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Determinants of the prognosis of idiopathic pulmonary fibrosis

F. NOVELLI, L. TAVANTI, S. CINI, F. AQUILINI, L. MELOSINI, C. ROMEI[1], P. SBRAGIA[1], F. FALASCHI[1], A. CELI, P. PAGGIARO

Cardio-Thoracic and Vascular Department, University of Pisa, Italy
[1]Radiology Unit, University Hospital of Pisa, Italy

Abstract. – OBJECTIVE: Fibrotic idiopathic interstitial pneumonias are chronic and progressive lung diseases with different prognosis, with idiopathic pulmonary fibrosis (IPF) having the worst prognosis. Many patients need a surgical lung biopsy for the definite diagnosis of IPF but age and the clinical context often contraindicate this procedure. The aim of this study is to identify predictors of survival, apart from lung biopsy, in patients with definite and possible IPF.

PATIENTS AND METHODS: We studied 42 patients with HRCT pattern of definite or possible IPF, by assessing the mortality in relationship with baseline HRCT and functional findings. HRCT was assessed both as prevalent pattern (definite vs possible UIP) and as score of the different abnormalities (in particular, honeycombing (HC) and total fibrotic score). Pulmonary function was assessed as baseline FVC, TLC and DLCO values, as well as change over 6 months of follow-up. Both univariate and multivariate analyses were performed in order to detect predictors of mortality.

RESULTS: During follow-up, 10 out of 42 patients died. Mortality rate was not different according to the qualitative pattern of fibrosis at HRCT. Among the different HRCT scores, a cut-off of 15% in the HC score differentiated patients with higher mortality rate. A lower baseline FVC, and a greater decrease in pulmonary function after 6 months, were both associated with higher mortality. In a logistic analysis taking in consideration clinical, radiological and functional findings, only baseline FVC and FVC change after 6 months resulted significant predictors of mortality.

CONCLUSIONS: Functional evaluation at the baseline and during follow-up is more relevant than HC score for the prognosis of patients with definite and possible IPF.

Key words:

High resolution computed tomography, Idiopathic pulmonary fibrosis, UIP, Forced vital capacity, Mortality, Predictors.

Introduction

Fibrotic idiopathic interstitial pneumonias (IIPs) are chronic and progressive lung diseases of unknown cause[1]. The natural history of fibrotic IIPs is a progressive decline in pulmonary function until eventual death from respiratory failure or complicating comorbidities[2]. An accurate diagnosis is important as the prognosis differs between IIPs, with idiopathic pulmonary fibrosis (IPF) having the worst prognosis[3,4]. Despite this, there is considerable individual overlap in survival between IPF and non-IPF IIPs[4]. According to the guidelines presented by ATS/ERS/JRS/ALAT in 2011, the diagnosis of IPF can be made without a surgical lung biopsy when the HRCT shows a definite usual interstitial pneumonia (UIP) pattern and no other causative factor of pulmonary fibrosis are present. Definite HRCT UIP pattern is characterized by the presence of honey-combing and reticular opacities, often associated with traction bronchiectasis. If honeycombing is absent, but the imaging features otherwise meet criteria for UIP, the pattern HRCT is possible UIP and surgical lung biopsy is necessary to make a definite diagnosis[5]. Unfortunately, many patients with possible UIP are elderly and have important comorbidities that increase the risk of a surgical lung biopsy[6,7]. In an epidemiological study of Raghu et al[8] on patients with IPF and NSIP, surgical lung biopsy could be performed in only a small percentage of cases (10%) because of advanced disease at the time of recruitment. For all these reasons, a recent study[9] tried to identify clinical variables than could predict the diagnosis of IPF, and found that increasing age and total HRCT interstitial score may predict a diagnosis of biopsy-confirmed IPF, thus saving some patients from a surgical lung biopsy. Many studies have investigated non-invasive predictors of survival in IIPs. Functional measurements, particularly longitudinal change in forced vital capacity

Corresponding Author: Federica Novelli, MD; e-mail: f.c.78@libero.it

(FVC), has been identified as predictor of mortality in IPF and other IIPs[10,11]. Several groups have demonstrated that also HRCT measurements, as the scores of fibrosis and honeycombing, are predictive of survival[12-14].

