbation was 0.57 (SD = 1.2) and 0.49 (SD = 1.0) per patient/year, respectively. The frequencies of admission and acute exacerbation tended to increase as the GAP stage increases, but the differences were not statistically significant ($p = 0.192$ and $p = 0.162$, respectively). 29 (10.8%) patients received mechanical ventilation, and there were significant differences between GAP stages ($p < 0.001$). 10 (3.7%) patients were diagnosed with lung cancer; 3 patients had small cell lung cancer (SCLC) (n = 3) and 2 had non-small cell lung cancer (NSCLC), which were bronchioloalveolar carcinoma (BAC) and squamous cell

carcinoma (n=1). 5 patients were diagnosed with lung cancer through the cytology examination by either sputum or bronchial washing specimen, but they refused to take a new evaluation process including tissue diagnosis. The mean time to diagnosis of lung cancer was 37.4 months and patients with higher GAP stages were detected lung cancer earlier than those with lower GAP stages ($p < 0.020$) (Table 2).

Characteristic	Total (n = 268)	GAP stage I (n = 157)	II (n = 73)	III (n = 38)	p-value
Readmission	0.57 (1.2)	0.50 (1.2)	0.58 (0.9)	0.89 (1.6)	0.192
Exacerbation	0.49 (1.0)	0.40 (1.0)	0.58 (0.9)	0.71 (1.1)	0.162
MV care	29 (10.8)	11 (7.0)	7 (9.6)	11 (28.9)	<0.001
Lung Ca after IPF Dx.	10 (3.7)	6 (3.8)	1 (1.4)	3 (7.9)	0.226
Time to Dx of lung Ca., Months	37.4 (18.4)	46.7 (12.1)	36.0 (0.0)	10.5 (2.1)	0.020
Follow up duration yr	4.64 (0.03 – 20.58)	6.33 (1.01 – 17.01)	4.29 (0.04 – 20.58)	3.14 (0.03 – 10.35)	<0.001
Death by any cause	157 (58.6)	74 (47.1)	51 (69.9)	32 (84.2)	<0.001
Observed 1-y death	28 (10.4)	4 (2.5)	16 (21.9)	8 (21.1)	<0.001
Observed 2-y death	56 (20.9)	13 (8.3)	28 (38.4)	15 (39.5)	<0.001
Observed 3-y death	83 (31.0)	26 (16.6)	37 (50.7)	20 (52.6)	<0.001

Table 2. Follow-up Outcomes and Mortality of Study patients

3. Survival Analyses and Validation of GAP model

The Median follow-up duration was 4.64 years (range, 0.03 to 20.6 years).

Out of 268 patients, 157 patients (58.6%) were found to be deceased. The median time to death was found to be 3.64 years (range, 0.04 to 10.4 years). Of 49 patients who had available data on cause of death, 41 (83.7%) deaths occurred from progression of lung fibrosis rather than commonly occurring comorbid conditions. 83 (31.0%) patients died within 3 years, and the observed cumulative mortality at 1, 2, and 3 years were 10.4%, 20.9%, 31.0%, respectively. The observed mortality differed significantly among GAP stages ($p < 0.001$), and we found no apparent differences in the observed and predicted risk of death (Table 3).

	IPF patients		
	Predicted by GAP calculator	Predicted by GAP index & staging system	Observed
1-y mortality, %	9.1	5.6	10.4
Stage I	5.7	5.6	2.5
Stage II	15.1	16.2	21.9
Stage III	32.7	39.2	21.1
2-y mortality, %	18.6	10.9	20.9
Stage I	11.8	10.9	8.3
Stage II	29.8	29.9	38.4
Stage III	57.5	62.1	39.5
3-y mortality	27.7	16.3	31.0
Stage I	18.1	16.3	16.6
Stage II	42.8	42.1	50.7
Stage III	74.1	76.8	52.6

Table3. The Comparison of Predicted and Observed Cumulative Mortality.

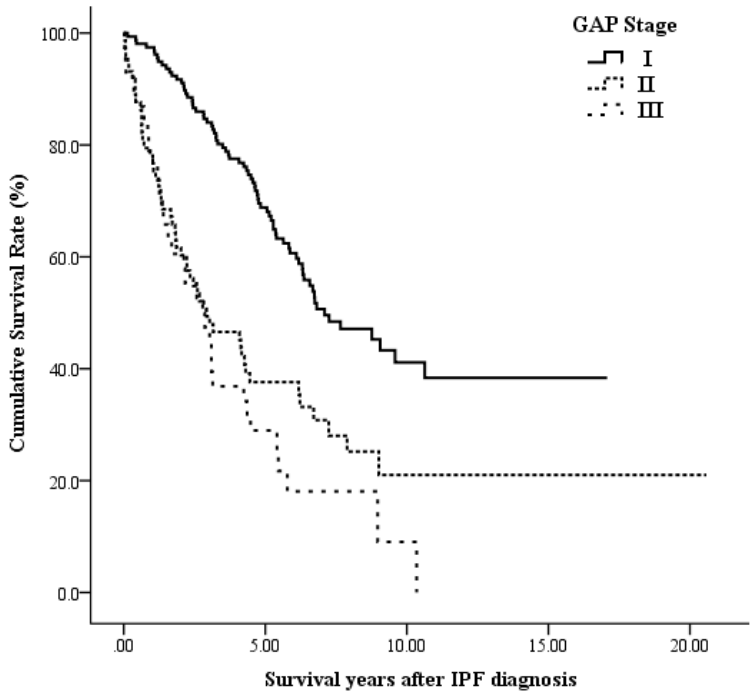
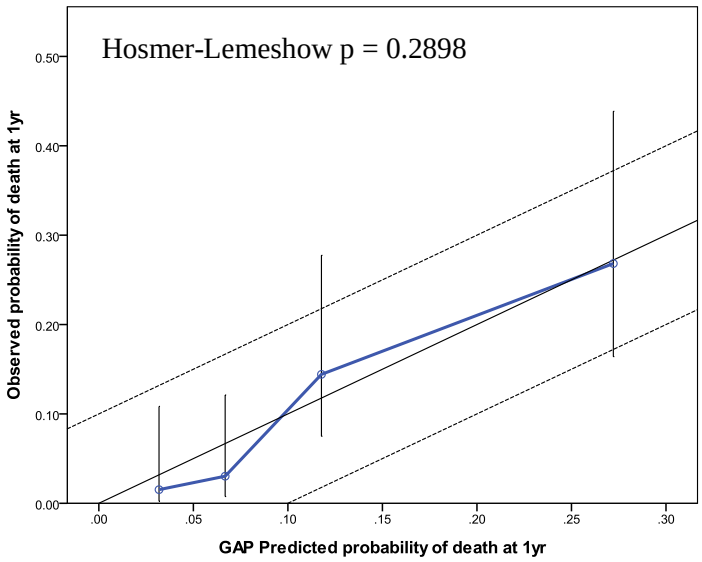


Figure 2. Kaplan-Meier plot of survival probability from the time of initial diagnosis in IPF patients.

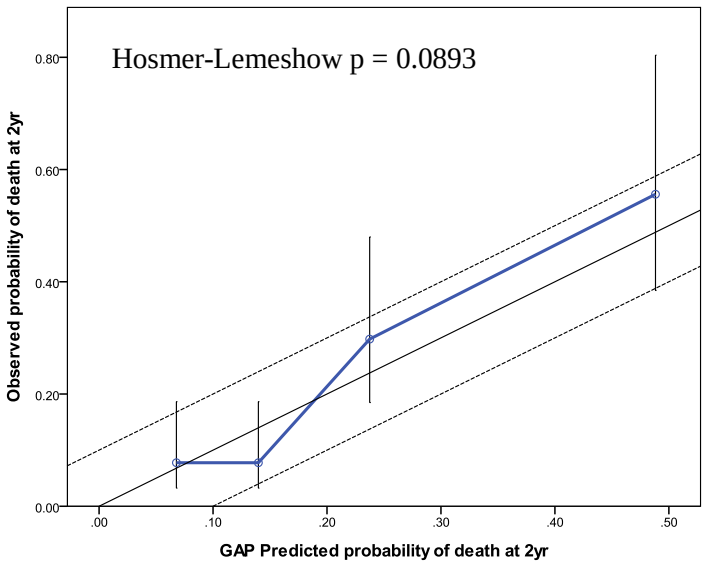
Figure 2 shows overall survival of study population according to GAP stage. The survival rate of patients with GAP stage I was significantly higher than that of patients with GAP stage II and III. The c-statistic for the GAP calculator at 1, 2, and 3 years were 0.74 (95% C.I. 0.35 - 1.00), 0.71 (95% C.I. 0.44 – 0.92), and 0.68 (95% C.I. 0.46 – 0.87), respectively. The GAP index & staging system showed lower c-statistic values than those of GAP calculator, which were 0.72 (95% C.I. 0.34 – 1.00), 0.69 (95% C.I. 0.42 – 0.91), and 0.66 (0.44 – 0.85), respectively. Finally, we compared the risk of death predicted by the GAP model with the observed mortality, with use of calibration plots and goodness-of-fit statistics (Hosmer-Lemeshow test). The GAP calculator

predicted 1 and 2-year mortality well and differences between predicted and observed risks were not significant. However, we found that the GAP calculator did not predicted the 3-year mortality accurately with significant difference between predicted and observed risks (Figure 3A, 3B, 3C).

