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Four –Year Survival in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease

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Abstract：Background：The forced expiratory volume in one second (FEV_1) is regarded as the most significant correlated factor of survival in chronic obstructive pulmonary disease (COPD) and it is also used as a measure of disease severity in the staging of COPD. However, the other factors of disease severity have not yet been comprehensively reported. Study objectives：We compared the effects of disease severity, as evaluated by the physical findings and pulmonary function tests, on the 4–year survival rate in patients with COPD. Design and methods：76 consecutive patients with moderate to severe COPD were enrolled in a 4–year, prospective study at Fukuoka University Hospital. Results：The overall survival information was available with certainty for all patients. The 4–year over all survival was 65.4%. Five patients died of malignancy or cerebral events. Excluding these patients, the patients demonstrating a poor pulmonary function also had a significantly worse long–term survival. A univariate analysis revealed the body mass index, %forced vital capacity (%FVC), $\%FEV_1$, %total lung capacity (% TLC), diffusing capacity for carbon monoxide (D_{LCO}) and % D_{LCO} to all be significant predictable factors. A multivariate Cox proportional hazards analysis revealed that $\%FEV_1$, PaO_2 and D_{LCO} were independent predictable factors for survival. Conclusion：This study suggests that not only an obstructive ventilatory defect but also a defect of the CO diffusing capacity should be included as variables for evaluating patients with COPD in terms of mortality.

Key words：Chronic obstructive pulmonary disease, Mortality, CO diffusing capacity

Introduction

Mortality has been an important outcome in chronic obstructive pulmonary disease (COPD), as it is currently the fourth leading cause of death in the world.[1] The severity of COPD has been based on the degree of airflow limitation, as defined by the forced expiratory volume at one second (FEV_1) because FEV_1 has been regarded as the most important predictor of mortality in addition to age.[2] Although an airflow limitation is the most obvious manifestation of COPD, COPD also has overinflation and a defect in the CO diffusing capacity. In addition, COPD has other extrapulmonary features and should be regarded as a systemic disorder.[3] Some researchers have questioned the use of FEV_1 as the best single evaluation

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parameter, and have pointed out that there is a need to better categorize and systemically evaluate patients with COPD.[4)5)] The present study was designed to prospectively evaluate the 4-year prognosis of COPD at Fukuoka University Hospital. The main objective of this report is to assess the survival of COPD and to analyze the independent predictable factors including the physical findings and pulmonary function tests.

Materials and Methods

Patients

All consecutive candidates 156 for lung volume reduction surgery who entered Fukuoka University Hospital by December 1999 were included in this evaluation. We excluded any cases with uncontrolled comorbidities likely to affect mortality, such as malignant disorders and cardiovascular diseases. No established rehabilitation program was administered. Eighty cases underwent lung volume reduction surgery whereas, 76 cases were treated by medical therapy. We analyzed the survival in 76 cases treated by medical therapy in this study.

Pulmonary function tests

Pulmonary function tests consisted of spirometry, flow volume curve, lung volume and the single breath diffusing capacity for carbon monoxide. These tests were examined when the patients were in clinically stable states using Chestac 55 V. We used the data of spirometry, a flow volume curve and lung volume obtained after inhaling procaterol with a spacer device. The American Thoracic Society standards[6)] were used for data collection. The CO diffusing capacity was measured three times by the single breath method and mean value was used for the evaluation. The breath holding time was preset to 10 seconds and a washout volume to 0.75 L. Arterial blood gas samples were obtained while the subjects were at rest and breathing room air. The predicted values of spirometry were those established by the Japan Society of Chest diseases.[7)] The BMI was calculated by dividing the patients' weight in kg by the height squared (m^2).

Study design

The survival status was assessed for all patients by either contacting them directly or their referring physicians. The latest data of known survival was recorded and the information regarding the cause of death was obtained from families or referring physicians. We investigated not only the survival rates for all cases but also those for cases excluding death by malignancy or cerebral events. The cutoff points for individual continuous variables were selected at near median values except for $\%FEV_1$ and $PaCO_2$. We established a cutoff point of 35% for $\%FEV_1$ according to COPD severity based on airflow limitations as defined by the American Thoracic Society.[8)] The cutoff point 45 mmHg for $PaCO_2$ is selected because most of patients showed a normal $PaCO_2$.