We retrospectively studied the outcome of a group of patients with IPF with HRCT pattern of definite and possible UIP, and we analyzed the HRCT pattern and score at diagnosis and the lung function tests at baseline and during the follow-up in these patients, in order to recognize in a multivariate logistic analysis the more important prognostic predictors of the disease.

Patients and Methods

Patients

We retrospectively studied 42 patients followed at our clinic for pulmonary fibrosis between January 1998 and September 2009, 27 with HRCT pattern of definite UIP and 15 with possible UIP. Diagnosis was based on a clinical history, absence of occupational and environmental exposure, pulmonary function test results, HRCT images of the lungs, and, if available, transbronchial or surgical lung biopsy slides.

All patients at the time of diagnosis underwent pulmonary function tests (spirometry: FVC, FEV1, TLC; diffusing capacity: DLCOsb) (Elite series pletismography, Medical Graphics, St Paul, MN, USA), resting blood gas samples and HRCT. No patients had an underlying connective tissue disease (negativity of history, clinical examination and ANA, ENA, ANCA and rheumatoid factor) or exposure to environmental agents or drugs known to cause pulmonary fibrosis.

HRCT

HRCT was performed with 1.0 mm thick sections taken at 1 cm intervals throughout the entire lung during inspiration in the supine position. Two experienced readers separately evaluated the HRCT performed at the time of diagnosis and defined each HRCT as definite UIP pattern or possible UIP pattern. We excluded patients with HRTC features inconsistent with UIP pattern. Discordant cases were discussed and a final decision was reached. The CT scans were classified as showing a definite UIP pattern in presence of bilateral, predominantly basal, predominantly subpleural reticular opacities, associated with honeycombing and traction bronchiectasis, in the absence of characteristics suggestive of an alternative diagnosis. The CT scans were classified as showing a pattern possible UIP in the presence of signs of fibrosis (reticular opacity and/or traction bronchiectasis) associated with ground glass opacity and in the absence or in minimal presence of honeycombing and in the absence of characteristics inconsistent with UIP [5,15]. After this evaluation we selected 27 patients with definite UIP pattern and 15 patients with possible UIP pattern. The radiologists made a subjective assessment of the overall extent of the pulmonary parenchymal abnormalities (in % of the total lung section): the extent of ground-glass opacity (GGO) away from reticulation, the extent of ground-glass opacity + reticulation, the extent of honey-combing (HC) and the number of lobes with traction bronchiectasis. GGO was defined as an area of increased attenuation without obscuration of underlying vascular markings. Reticulation was defined as the innumerable, interlacing lines suggesting a mesh. HC was regarded present when clustered cystic airspaces of 3-10 mm in diameter with shared well-defined walls were identified with layering in the subpleural areas of the lungs. The extent of the parenchymal abnormality was scored to the nearest 5%. A total fibrotic score was computed, as the sum of the honey-combing score and reticulation (with or without association of GGO). As for the overall extent of pulmonary parenchymal abnormalities, there was a good agreement between the two observers as regards the scores measured on HRCT (intra-class correlation coefficient for GGO: 0.55; for GGO+reticulation: 0.86; for HC: 0.90).

In a subset of patients, bronchoalveolar lavage (BAL) was performed on aliquots of 50 mL of sterile normal saline instilled through the bronchoscope. Methods for the analysis of cellular BAL fluid components were standardized according to international recommendations[16].

Follow-up Evaluation

Patients were assessed every 6 months, by repeating spirometry and DLCO and blood gas analysis. After 6 months of follow-up, improvement and deterioration were defined as more than a 10% change in FVC or TLC, and more than a 15% change in DLCO.

Statistical Analysis

Data were expressed as mean ± standard deviation, or median and range. Categorical data were compared using Pearson's c2 statistics. Continuous data were compared using unpaired Student t test or Mann-Whitney test.

Survival was compared using the log rank test and displayed using Kaplan-Meier curves. Multivariate logistic analysis was used to identify significant variables predicting mortality. A $p < 0,05$ was considered statistically significant.

Results

Baseline demographic, clinic, physiologic, BAL and HRCT characteristics of 42 patients, subdivided according to the HRCT pattern (see Methods), are reported in Table I. Patients were mostly over 60 years old, and showed at presentation a moderate-to-severe dyspnoea score, a moderate restrictive pulmonary defect and a severe reduction in diffusing capacity. Respiratory failure was present in only 5 (11.9%) (all with definite UIP pattern). Lung biopsy was obtained in 7 out of 15 patients with possible UIP at HRCT; in all of them the diagnosis of UIP was confirmed.