A)



B)



C)

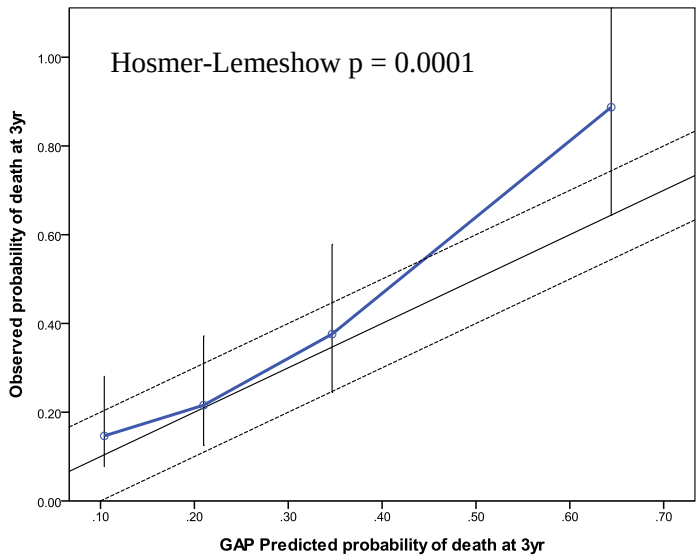
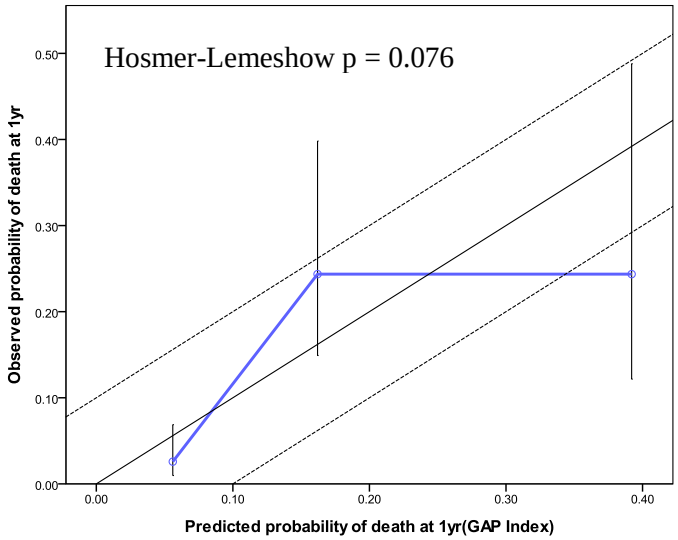


Figure3. Calibration plots of the GAP calculator in IPF patients.

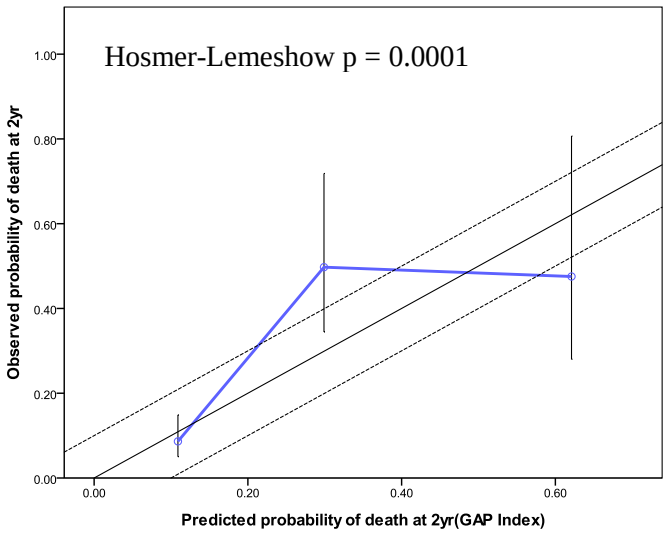
The x-axis shows that the 1-year (a), 2-year (b), and 3-year (c) risk of mortality as predicted by the GAP model and the y-axis shows the observed risk. Every spot represents a risk class with a corresponding predicted and an observed risk. The blue solid line represents perfect agreement between predicted and observed risks and the dashed line represents ± 10% differences from between them. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes

Furthermore, the GAP index & staging system revealed the significant differences between predicted and observed risk of mortality at 1-, 2-, and 3-year (Figure 4A, 4B, 4C). The median predicted 3-year risk of mortality by GAP calculator and GAP index and staging system were 27.7 % (IQR 2.3 – 91.9) and 16.3% (IQR 16.3 – 76.8) compared with 31.0% observed 3-year mortality, corresponding to a relative underprediction of 12.9% and 47.4% respectively (Table 3).

A)


Hosmer-Lemeshow p = 0.076
Observed probability of death at 1yr
0.00
0.10
0.20
0.30
0.40
0.50
0.00
0.10
0.20
0.30
0.40
Predicted probability of death at 1yr(GAP Index)

B)


Hosmer-Lemeshow p = 0.0001
Observed probability of death at 2yr
0.00
0.20
0.40
0.60
0.80
1.00
0.00
0.20
0.40
0.60
Predicted probability of death at 2yr(GAP Index)

C)

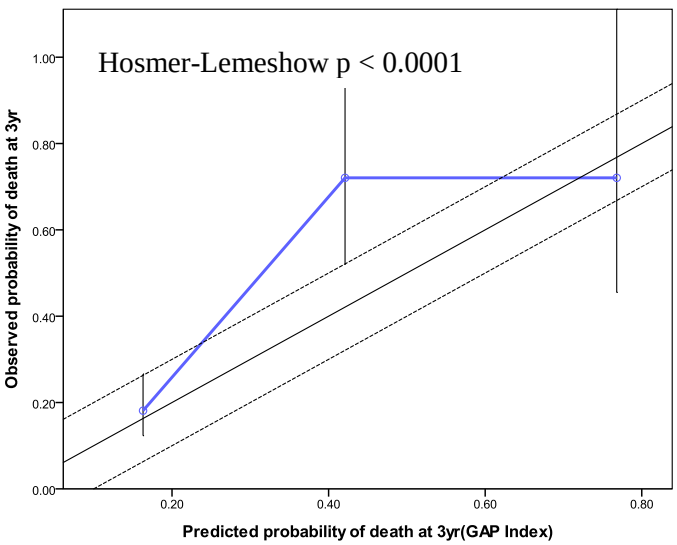

Hosmer-Lemeshow p < 0.0001
Observed probability of death at 3yr
0.00
0.20
0.40
0.60
0.80
1.00
0.20
0.40
0.60
0.80
Predicted probability of death at 3yr(GAP Index)

Figure4. Calibration plots of the GAP index & staging system in IPF patients. The x-axis shows that the 1-year (a), 2-year (b), and 3-year (c) risk of mortality as predicted by the GAP model and the y-axis shows the observed risk. Every spot represents a risk class with a corresponding predicted and an observed risk. The blue solid line represents perfect agreement between predicted and observed risks and the dashed line represents ± 10% differences from between them. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes.

DISCUSSION

Predicting survival time in patients with IPF has been the focus of much study over the last 30 years (7, 28-33), and there are many individual clinical variables that have been shown to predict survival in IPF including age, smoking history, body mass index (BMI), physiologic parameters, radiologic extent of disease, and the development of other complications or conditions (7, 34-36). By extension, clinical prediction models have been developed in IPF as they are used in many areas of medicine (7-10). Among these four models, the GAP model is one of the most simple clinical prediction models for mortality in IPF and it has been validated already in western countries (10). However, no Asian-based validation study has been performed for regional application. Therefore, before applying the GAP model to our local population, we decided to verify it in terms of discrimination and calibration. Discrimination refers to the ability of the prognostic index to distinguish between patients who will or will not die over a specific period of time. However, discrimination is not the only property that is relevant for prognostic indices. To be useful in practice, prognostic instrument should accurately predict the absolute risk of an event in individual patients (37). Therefore, the absolute risks as predicted by risk scores should be compared with the observed risks in at least one another population, so-called calibration (38-40). In the present study, we retrospectively evaluated 268 patients who met either histologic (n = 54) or clinical criteria of IPF in