Statistical analysis

Results are presented as the mean±standard deviation. The survival status of the subjects was estimated using the Kaplan-Meier method. Differences in survival after stratification by the variables were tested using the log-rank test. Univariate and multivariate Cox proportional hazards analyses were performed to investigate the relationship between the clinical indices and mortality. Any factors $p<0.25$ based on the univariate analysis were adopted for the multivariate analysis. Clinical variables were used as continuous variables. The results of a regression analysis were presented in terms of the hazards ratio (HR) with the corresponding 95% confidence intervals. A p values of less than 0.05 were considered to be statistically significant.

Results

1. Characteristics of the subjects

The baseline characteristics of the 76 patients with COPD registered in the study are summarized in Table 1. All consecutive 76 subjects were ex-smokers but they had an extensive smoking history. The patients were characterized according to their severe fixed expiratory airflow limitation, hyperinflation and defect in the CO diffusing capacity, which were present findings consistent with COPD. When the patients were classified ac-

Table 1. Characteristics of subjects

Age		69.5± 6.6
Height	(cm)	160.5± 6.6
Body weight	(kg)	50.9±11.5
BMI		19.7± 3.7
Tp	(g/dl)	6.5± 0.6
Alb	(g/dl)	3.7± 0.4
Hb	(mg/dl)	13.8± 1.6
MRC scale		3.4± 0.8
FVC	(ml)	2830±860
%FVC	(%)	87.3±21.0
FEV_1	(ml)	950±390
$\%FEV_1$	(%)	37.0±13.1
%RV	(%)	198.8±47.4
RV/TLC%	(%)	52.6± 8.9
$\%D_{LCO}$	(%)	57.5±24.8
PaO_2	(mmHg)	70.1±10.9
$PaCO_2$	(mmHg)	46.0± 8.5

Definition of abbreviations : FVC=forced vital capacity ;
FEV_1=forced expiratory volume in one second ;
RV=residual volume ; RV/TLC=residual volume/total lung capacity ;
D_{LCO}=diffusing capacity for carbon monoide

cording to COPD severity based on FEV_1 as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[8] no patients (0%) were classified as mild (80% or more predicted), while twelve (16%) were classified as moderate (50–80% predicted), thirty-eight (50%) as severe (30－49%predicted)and twenty－six (34%) as very severe (less than 30% predicted).

2. Overall Survival

The overall survival information was known with certainty for all patients. The cutoff data for 48 months was evaluated. The 1-year, 2-year, 3-year and 4-year survival rates were 89.7% 83.3% 78.2% and 65.4%, respectively. The most popular cause for death was respiratory failure (18 cases). Five cases died of malignancy or cerebral events. We evaluated the survival rates of 71 cases excluding the cases that died of malignancy and cerebral events. According to this evaluation, The 1-year, 2-year, 3-year and 4-year survival rates in the groups were 90.4%, 84.9%, 75.3%, 69.9%, respectively. We investigated the survival rates excluding any cases that died of malignancy or cerebral events while setting the cutoff points as described above.

3. Age

Younger patients ＜70 years old tended to show an improved long－term survival in comparison with older patients ≧70 years old in the patients, however, the difference was not significant(Fig. 2).

4. FEV_1

We classified the patients as $\%FEV_1 \geqq 35\%$ and $\%FEV_1 < 35\%$ according to the COPD severity based on the airflow limitations as defined by the American Thoracic Society.[9] In the groups, the survival for higher baseline $\%FEV_1 \geqq 35\%$ was significantly higher than that for $\%FEV_1 < 35\%$ (Fig. 3).