The comparison between the two groups according to the HRCT pattern did not show any significant difference as regards the baseline characteristics, except for duration of symptoms, previous use of systemic corticosteroids and HRCT scores (Table I).

Table I. Baseline characteristics of patients, subdividing according high resolution computed tomography (HRCT) pattern.

	Total	Definite UIP	Possible UIP	p value
Number of patients	42	27	15	
Age, yr	67.2±6.3	67.7±6.2	66.5±6.8	
Male/Female	22/20	16/11	6/9	
Duration of follow-up, mo	24 (6-156)	24 (6-108)	27 (6-156)	
Smoking (41 subjects)				
Never-smokers	21	11	10	
Ex-smokers	16	13	3	
Smokers	3	2	1	
Pack-years	0 (0-80)	16 (0-80)	0 (0-50)	
Duration of symptoms, mo	12 (3-240)	28.5 (4-240)	12.0 (3-36)	p=0.05
Score of dyspnoea (MRC score)				
Score 1 (% of subjects)	35.7	25.9	53.3	
Score 2 (% of subjects)	42.9	40.7	46.7	
Score 3 (% of subjects)	19.0	29.6	0	
Score 4 (% of subjects)	2.4	3.7	0	
Basal steroid therapy Yes/No	8/34	8/19	0/14	p=0.03
Arterial blood gas at rest				
PaO_2, mmHg	74.6±9.3	73.5±9.6	76.9±8.5	
$PaCO_2$, mmHg	38.7±4.5	39.2±4.5	37.7±4.5	
Basal pulmonary function test				
FVC, Lt	2.27±0.79	2.40±0.83	2.06±0.68	
FVC, % predicted	73.6±17.8	75.3±18.4	70.5±16.8	
FEV1, Lt	1.94±0.64	2.06±0.65	1.74±0.57	
FEV1, % predicted	80.4±18.1	82.9±17.3	75.7±19.2	
TLC, Lt	3.69±1.07	3.92±1.11	3.32±0.91	
TLC, % predicted	66.2±13.0	67.5±12.6	64.1±13.9	
DLCO, ml/min/mmHg	10.6±3.6	10.05±3.59	11.16±4.19	
DLCO, % predicted	46.8±15.8	45.1±15.3	50.5±17.0	
BAL findings		n=15	n=10	
Cellular count, cells/ml	289.0 (50-1200)	320.0 (50-1200)	212.0 (97-750)	
Neutrophils, %	8.9 (1.5-58.8)	17.4 (1.5-50.4)	5.3 (2.4-49.9)	
Eosinophils, %	2.8 (0-49.3)	2.8 (0-49.3)	2.8 (1.4-5.2)	
Lymphocytes, %	4.1 (0-14.0)	4.2 (0-14.0)	3.7 (1.2-12.5)	
HRCT findings				
Ground-glass score	0 (0-30)	0 (0-25)	0 (0-35)	
Ground glass + reticulation score	20 (5-67.5)	15 (5-60)	40 (20-60)	p=<0.001
Honeycombing score	15 (0-67.5)	25 (10-55)	5 (0-5)	p=<0.001
Fibrotic score	42.5 (25-97.5)	37.5 (25-95)	42.5 (25-65)	
Bronchiectasis	4 (0-6)	5 (1-6)	2 (0-6)	p=0.01

Data are expressed as M±SD or median and range. Definition of abbreviations: UIP = usual interstitial pneumonia; MRC = Medical Research Council; SVC = slow vital capacity; FVC = forced vital capacity; FEV1 = forced expiratory volume in the 1st second; TLC = total lung volume; DLCO = diffusion capacity for carbon monoxide; BAL = bronchoalveolar lavage.

The median duration of follow-up was 24 months (range: 6-156 months). During this period, 10 patients died, after a median of 12 months (range: 10-60). At 6 months of follow-up, 13 patients deteriorated (in terms of FVC and/or DLCO decrease from baseline). The percentage of these patients, as well as the decline in FVC and other pulmonary function tests at 6 months of follow-up, were not significantly different in the two groups according to the HRCT pattern.