Korea. In univariate analysis, mortality was associated with gender ($p = 0.008$), age ($p < 0.001$), lower FVC ($p < 0.001$), lower FEV1 ($p < 0.037$), and lower DLco ($p = 0.015$). In multivariate analysis, mortality of our study population found to be independently correlated with gender ($p = 0.013$), age ($p = 0.001$), lower FVC ($p = 0.003$), and lower DLco ($p= 0.015$), which were exactly same variables that included in the GAP model. However, the GAP model performance was not satisfactory in our study population. The discrimination ability of GAP model was good only in the first year (The c-statistics range from 0.72 – 0.74). The performance of GAP model tended to become worse over the 3 years. Furthermore, the calibration for 3-year mortality was poor, which means the GAP model did not accurately predict the 3-year mortality in Korean IPF patients (Figure 3, 4). There are several potential reasons why the GAP model did not do well in our external validation. First, Lung function of our study population was not fairly similar to the original two GAP cohorts (derivation cohort and validation cohort). The mean predicted FVC, FEV1, and DLco were higher than those of the original GAP cohort (FVC: 77.8 *vs* 68.8, FEV1: 89.8 *vs* 77.0, and DLco: 65.9 *vs* 44.2). Interestingly, the lung function of patients with stage III was similar to the overall average in GAP cohorts (FVC 63.3 and FEV1 77.1, and DLco 34.7). When the subset of patients that had undergone a diagnostic surgical lung biopsy was analyzed separately, the lung function parameters were still better than those of GAP cohorts (FVC 70.4, FEV1 80.2, and DLco 59.8). As a result, the points assigned for 2 lung physiology variables (predicted FVC and predicted DLco) might not contribute to a total point score which is used to

classify patients as stage I (0 – 3 points), stage II (4 – 5 points), or stage III (6 – 8 points) in the GAP model (10). Actually, the Korean IPF patients tended to show less impairment in lung function compare to other western countries even though no definite distinction was noted in patients characteristics such as age between them (41-46). However, the data from these studies is not comparable between countries due to various and heterogeneous methods used by researchers, and well-designed multinational studies might be needed to check the real differences between countries. Our broad diagnostic criteria may also explain some of the observed variation. We included the patients who confirmed their diagnoses by multidisciplinary discussion. Therefore, possible or probable IPF cases may have also included in our study population. Second, our patients were younger than the patients in GAP cohorts. The mean age at diagnosis of IPF was 65.9 (SD = 9.6) in our study. In original GAP study, the mean age of derivation cohort and validation cohort were 69.7 (SD = 8.7) and 66.3 (SD = 8.7), respectively. Therefore, it might be reasonable that lung physiology parameters should achieve less weight in risk scores than should strong predictors such as age in our study, even though decreased lung volume and gas exchange abnormalities are generally recognized as important prognostic factors in the previous studies (7, 10, 34). Third, differences in the incidence of risk factors of IPF could affect the performance of GAP model when it is applied to different geographical and ethnic populations. In the previous study, detailed data about the demographics of study patients in each GAP stage were not specified. Therefore, it is difficult to assume how the prognostic factors of IPF such as

lung volume or concomitant disease distributed within three stages, and whether the clinical characteristics of patients with specific GAP stage differ with those of our study patients. However we can find a clue when we further analyze the patients by comparing each stage. The predicted FVC, predicted FEV1 and airflow limitation (FEV1/FVC) were not significantly different in GAP stage II and III ($p = 0.108$, $p = 0.145$, and $p = 0.780$). However, the patients with GAP stage I noted much higher lung volume (predicted FVC, predicted FEV1), predicted DLco, and FEV1/FVC, and they were younger than the patients with stage II or III, or both ($p < 0.0001$). This discrepancy suggests that modification or recalibration of GAP model might be needed to classify GAP stage II and III clearly before incorporating into clinical practice in Korea. Lastly, the GAP model had originally slightly compromised calibration performance in lower risk groups, while it showed satisfactory discrimination performance in the previous GAP study (10). In fact, the risks of death were overpredicted in GAP stage I and III groups, and underpredicted in stage II group in the present study (Table 3). Because of the relatively poor calibration of the GAP model, it is necessary to revalidate and update this scoring system in different populations.

Compared to other studies, the overall prognosis of IPF was better in our patients. According to the original GAP study, categorization of 3 stages corresponded to estimated 1-year mortality risks of less than 10%, 10% to 30%, and greater than 30%, respectively. But, the observed 1-year mortality was less than 25% even in the stage III in our study. Furthermore, only 83 (31.0%) and 119 (44.4%) patients died within 3 and 5 years, respectively.

More than half of the patients remained stable over the study period. Generally, it has been known that about two-third of the IPF patients would die within 5 years according to the previous studies. For example, the 3- and 5-year mortalities for patients with IPF were 43% and 57%, respectively in the UK. In the USA, the 5-year mortality rate ranged between 50% and 70%. (22, 33, 47-51). We suspected that broad inclusion criteria or less compromised lung function might be the reason of good prognosis of our patients. However, when we analyzed surgical biopsy-proven definite IPF patients separately, the 3- and 5-year mortality rates revealed as 16.7% and 31.5%, respectively, even though they had worse lung function than the other patients (FVC: $p = 0.001$, FEV1: $p < 0.001$, and DLco: $p = 0.034$, respectively). Estimates of survival in IPF are dependent on time point from which they are calculated. Our hospital is a tertiary referral hospital and asymptomatic IPF patients could be easily found. They are relatively young also. In fact, less than half of the patients were asymptomatic and 119 (44.4%) patients were less than 65 year-old. They were diagnosed by radiographic abnormalities found on routine chest X-ray screening and lung biopsy showing UIP. Therefore, increase in clinical recognition of asymptomatic IPF would be another plausible explanation to that trend.

The GAP risk assessment system consists of two complimentary tools, the GAP index and staging system and the GAP calculator. The GAP calculator provides an estimation of individual risk of mortality for IPF patients, while the GAP index and staging system provides a simple screening method for determining the average risk of mortality of patients by GAP stage. We used

both methods to predict mortality in IPF patients, because both methods were validated and performed similarly in the previous study (10). However, we found that the GAP index and staging system were inferior to the GAP calculator in term of discrimination and calibration in the present study. We attempted to update or modify the GAP model by adding other independent prognostic variables of IPF such as extent of fibrosis on HRCT or BMI, but it was discouraged. Because, Brett Ley at al. reported that extent of fibrosis by HRCT does not improve the predictive performance of the GAP model (52). In addition, we could not obtain the each patient's BMI. Because, most of our study patients were diagnosed IPF in the outpatient clinic where measurement of BMI is not routinely performed.

The main strength of this study is that we obtained and reviewed detailed clinical, radiologic, and histologic data if possible from IPF patients. It allowed us to compare those characteristics according to GAP stage. The GAP model was developed to predict mortality of IPF only, and formation about other outcomes was not available in the previous study. We found that the frequencies of the mechanical ventilator care were significantly related to GAP stages ($p < 0.0001$), and the patients with higher GAP stages were detected lung cancer earlier than those with lower GAP stages ($p < 0.020$). Respiratory admission and acute exacerbation of IPF seemed to be related to GAP stages also, but statistically not significant (Table 2). Therefore, GAP model could provide additional prognostic information other than risk of death in IPF patient. Secondly, we evaluated IPF patients for a long period of time. The mean follow-up duration was 4.98 years (range, 0.3-20.6 years; 95%

C.I. 4.6 – 5.4). Therefore, we could assess the natural history of Korean IPF patients about asymptomatic period, acute exacerbation, and even death. Additional strength is the use of robust statistical techniques with help of MRCC in SNUH to verify the ability of the GAP model to predict mortality of IPF in new populations. Furthermore, our findings have potentially important implications for clinical practice. Although clinical prediction models including GAP model were validated already in the previous studies, revalidation and/or modification might be needed before applying them to different populations.

This retrospective study has certain limitations and biases. First, some of the patients were unable to perform the DLco test due to respiratory limitations or did not perform it even though it was ordered (n= 48). It may affect the classification of patients into three GAP stages and the performance of GAP model. Second, we enrolled the patients who were diagnosed IPF between 2005 and 2009 to gain the enough 3-year mortality data from them. Lung transplantation, which has been shown to improve lung function and survival in IPF patients, was not quite popular in those days. In the GAP study, 15 (6.6%) and 20 (6.1%) lung transplantations occurred in the derivation cohort and validation cohort, respectively. However, we found only one patient who referred to other hospital for lung transplantation. Therefore, the recent prognosis of IPF may be different from the data of our study. Third, we could not assess the information about treatment. A lot of patients were asymptomatic and most of them did not take any medications regularly. Also, it was hard to check the patients' drug compliance due to the limitation of

retrospective study such as follow-up loss. Lastly, this validation of the GAP model was conducted only in one tertiary referral hospital. Because of that, many asymptomatic IPF patients were included in our study and the mean age was younger than previous studies. There may be several confounding variables and biases in our study also. Therefore, these results might not be generalizable to locations with other populations. A prospective multicenter validation study of the GAP model is needed to confirm our data in Korea.

In conclusion, the GAP model may be a valuable tool to for determining prognosis and guiding management. However, the GAP model did not accurately predict the absolute risks of death in individual IPF patients in Korea. Additional research is needed to confirm our findings and to validate the applicability and accuracy of this risk assessment system.

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국문 초록

서론: 본 연구는 한국인 특발성폐섬유화증 환자들을 대상으로 이들의 임상경과에 대해서 살펴보고, 서구에서 이미 유용성이 입증된 GAP 모델을 적용하는 것이 사망률 예측에 유용한지를 검증하였다.

방법: 2005 년부터 2009 년 사이에 서울대병원에서 특발성폐섬유화증으로 확진 된 268 명의 환자들을 대상으로, 인구학적 자료, 진단 당시의 폐기능 검사 결과, 급성악화 및 호흡기 증상으로 인한 입원 횟수, 기계 환자 여부 및 사망 여부를 확인하였다. GAP 모델의 유용성은 GAP 계산기 (calculator)와 GAP 지표 및 병기체계 (index & staging system) 모두에 대해서 이루어졌으며, 사망률에 대한 예측력 (discrimination)과 적합도 (calibration)의 측면에서 검증이 이루어졌다.

결과: 181 명이 남성이었으며, 평균 연령은 65.9 세였고, 진단 당시의 FVC 및 DLco 의 평균 예측치는 각각 77.8%, 65.9%이었다. 진단을 위해 수술적 폐 생검을 실시한 환자는 54 명 (20.1%)이었다. 평균 4.64 년의 추적관찰이 이루어졌는데, 특발성폐섬유화증 진단 이후에 10 명의 환자에서 폐암이 발생하였고, 157 명 (58.6%)의 환자가 사망하였다. 진단 후 1 년, 2 년, 3 년 째 사망률은 10.4%,

20.9%, 31.0%이었으며, GAP 병기에 따라 유의한 차이를 보였다. ($p < 0.001$) 사망률 예측에 있어 GAP 계산기는 2 년째까지는 받아들일 수 있을 만한 결과를 보였지만, 3 년째에는 저조한 결과를 보였고, GAP 지표 및 병기체계는 3 년째에 이르기까지 예측력 및 적합도 측면 모두 저조한 성적을 보였다.

결론: 결론적으로 본 연구에서 GAP 모델은 한국인 특발성폐섬유화증 환자들의 사망률을 정확하게 예측하지 못하였다. GAP 모델을 한국 특발성폐섬유화증 환자들의 진료에 활용하기 위해서는 GAP 모델의 유용성에 대한 추가적인 검증 및 수정 작업이 필요할 것으로 사료된다.

주요어 : 특발성폐섬유화증, GAP 모델, 사망률
학 번 : 2012-21681

의학석사 학위논문

Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis

한국인 특발성폐섬유화증 환자에서 GAP 점수의 유용성 검증

2014 년 2 월

서울대학교 대학원

의학과 내과학 전공

김 은 선

Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis		2014		Eun Sun Kim	
2cm		2.5cm	4cm	3cm	2cm

의학석사 학위논문

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A thesis of the Degree of Master of Science in Medicine

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Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis

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Validation of GAP score in Korean patients with Idiopathic Pulmonary Fibrosis

by
Kim Eun Sun

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한국인 특발성폐섬유화증 환자에서 GAP 점수의 유용성 검증

지도 교수 이 상 민

이 논문을 의학석사 학위논문으로 제출함

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의학과 내과학 전공
김은선

김은선의 의학석사 학위논문을 인준함

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ABSTRACT

Introduction: The GAP model has been validated in independent cohorts in western countries. However, no study has assessed whether the risk of mortality predicted by GAP model matches the observed mortality in different populations. We evaluated the clinical course of IPF and validated the GAP model in Korean IPF patients.

Methods: We included 268 patients who had been diagnosed with IPF according to established clinical and histologic criteria in Seoul National University Hospital between 2005 and 2009. For each patient, demographics, and lung physiologic parameters such as percent predicted functional vital capacity (FVC), percent predicted carbon monoxide diffusing capacity (DLco) at the diagnosis of IPF were evaluated. The occurrence of respiratory hospitalization, acute exacerbation of IPF, mechanical ventilator care, and death were also evaluated. Finally, we validated the GAP model using discrimination and calibration to predict the risk of death in Korean IPF patients.

Results: The study population consisted of 181 men and 87 women, with a mean age of 65.9 year (SD = 9.6). Mean baseline of percent predicted FVC was 77.8 (SD = 18.8) and percent predicted DLco was 65.9 (SD = 21.7). 54 (20.1%) patients underwent surgical lung biopsy to confirm the diagnosis, and 10 (3.7%) were diagnosed with lung cancer. 157 (58.6%) deaths occurred

during the follow-up period, and median time to death was 4.64 years. Observed cumulative mortality at 1, 2, and 3 years were 10.4%, 20.9%, and 31.0%, respectively and cumulative mortality incidence differed substantially among GAP stages ($p < 0.001$). The GAP model produced estimates of 1-year mortality risk consistent with observed data (c-statistics: GAP calculator 0.74 and GAP index and staging system 0.72, $p < 0.29$). However, Calibration (c-statistics: GAP calculator 0.68 and GAP index and staging system 0.69) and discrimination ($p < 0.001$) of GAP model were compromised with under-prediction of 3-year risk of death.

Conclusions: The GAP model did not predict the 3-year risk of death accurately in Korean IPF patients. Further external validation or modification of the GAP model is needed before using it in a clinical setting in Korea.

Keywords: Idiopathic pulmonary fibrosis, GAP model, mortality
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LIST OF ABBREVIATIONS

IPF - Idiopathic Pulmonary Fibrosis

GAP - Gender, Age, and 2 Physiology variables

(FVC and DL_{co})

FVC - Forced Vital Capacity

FEV1 - Forced Expiratory Volume in 1 second

DL_{co} - Diffusing capacity from carbon monoxide

PFT - Pulmonary Function Test

DM – Diabetes Mellitus

HTN – Hypertension

TB – Tuberculosis

CLD – Chronic Liver Disease

CKD – Chronic Kidney Disease

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease of unknown etiology, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). IPF is the most common of the idiopathic pulmonary pneumonias and carries the worst prognosis, with median survival ranging from 2.5 to 3.5 years, and, to date, no proven effective therapies are available for the treatment of IPF beyond lung transplantation (1-6). Although IPF has an overall poor prognosis, the clinical course of individual patients varies from slow progression to acute decompensation and death. Physicians caring for IPF patients are frequently required to make complex and difficult decisions regarding whether or not to start, intensify, or stop treatment; or when to recommend referral of the patient for lung transplantation. These decisions would be made easier if accurate and objective measurements of patient's current clinical status and risk of progression to death were available. To date, several clinical prediction models have been developed for patients with IPF (7-9). However, they have not been widely adopted in clinical practice because they lack formal external validation and use some variables that are not routinely measured in current clinical practice. Recently, a new GAP model has been developed using four simple variables including gender (G), age (A), and 2 lung physiology variables (P) (forced vital capacity, FVC and carbon monoxide diffusing capacity, DLco). The GAP model is the first prediction model in IPF based on

competing-risks analysis, and it is the only predictor model that have been externally validated in a distinct cohort of patients with IPF (10). However, it has a limitation that both the derivation and validation cohorts were drawn from western countries only.

The number of incidental and prevalent IPF cases varied greatly in the presented studies (prevalence from 0.5 to 27.9 cases per 100,000) (11-13). The prevalence of IPF has been estimated between 14 and 63 cases per 100,000 persons based on a USA analysis of healthcare claims data with variation depending on the case definitions used in this analysis (14). In the Europe, a range of sources estimate an prevalence of 1.25 to 23.4 cases per 100,000 (13). Few studies of IPF incidence or prevalence were available in geographic regions other than the USA or Europe. However, there were some differences in the epidemiology of IPF between Asian and western countries. For example, a large population-based study conducted in Taiwan revealed that the incidence and prevalence (0.5 – 6.4 per 100,000 and 0.5 – 1.4 per 100,000, respectively) were found to be relatively lower in Asian than in western countries (15). Another study from Japan did not directly report the prevalence of IPF, although the data was used to calculate approximate estimates. The estimate of overall IPF prevalence was of 2.95 per 100,000 which was lower than those reported in the western counties(16). Furthermore, there have been several studies about racial and ethnic disparities of IPF (17-21). In this study, we hypothesized that the GAP model would not predict the risk of death accurately in the Korean IPF patients.

MATERIALS AND METHODS

1. Study design and patients

Patients diagnosed with IPF between 2005 and 2009 at Seoul National University hospital (SNUH), a university-affiliated tertiary care hospital in Korea, were included. The diagnosis of IPF was made by the ward pulmonolgists based on medical history, available pulmonary function test (PFT), high-resolution CT (HRCT), and/or surgical lung biopsy following the established criteria (1, 6, 22-24). Briefly, eligible patients were required to have a HRCT scan showing features consistent with defined criteria for a definite diagnosis of IPF. Surgical lung biopsy was required to confirm a diagnosis of probable IPF, regardless of the degree of certainty associated with the clinical and radiographic diagnoses. However, when the radiographic and histopathologic patterns are discordant, diagnosis of IPF was accomplished with a multidisciplinary discussion among experienced clinical experts in the field of interstitial lung diseases. Patients were excluded from the study if there was no available PFT at diagnosis, or if there was clinical evidence of a connective tissue disease, lung cancer or lung metastasis from other malignancy, an occupational or environmental exposure that may result in interstitial lung disease (ILD), or a history of ingestion of a drug or an agent known to cause pulmonary fibrosis (Figure 1). The study was approved by Institutional Review Board and Ethics Committee of SNUH (IRB No. H-1304-018-477) and conducted in compliance with the declaration of Helsinki.