HRCT pattern (definite UIP vs possible UIP) was not associated with a different mortality rate during the follow-up (Figure 1a). We evaluated the prognostic significance of HRCT scores. The ground-glass and the total fibrotic score did not predict survival. Also the HC score did not predict survival when examined as a continuous variable, but the subdivision of the patients in two groups with HC score lower and higher than the median value (15) showed that this threshold was associated with an increased risk of mortality (Figure 1b). Therefore, we evaluated the baseline characteristics and the change in pulmonary function after 6 months, according to the baseline HC score higher or lower than 15%. There were more smokers and subjects with a heavier smoking history (as assessed by the PY: 27.3 vs 8.4, $p = 0.01$) among patients with HC ≥ 15%. These patients were also more dyspnoeic (as assessed by MRC score), had a lower DLCO (40.3% vs 53.6% of predicted, $p = 0.01$) and higher score of reticulation (32.7 vs 16.2, $p < 0.001$) and bronchiectasis (4.8 vs 2.7, $p < 0.001$) than the other patients. Instead, we have not showed a difference in the changes of FVC or DLCO at 6 months between the two groups.

Among the pulmonary functional tests performed by the patients, as described in the literature, we have used the baseline FVC and the 6-month changes in FVC to analyze their prognostic significance in our sample of patients. Subdividing the patients according to the baseline FVC, patients with FVC > 72.5% pred (median value) have a better survival than patients with FVC ≤ 72.5% pred (Figure 2a). Patients with lower baseline FVC had also a lower PaO2 (70.5 vs 78.7 mmHg, $p = 0.004$) and DLCO (38% vs 53%, $p = 0.003$) and a trend of a higher reticulation score (28% vs 20%, $p = 0.06$). We have not observed a difference in the changes of FVC or DLCO at 6 months between the two groups.

Subdividing the patients according to FVC change at 6 months (worsened FVC vs stable-improved FVC), patients with stable-improved FVC have a better survival than patients with worsened FVC (Figure 2b). The comparison of baseline characteristics in these two groups of patients showed that patients with worsened FVC at 6 months had a lower baseline DLCO (38.0% vs 49.4%, $p = 0.02$).

In a multivariate logistic analysis, we examined the mortality in relationship to age, gender, smoking habit, HC score, baseline FVC, FVC trend after 6 months (Table II). Baseline FVC and FVC change at 6 months were the only two variables associated with mortality. HC score did not significantly enter in the analysis.

Discussion

In this study, we examined the role of HRCT and functional parameters as possible predictors of mortality in patients with definite or possible UIP. We found that both a high HC score, and a low baseline FVC and/or a worsening of FVC at 6 months were significant predictors of mortality during the follow-up, but that the weight of baseline FVC and FVC 6-month decline was more relevant than HC score in the multivariate logistic analysis. These data support the importance of the pulmonary function evaluation and monitoring in the assessment of the prognosis of IPF.

Our results are consistent with those of other studies. In the study by Collard et al[17] on 81 patients with IPF, the changes in FVC, TLC, DLCO and PaO_2 over 6 months were predictive of mor-

Table II. Results of multivariate logistic analysis of predictors of mortality in patients with IPF.

Variables		Hazard Ratio	95% CI	*p* value
Age		1.01	0.8-1.2	NS
Sex	Male vs female	1.8	0.2-13.6	NS
Smoke	Smoker vs no smoker	0.6	0.05-7.4	NS
	Ex smoker vs smoker	0.8	0.04-14.6	NS
HC score	HC>15 vs HC≤15	4.9	0.8-31.2	p=0.08
Baseline FVC	FVC < vs > median value	16.4	2-131.8	p=0.009
Trend of FVC at 6 months	Worsened vs stable-improved	13.1	12.4-70.2	p=0.003