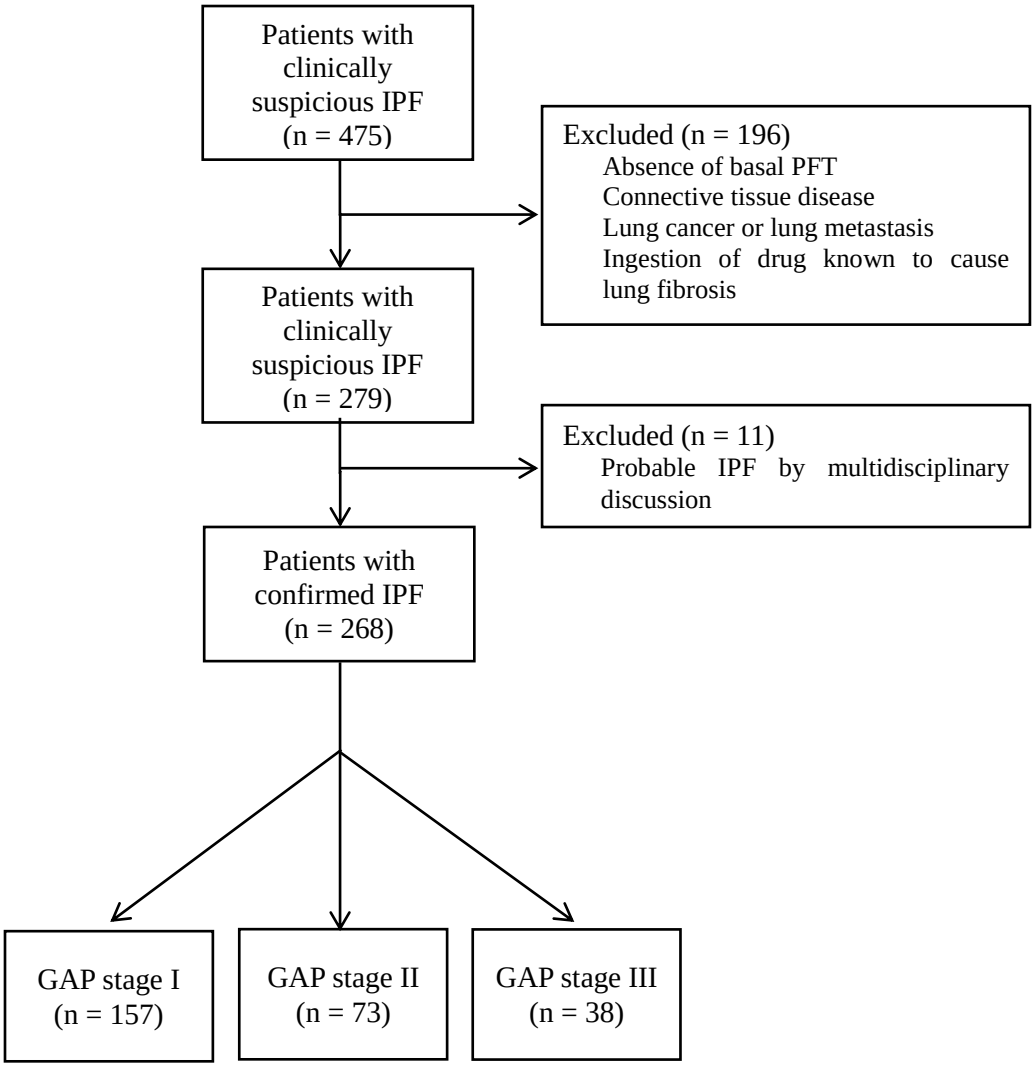


Figure1. Flow chart of patient enrollment into the study

2. Clinical Assessment and Outcome

We assessed patients' demographic characteristics including smoking status and clinical characteristics. Information on respiratory hospitalization, acute exacerbation of IPF, mechanical ventilator care and death were also

evaluated by medical chart review and interview. Acute exacerbation of IPF was defined by the onset of rapid deterioration (within days to a few weeks) in symptoms, lung function, and radiographic appearance (bilateral ground-glass opacities and consolidation superimposed on a reticular pattern on HRCT) in the absence of infection, heart failure, pulmonary embolism, or other identifiable cause (25-27). Vital status was ascertained through a record linkage with the Korea mortality registry for the years between January 2005 and July 2013. The cause of death was obtained by review of the hospital discharge information when available. Additional institutional ethical approval for the linkage was obtained. Both of the GAP calculator and GAP index & staging system were applied to each patient to obtain the GAP index, stage, and predicted 1-, 2-, and 3-year mortality. Finally we compared the observed risk of all-cause mortality with the mortality risk predicted by the GAP model.

3. Statistical analysis

Descriptive data were expressed as mean (standard deviation, SD), unless otherwise specified. Student's t-test was used to compare continuous variables, and chi-square or Fisher's exact tests were used to compare categorical variables. Survival curves were estimated using the Kaplan-Meier method, and differences in survival time between the three GAP stage groups were calculated by the log-rank test. On the basis of the reported Cox proportional hazard, we calculated 1-, 2-, and 3-year risk for all-cause mortality for all

patients, and compared the risk of death predicted by the GAP model with the observed mortality, with use of calibration plots and goodness-of-fit statistics (Hosmer-Lemeshow test). Finally, we calculated the c-statistic for the GAP model as a measure of discrimination. Unless otherwise noted, all tests were two-sided and performed at the 0.05 significance level. Analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA), and the Medical Research Collaborating Center (MRCC) of SNUH reviewed the statistical analyses.

RESULTS

1. Patient characteristics

The characteristics of the 268 patients with IPF registered in the study are summarized in Table 1. Mean age was 65.9 year (SD = 9.6), 181 (67.5%) patients were male, and 151 (56.3%) had a positive smoking history. Patients were designated as current smokers if they had smoked cigarettes regularly within previous three months (n = 35), ex-smokers if they had not smoked cigarettes in the previous three months but had smoked in the past (n = 116), and never smokers (n = 117). Surgical lung biopsy was performed for IPF in 54 (20.1%) patients. 2 patients had family history of IPF, and they had at least two affected first or second-degree relatives. Mean baseline percent predicted FVC was 77.8 (SD = 18.8), percent predicted FEV1 89.8 (SD = 21.5), and percent predicted DLco was 65.9 (SD = 21.7). There were 157 (58.6%) patients with GAP stage I, 73 (27.2%) with GAP stage II, and 38 (14.2%) with GAP stage III, based on GAP risk assessment system.

Characteristic	Total (n = 268)	GAP stage I (n = 157)	GAP stage II (n = 73)	GAP stage III (n = 38)	p-value
Age, y	65.9 (9.6)	63.9 (9.6)	67.1 (8.7)	71.5 (8.6)	<0.001
Male sex	181 (67.5)	100 (63.7)	50 (68.5)	31 (81.6)	0.105
Smoking					0.102
Never	117 (43.7)	76 (48.4)	30 (41.1)	11 (28.9)	

Ex-smoker	116 (43.3)	58 (36.9)	36 (49.3)	22 (57.9)	
Current-smoker	35 (13.0)	23 (14.7)	7 (9.6)	5 (13.2)	
Smoking PY	16.8 (22.8)	14.8 (21.7)	20.0 (26.2)	18.8 (22.8)	0.291
DM	47 (17.5)	25 (15.9)	14 (19.2)	8 (21.0)	0.690
HTN	57 (21.3)	39 (24.8)	13 (17.8)	5 (13.2)	0.201
TB	41 (15.3)	19 (12.1)	15 (20.5)	7 (18.4)	0.215
CLD	11 (4.1)	6 (3.8)	5 (6.8)	0 (0.0)	0.217
CKD	10 (3.7)	7 (4.5)	2 (2.7)	1 (2.6)	0.756
Malignancy	25 (9.3)	16 (10.2)	4 (5.5)	5 (13.2)	0.354
Biopsy-proven	54 (20.1)	34 (21.7)	14 (19.2)	6 (15.8)	0.700
FVC (% pred.)	77.8 (18.8)	85.5 (15.8)	68.9 (15.8)	63.3 (19.9)	<0.001
FEV1 (% pred.)	89.8 (21.5)	96.2 (20.6)	82.8 (17.9)	77.1 (22.1)	<0.001
DLCO (% pred.)	65.9 (21.7)	72.4 (20.3)	53.1 (16.3)	34.7 (8.8)	<0.001

Table1. Demographic Characteristics of Study patients

2. Clinical Assessment

The mean number of admission and acute exacerbation was 0.57 (SD = 1.2) and 0.49 (SD = 1.0) per patient/year, respectively. The frequencies of admission and acute exacerbation tended to increase as the GAP stage increases, but the differences were not statistically significant ($p = 0.192$ and $p = 0.162$, respectively). 29 (10.8%) patients received mechanical ventilation, and there were significant differences between GAP stages ($p < 0.001$). 10 (3.7%) patients were diagnosed with lung cancer; 3 patients had small cell lung cancer (SCLC) (n = 3) and 2 had non-small cell lung cancer (NSCLC), which were bronchioloalveolar carcinoma (BAC) and squamous cell

carcinoma (n=1). 5 patients were diagnosed with lung cancer through the cytology examination by either sputum or bronchial washing specimen, but they refused to take a new evaluation process including tissue diagnosis. The mean time to diagnosis of lung cancer was 37.4 months and patients with higher GAP stages were detected lung cancer earlier than those with lower GAP stages ($p < 0.020$) (Table 2).

Characteristic	Total (n = 268)	GAP stage I (n = 157)	II (n = 73)	III (n = 38)	p-value
Readmission	0.57 (1.2)	0.50 (1.2)	0.58 (0.9)	0.89 (1.6)	0.192
Exacerbation	0.49 (1.0)	0.40 (1.0)	0.58 (0.9)	0.71 (1.1)	0.162
MV care	29 (10.8)	11 (7.0)	7 (9.6)	11 (28.9)	<0.001
Lung Ca after IPF Dx.	10 (3.7)	6 (3.8)	1 (1.4)	3 (7.9)	0.226
Time to Dx of lung Ca., Months	37.4 (18.4)	46.7 (12.1)	36.0 (0.0)	10.5 (2.1)	0.020
Follow up duration yr	4.64 (0.03 – 20.58)	6.33 (1.01 – 17.01)	4.29 (0.04 – 20.58)	3.14 (0.03 – 10.35)	<0.001
Death by any cause	157 (58.6)	74 (47.1)	51 (69.9)	32 (84.2)	<0.001
Observed 1-y death	28 (10.4)	4 (2.5)	16 (21.9)	8 (21.1)	<0.001
Observed 2-y death	56 (20.9)	13 (8.3)	28 (38.4)	15 (39.5)	<0.001
Observed 3-y death	83 (31.0)	26 (16.6)	37 (50.7)	20 (52.6)	<0.001

Table 2. Follow-up Outcomes and Mortality of Study patients

3. Survival Analyses and Validation of GAP model

The Median follow-up duration was 4.64 years (range, 0.03 to 20.6 years).

Out of 268 patients, 157 patients (58.6%) were found to be deceased. The median time to death was found to be 3.64 years (range, 0.04 to 10.4 years). Of 49 patients who had available data on cause of death, 41 (83.7%) deaths occurred from progression of lung fibrosis rather than commonly occurring comorbid conditions. 83 (31.0%) patients died within 3 years, and the observed cumulative mortality at 1, 2, and 3 years were 10.4%, 20.9%, 31.0%, respectively. The observed mortality differed significantly among GAP stages ($p < 0.001$), and we found no apparent differences in the observed and predicted risk of death (Table 3).

	IPF patients		
	Predicted by GAP calculator	Predicted by GAP index & staging system	Observed
1-y mortality, %	9.1	5.6	10.4
Stage I	5.7	5.6	2.5
Stage II	15.1	16.2	21.9
Stage III	32.7	39.2	21.1
2-y mortality, %	18.6	10.9	20.9
Stage I	11.8	10.9	8.3
Stage II	29.8	29.9	38.4
Stage III	57.5	62.1	39.5
3-y mortality	27.7	16.3	31.0
Stage I	18.1	16.3	16.6
Stage II	42.8	42.1	50.7
Stage III	74.1	76.8	52.6

Table3. The Comparison of Predicted and Observed Cumulative Mortality.

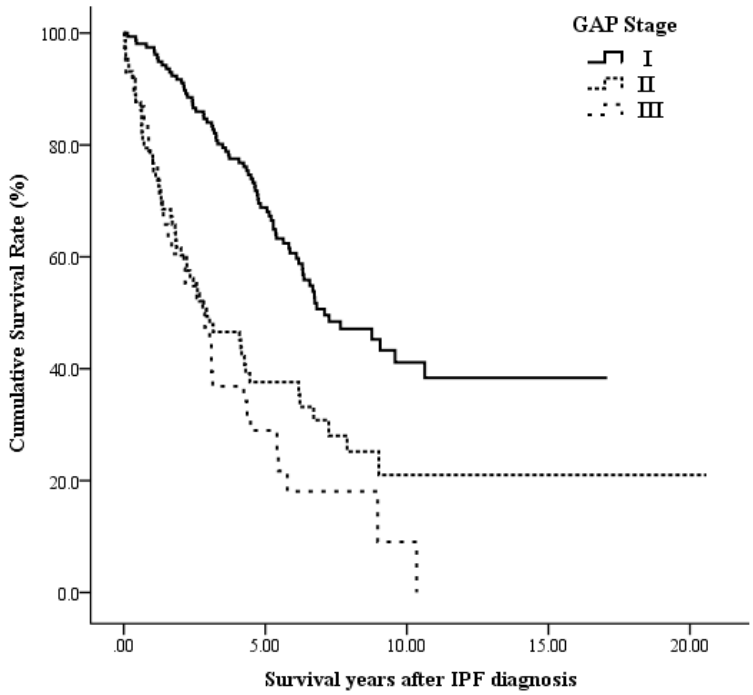
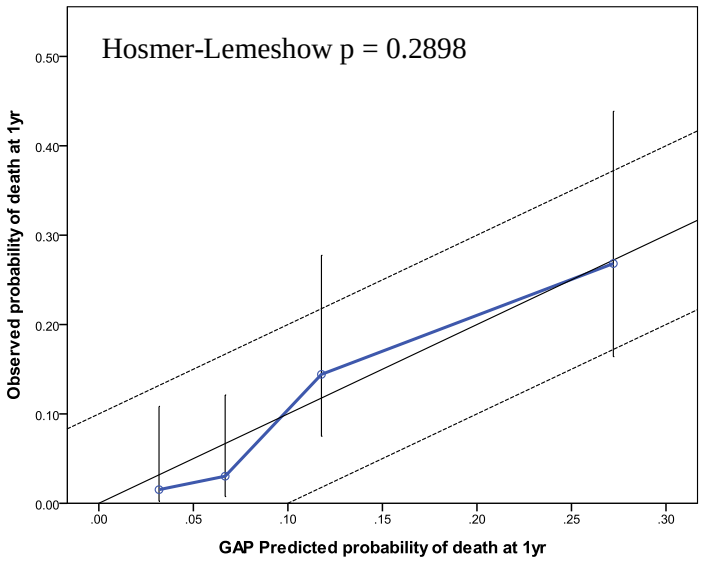


Figure 2. Kaplan-Meier plot of survival probability from the time of initial diagnosis in IPF patients.

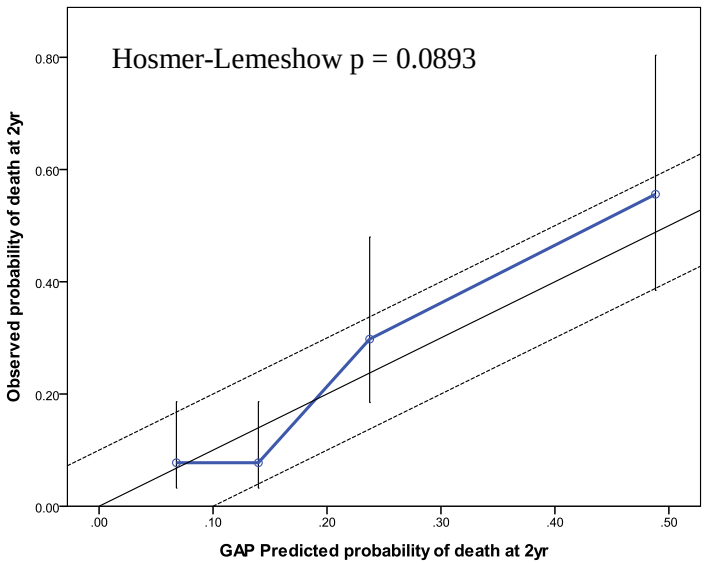
Figure 2 shows overall survival of study population according to GAP stage. The survival rate of patients with GAP stage I was significantly higher than that of patients with GAP stage II and III. The c-statistic for the GAP calculator at 1, 2, and 3 years were 0.74 (95% C.I. 0.35 - 1.00), 0.71 (95% C.I. 0.44 – 0.92), and 0.68 (95% C.I. 0.46 – 0.87), respectively. The GAP index & staging system showed lower c-statistic values than those of GAP calculator, which were 0.72 (95% C.I. 0.34 – 1.00), 0.69 (95% C.I. 0.42 – 0.91), and 0.66 (0.44 – 0.85), respectively. Finally, we compared the risk of death predicted by the GAP model with the observed mortality, with use of calibration plots and goodness-of-fit statistics (Hosmer-Lemeshow test). The GAP calculator

predicted 1 and 2-year mortality well and differences between predicted and observed risks were not significant. However, we found that the GAP calculator did not predicted the 3-year mortality accurately with significant difference between predicted and observed risks (Figure 3A, 3B, 3C).

A)



B)



C)

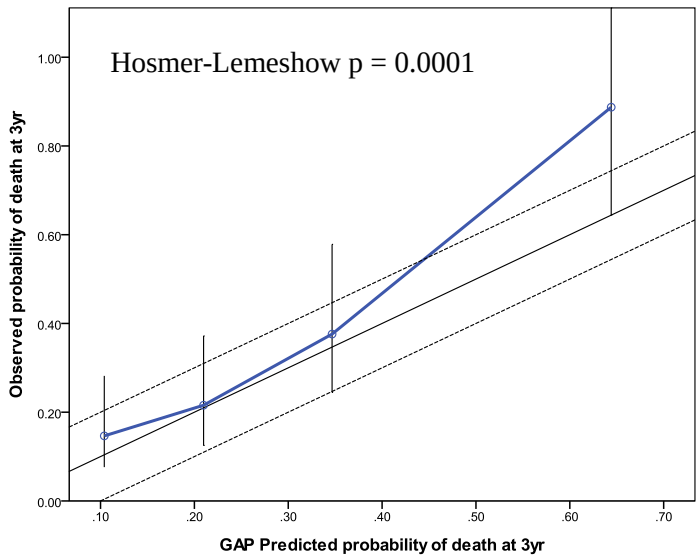
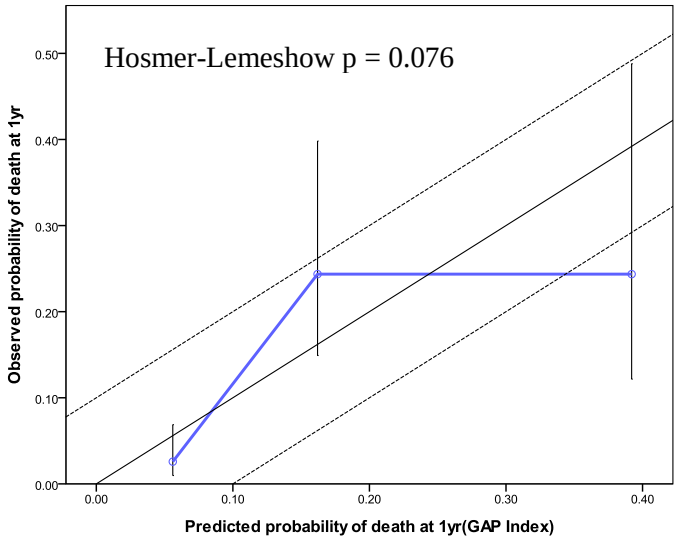


Figure3. Calibration plots of the GAP calculator in IPF patients.