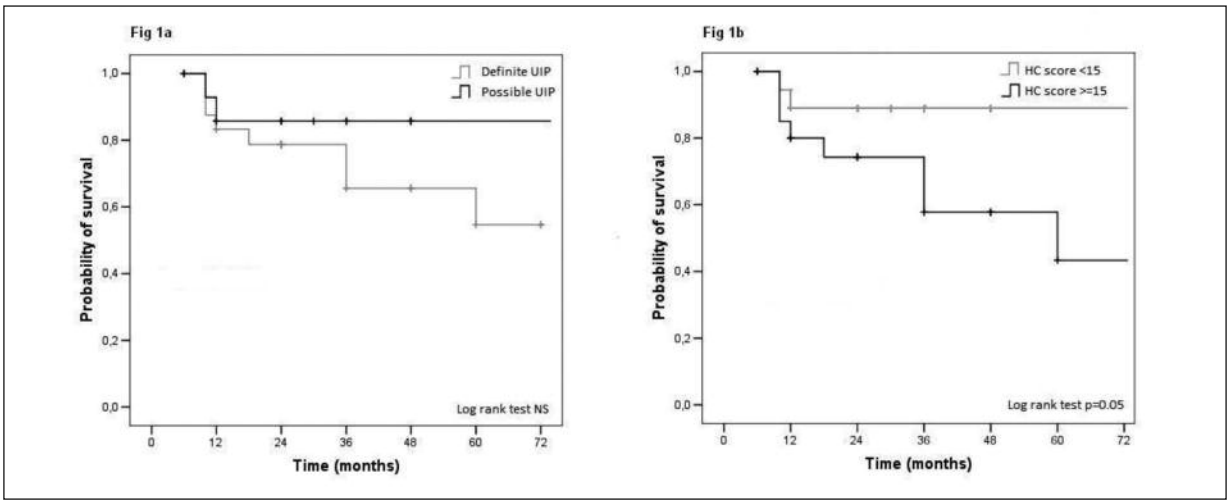

Figure 1. Kaplan-Meier survival curves for patients with definite and possible UIP (Figure 1a) and for patients with honeycombing (HC) score above and below median value (15%) (Figure 1b).

tality. Jegal et al[11] studied 131 patients with IPF and 48 patients with NSIP, and reported that 6 months change in FVC was the most important predictor of mortality, superior even to the histological classification. Also in a study by Flaerthy et al[18] on 80 patients with UIP and 29 patients with NSIP, a decrease in FVC was an independent risk factor for mortality, also in a Cox proportional hazard model taking into consideration histologic diagnosis, gender, smoking history, baseline FVC, and 6-month change in FVC. More recently, in more homogeneous groups of patients with IPF, pulmonary function evaluation (at baseline and during the follow-up) resulted as a significant predictor of mortality[19,20].

In our study, baseline DLCO and DLCO change at 6 months were not important prognostic factors for mortality, unlike previously reported in some articles. Latsi et al[10] retrospectively analyzed 63 patients with IPF and 41 patients with NSIP, and found that in patients with baseline severe functional impairment (DLCO < 35% of predicted) the 3-year mortality was similar between UIP and NSIP patients, and that at 12 months of follow-up the only prognostic factor for mortality was the change of DLCO. In our study, the lack of prognostic significance of DLCO may be due to the smaller number of patients studied in comparison with the study by Latsi et al, or to the lack of DLCO measure in the patients with more severe

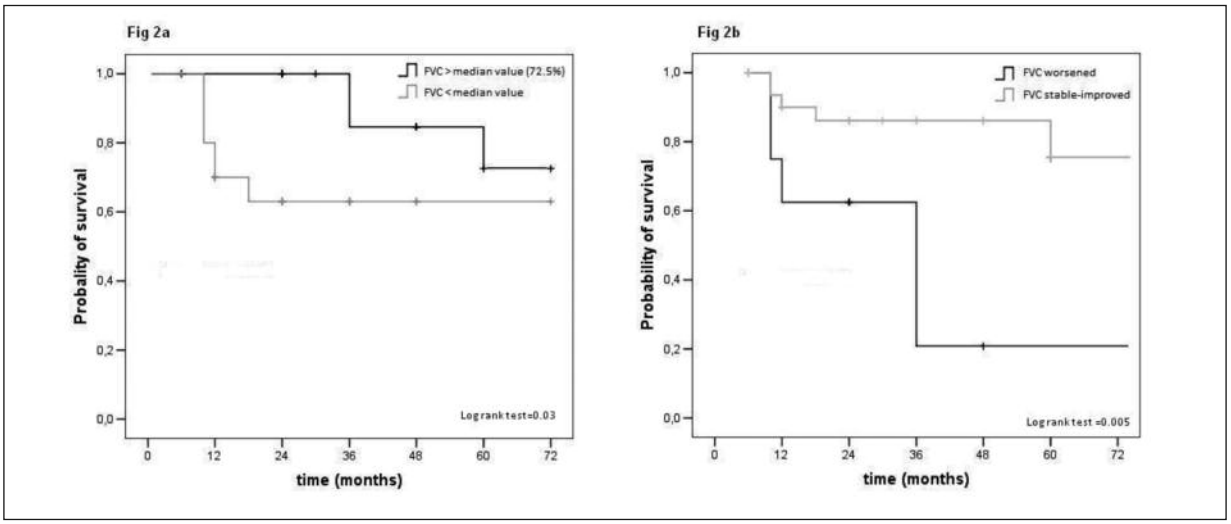

Figure 2. Kaplan-Meier survival curves for patients with baseline Forced Vital Capacity (FVC) greater and less than median value (73% of predicted) (Figure 2a) and for patients with 6 month FVC worsened and stable-improved (Figure 2b).

functional impairment [21] or to the greater variability of DLCO[22]. Despite these limitations, there was a significant difference in mortality between patients with worsened DLCO and patients with stable-improved DLCO at 1 year ($p = 0.004$).

In our study, among all HRCT parameters only a threshold HC score of 15% predicted mortality. We did not find any difference in survival considering the HRCT pattern (definite vs possible UIP) or other parameters such as total fibrotic score or bronchiectasis score. In the literature, the role of HRTC pattern in predicting mortality is controversial. Flaerthy et al[23] studied 73 patients with IPF and 23 patients with NSIP: patients with HRTC pattern of UIP had a worse prognosis that patients with HRTC pattern of NSIP (median survival 2.08 vs 5.81 years, $p = 0.001$). On the contrary, in the study by Sumikawa et al[14] on 98 patients with histological diagnosis of UIP, the HRCT pattern (UIP vs alternative diagnosis) did not provide prognostic information, while the prognosis was influenced by traction bronchiectasis and fibrotic scores.

Few studies have considered both HRCT findings and pulmonary function data in the same logistic analysis as predictor of survival. Lynch et al[15] studied 315 patients with IPF and found that a higher extent of fibrosis score and a lower DLCO increased the risk of death. Similarly, Mogulkoc et al[24] studied 115 patients with IPF and found that the best prediction of survival was derived from a combination of DLCO percent/predicted and HRCT fibrotic score. Shin et al[25] studied 108 patients with UIP and fibrotic NSIP and came to the same conclusion. The novelty of our study, in comparison with other studies on this topic, is to have considered both basal HRCT, pulmonary function findings and pulmonary function change at 6 months in the same logistic analysis. Both radiological and functional findings resulted separately as significant predictors of mortality, but in the multivariate logistic analysis only functional findings resulted as significant predictors. This fact suggests that, although a relationship between radiological and functional findings may be expected, the weight of functional evaluation in predicting the mortality may be more relevant than HRCT findings.

It is interesting to note that our patients with HC score above 15% had a greater smoking history and a lower DLCO values and a higher dyspnoea score, indices of a more advanced stage of disease[26,27].

Our is retrospective and the treatment was not the same in all patients. The efficacy of the treatment regimens (prednisone alone or prednisone plus azathioprine or prednisone plus azathioprine plus acetylcysteine) used for these patients is minimal[28]. We are lacking of lung biopsy confirming IPF in all patients with possible UIP at HRCT. However, in the 7 patients of this group who performed lung biopsy, the diagnosis of UIP was confirmed. However, lung biopsy is not frequently performed, particularly in hospitals of primary or secondary care level, also for the possible complications in patients with more advanced disease[6,7].

Conclusions

In patients with definite and possible IPF, baseline FVC and FVC change at 6 months are the most important predictors of mortality, even more than HRCT score. An accurate functional evaluation at the baseline and during the short follow-up may, then, produce important information for the prognosis of this disease.

Conflict of Interest

Paggiaro PL has received in the last 5 years funds for istitutional educational and research activities from AstraZeneca, Abbott, Boehringer Ingelheim, Chiesi Pharmaceutical, GlaxoSmithKline, MerckSharp&Dohme, Menarini, Novartis, Nycomed and Valeas for teaching and research activities. All other authors have no competing interests to declare.

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