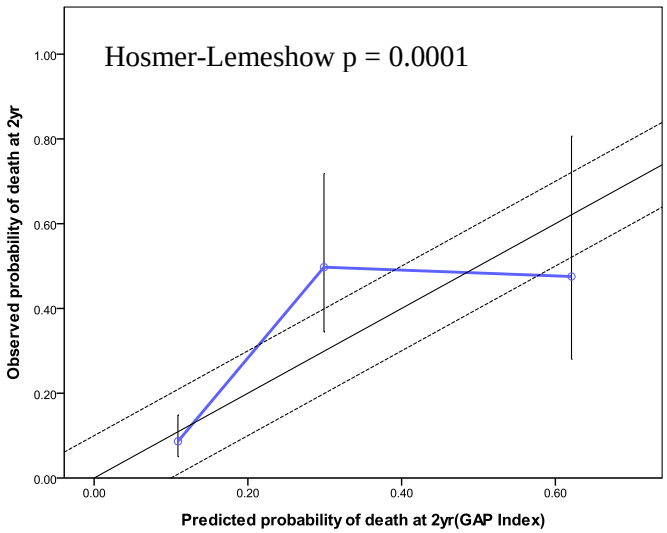
The x-axis shows that the 1-year (a), 2-year (b), and 3-year (c) risk of mortality as predicted by the GAP model and the y-axis shows the observed risk. Every spot represents a risk class with a corresponding predicted and an observed risk. The blue solid line represents perfect agreement between predicted and observed risks and the dashed line represents ± 10% differences from between them. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes

Furthermore, the GAP index & staging system revealed the significant differences between predicted and observed risk of mortality at 1-, 2-, and 3-year (Figure 4A, 4B, 4C). The median predicted 3-year risk of mortality by GAP calculator and GAP index and staging system were 27.7 % (IQR 2.3 – 91.9) and 16.3% (IQR 16.3 – 76.8) compared with 31.0% observed 3-year mortality, corresponding to a relative underprediction of 12.9% and 47.4% respectively (Table 3).

A)


Hosmer-Lemeshow p = 0.076
Observed probability of death at 1yr
0.00
0.10
0.20
0.30
0.40
0.50
0.00
0.10
0.20
0.30
0.40
Predicted probability of death at 1yr(GAP Index)

B)


Hosmer-Lemeshow p = 0.0001
Observed probability of death at 2yr
0.00
0.20
0.40
0.60
0.80
1.00
0.00
0.20
0.40
0.60
Predicted probability of death at 2yr(GAP Index)

C)

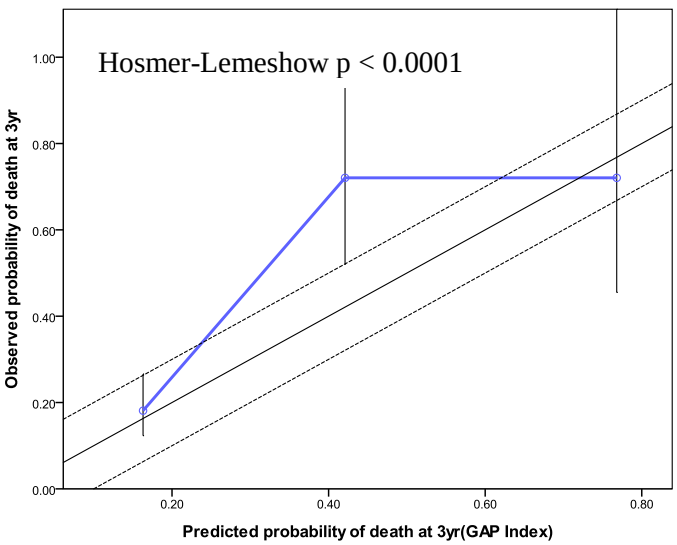

Hosmer-Lemeshow p < 0.0001
Observed probability of death at 3yr
0.00
0.20
0.40
0.60
0.80
1.00
0.20
0.40
0.60
0.80
Predicted probability of death at 3yr(GAP Index)

Figure4. Calibration plots of the GAP index & staging system in IPF patients. The x-axis shows that the 1-year (a), 2-year (b), and 3-year (c) risk of mortality as predicted by the GAP model and the y-axis shows the observed risk. Every spot represents a risk class with a corresponding predicted and an observed risk. The blue solid line represents perfect agreement between predicted and observed risks and the dashed line represents ± 10% differences from between them. The Hosmer-Lemeshow statistic tests whether predicted and observed risk differ significantly across all risk classes.

DISCUSSION

Predicting survival time in patients with IPF has been the focus of much study over the last 30 years (7, 28-33), and there are many individual clinical variables that have been shown to predict survival in IPF including age, smoking history, body mass index (BMI), physiologic parameters, radiologic extent of disease, and the development of other complications or conditions (7, 34-36). By extension, clinical prediction models have been developed in IPF as they are used in many areas of medicine (7-10). Among these four models, the GAP model is one of the most simple clinical prediction models for mortality in IPF and it has been validated already in western countries (10). However, no Asian-based validation study has been performed for regional application. Therefore, before applying the GAP model to our local population, we decided to verify it in terms of discrimination and calibration. Discrimination refers to the ability of the prognostic index to distinguish between patients who will or will not die over a specific period of time. However, discrimination is not the only property that is relevant for prognostic indices. To be useful in practice, prognostic instrument should accurately predict the absolute risk of an event in individual patients (37). Therefore, the absolute risks as predicted by risk scores should be compared with the observed risks in at least one another population, so-called calibration (38-40). In the present study, we retrospectively evaluated 268 patients who met either histologic (n = 54) or clinical criteria of IPF in

Korea. In univariate analysis, mortality was associated with gender ($p = 0.008$), age ($p < 0.001$), lower FVC ($p < 0.001$), lower FEV1 ($p < 0.037$), and lower DLco ($p = 0.015$). In multivariate analysis, mortality of our study population found to be independently correlated with gender ($p = 0.013$), age ($p = 0.001$), lower FVC ($p = 0.003$), and lower DLco ($p= 0.015$), which were exactly same variables that included in the GAP model. However, the GAP model performance was not satisfactory in our study population. The discrimination ability of GAP model was good only in the first year (The c-statistics range from 0.72 – 0.74). The performance of GAP model tended to become worse over the 3 years. Furthermore, the calibration for 3-year mortality was poor, which means the GAP model did not accurately predict the 3-year mortality in Korean IPF patients (Figure 3, 4). There are several potential reasons why the GAP model did not do well in our external validation. First, Lung function of our study population was not fairly similar to the original two GAP cohorts (derivation cohort and validation cohort). The mean predicted FVC, FEV1, and DLco were higher than those of the original GAP cohort (FVC: 77.8 *vs* 68.8, FEV1: 89.8 *vs* 77.0, and DLco: 65.9 *vs* 44.2). Interestingly, the lung function of patients with stage III was similar to the overall average in GAP cohorts (FVC 63.3 and FEV1 77.1, and DLco 34.7). When the subset of patients that had undergone a diagnostic surgical lung biopsy was analyzed separately, the lung function parameters were still better than those of GAP cohorts (FVC 70.4, FEV1 80.2, and DLco 59.8). As a result, the points assigned for 2 lung physiology variables (predicted FVC and predicted DLco) might not contribute to a total point score which is used to

classify patients as stage I (0 – 3 points), stage II (4 – 5 points), or stage III (6 – 8 points) in the GAP model (10). Actually, the Korean IPF patients tended to show less impairment in lung function compare to other western countries even though no definite distinction was noted in patients characteristics such as age between them (41-46). However, the data from these studies is not comparable between countries due to various and heterogeneous methods used by researchers, and well-designed multinational studies might be needed to check the real differences between countries. Our broad diagnostic criteria may also explain some of the observed variation. We included the patients who confirmed their diagnoses by multidisciplinary discussion. Therefore, possible or probable IPF cases may have also included in our study population. Second, our patients were younger than the patients in GAP cohorts. The mean age at diagnosis of IPF was 65.9 (SD = 9.6) in our study. In original GAP study, the mean age of derivation cohort and validation cohort were 69.7 (SD = 8.7) and 66.3 (SD = 8.7), respectively. Therefore, it might be reasonable that lung physiology parameters should achieve less weight in risk scores than should strong predictors such as age in our study, even though decreased lung volume and gas exchange abnormalities are generally recognized as important prognostic factors in the previous studies (7, 10, 34). Third, differences in the incidence of risk factors of IPF could affect the performance of GAP model when it is applied to different geographical and ethnic populations. In the previous study, detailed data about the demographics of study patients in each GAP stage were not specified. Therefore, it is difficult to assume how the prognostic factors of IPF such as

lung volume or concomitant disease distributed within three stages, and whether the clinical characteristics of patients with specific GAP stage differ with those of our study patients. However we can find a clue when we further analyze the patients by comparing each stage. The predicted FVC, predicted FEV1 and airflow limitation (FEV1/FVC) were not significantly different in GAP stage II and III ($p = 0.108$, $p = 0.145$, and $p = 0.780$). However, the patients with GAP stage I noted much higher lung volume (predicted FVC, predicted FEV1), predicted DLco, and FEV1/FVC, and they were younger than the patients with stage II or III, or both ($p < 0.0001$). This discrepancy suggests that modification or recalibration of GAP model might be needed to classify GAP stage II and III clearly before incorporating into clinical practice in Korea. Lastly, the GAP model had originally slightly compromised calibration performance in lower risk groups, while it showed satisfactory discrimination performance in the previous GAP study (10). In fact, the risks of death were overpredicted in GAP stage I and III groups, and underpredicted in stage II group in the present study (Table 3). Because of the relatively poor calibration of the GAP model, it is necessary to revalidate and update this scoring system in different populations.

Compared to other studies, the overall prognosis of IPF was better in our patients. According to the original GAP study, categorization of 3 stages corresponded to estimated 1-year mortality risks of less than 10%, 10% to 30%, and greater than 30%, respectively. But, the observed 1-year mortality was less than 25% even in the stage III in our study. Furthermore, only 83 (31.0%) and 119 (44.4%) patients died within 3 and 5 years, respectively.

More than half of the patients remained stable over the study period. Generally, it has been known that about two-third of the IPF patients would die within 5 years according to the previous studies. For example, the 3- and 5-year mortalities for patients with IPF were 43% and 57%, respectively in the UK. In the USA, the 5-year mortality rate ranged between 50% and 70%. (22, 33, 47-51). We suspected that broad inclusion criteria or less compromised lung function might be the reason of good prognosis of our patients. However, when we analyzed surgical biopsy-proven definite IPF patients separately, the 3- and 5-year mortality rates revealed as 16.7% and 31.5%, respectively, even though they had worse lung function than the other patients (FVC: $p = 0.001$, FEV1: $p < 0.001$, and DLco: $p = 0.034$, respectively). Estimates of survival in IPF are dependent on time point from which they are calculated. Our hospital is a tertiary referral hospital and asymptomatic IPF patients could be easily found. They are relatively young also. In fact, less than half of the patients were asymptomatic and 119 (44.4%) patients were less than 65 year-old. They were diagnosed by radiographic abnormalities found on routine chest X-ray screening and lung biopsy showing UIP. Therefore, increase in clinical recognition of asymptomatic IPF would be another plausible explanation to that trend.

The GAP risk assessment system consists of two complimentary tools, the GAP index and staging system and the GAP calculator. The GAP calculator provides an estimation of individual risk of mortality for IPF patients, while the GAP index and staging system provides a simple screening method for determining the average risk of mortality of patients by GAP stage. We used

both methods to predict mortality in IPF patients, because both methods were validated and performed similarly in the previous study (10). However, we found that the GAP index and staging system were inferior to the GAP calculator in term of discrimination and calibration in the present study. We attempted to update or modify the GAP model by adding other independent prognostic variables of IPF such as extent of fibrosis on HRCT or BMI, but it was discouraged. Because, Brett Ley at al. reported that extent of fibrosis by HRCT does not improve the predictive performance of the GAP model (52). In addition, we could not obtain the each patient's BMI. Because, most of our study patients were diagnosed IPF in the outpatient clinic where measurement of BMI is not routinely performed.

The main strength of this study is that we obtained and reviewed detailed clinical, radiologic, and histologic data if possible from IPF patients. It allowed us to compare those characteristics according to GAP stage. The GAP model was developed to predict mortality of IPF only, and formation about other outcomes was not available in the previous study. We found that the frequencies of the mechanical ventilator care were significantly related to GAP stages ($p < 0.0001$), and the patients with higher GAP stages were detected lung cancer earlier than those with lower GAP stages ($p < 0.020$). Respiratory admission and acute exacerbation of IPF seemed to be related to GAP stages also, but statistically not significant (Table 2). Therefore, GAP model could provide additional prognostic information other than risk of death in IPF patient. Secondly, we evaluated IPF patients for a long period of time. The mean follow-up duration was 4.98 years (range, 0.3-20.6 years; 95%

C.I. 4.6 – 5.4). Therefore, we could assess the natural history of Korean IPF patients about asymptomatic period, acute exacerbation, and even death. Additional strength is the use of robust statistical techniques with help of MRCC in SNUH to verify the ability of the GAP model to predict mortality of IPF in new populations. Furthermore, our findings have potentially important implications for clinical practice. Although clinical prediction models including GAP model were validated already in the previous studies, revalidation and/or modification might be needed before applying them to different populations.

This retrospective study has certain limitations and biases. First, some of the patients were unable to perform the DLco test due to respiratory limitations or did not perform it even though it was ordered (n= 48). It may affect the classification of patients into three GAP stages and the performance of GAP model. Second, we enrolled the patients who were diagnosed IPF between 2005 and 2009 to gain the enough 3-year mortality data from them. Lung transplantation, which has been shown to improve lung function and survival in IPF patients, was not quite popular in those days. In the GAP study, 15 (6.6%) and 20 (6.1%) lung transplantations occurred in the derivation cohort and validation cohort, respectively. However, we found only one patient who referred to other hospital for lung transplantation. Therefore, the recent prognosis of IPF may be different from the data of our study. Third, we could not assess the information about treatment. A lot of patients were asymptomatic and most of them did not take any medications regularly. Also, it was hard to check the patients' drug compliance due to the limitation of

retrospective study such as follow-up loss. Lastly, this validation of the GAP model was conducted only in one tertiary referral hospital. Because of that, many asymptomatic IPF patients were included in our study and the mean age was younger than previous studies. There may be several confounding variables and biases in our study also. Therefore, these results might not be generalizable to locations with other populations. A prospective multicenter validation study of the GAP model is needed to confirm our data in Korea.

In conclusion, the GAP model may be a valuable tool to for determining prognosis and guiding management. However, the GAP model did not accurately predict the absolute risks of death in individual IPF patients in Korea. Additional research is needed to confirm our findings and to validate the applicability and accuracy of this risk assessment system.

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국문 초록

서론: 본 연구는 한국인 특발성폐섬유화증 환자들을 대상으로 이들의 임상경과에 대해서 살펴보고, 서구에서 이미 유용성이 입증된 GAP 모델을 적용하는 것이 사망률 예측에 유용한지를 검증하였다.

방법: 2005 년부터 2009 년 사이에 서울대병원에서 특발성폐섬유화증으로 확진 된 268 명의 환자들을 대상으로, 인구학적 자료, 진단 당시의 폐기능 검사 결과, 급성악화 및 호흡기 증상으로 인한 입원 횟수, 기계 환자 여부 및 사망 여부를 확인하였다. GAP 모델의 유용성은 GAP 계산기 (calculator)와 GAP 지표 및 병기체계 (index & staging system) 모두에 대해서 이루어졌으며, 사망률에 대한 예측력 (discrimination)과 적합도 (calibration)의 측면에서 검증이 이루어졌다.

결과: 181 명이 남성이었으며, 평균 연령은 65.9 세였고, 진단 당시의 FVC 및 DLco 의 평균 예측치는 각각 77.8%, 65.9%이었다. 진단을 위해 수술적 폐 생검을 실시한 환자는 54 명 (20.1%)이었다. 평균 4.64 년의 추적관찰이 이루어졌는데, 특발성폐섬유화증 진단 이후에 10 명의 환자에서 폐암이 발생하였고, 157 명 (58.6%)의 환자가 사망하였다. 진단 후 1 년, 2 년, 3 년 째 사망률은 10.4%,

20.9%, 31.0%이었으며, GAP 병기에 따라 유의한 차이를 보였다. ($p < 0.001$) 사망률 예측에 있어 GAP 계산기는 2 년째까지는 받아들일 수 있을 만한 결과를 보였지만, 3 년째에는 저조한 결과를 보였고, GAP 지표 및 병기체계는 3 년째에 이르기까지 예측력 및 적합도 측면 모두 저조한 성적을 보였다.

결론: 결론적으로 본 연구에서 GAP 모델은 한국인 특발성폐섬유화증 환자들의 사망률을 정확하게 예측하지 못하였다. GAP 모델을 한국 특발성폐섬유화증 환자들의 진료에 활용하기 위해서는 GAP 모델의 유용성에 대한 추가적인 검증 및 수정 작업이 필요할 것으로 사료된다.

주요어 : 특발성폐섬유화증, GAP 모델, 사망률
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