5. %Residual lung volume (%RV) and Residual lung volume/Total lung capacity% (RV/TLC%)

Patients with a more inflated (RV/TLC%≧52%) had a significantly poor survival in comparison to patients with a less inflated (RV/TLC%＜52%) (Fig. 4). The %RV showed a similar tendency to RV/TLC%

6. Gas exchange

A higher baseline PaO_2 ($PaO_2 \geqq 70$ mmHg) did not improve survival in comparison with a lower baseline PaO_2 ($PaO_2 < 70$ mmHg) in the patients. Over

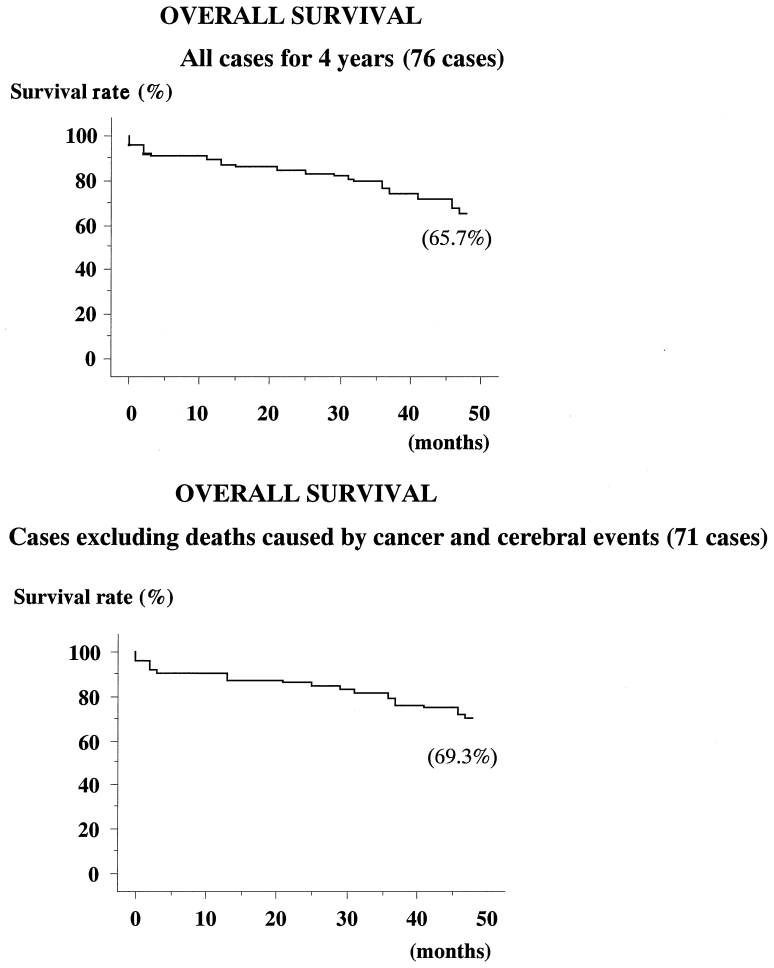

Fig. 1. Kaplan–Meier survival curves in overall patients and in the patients after excluding any cases who died of malignancy or cerebral events. The time in months is shown on the X–axis. The ratio of original patients surviving is shown on the y–axis. The 4–year survival rate of the overall patients is 65.4%. The survival curve excluding the cases died of malignancy and cerebral events is shown below. According to this evaluation, the 4–year survival rate in the group is 69.9%.

50% of the patients (40 of the 71 cases in the patients) showed a normal $PaCO_2$ ($PaCO_2 \leqq 45$ mmHg). A higher baseline $PaCO_2$ ($PaCO_2 > 45$ mmHg) tended to have a worse survival in comparison with a lower baseline $PaCO_2$ ($PaCO_2 \leqq 45$ mmHg), however, the difference was not significant. We classified the patients, CO diffusing capacity (D_{LCO}) $\geqq 8$ ml/min.mmHg and $D_{LCO} < 8$ ml/min.mmHg according to the median value. The D_{LCO} levels were significantly associated with the long–term survival in the patients (Fig. 5).

7. Univariate and Multivariate analysis

A univariate analysis revealed the following factors to be potential factors : the body mass index, %forced vital capacity (%FVC), $\%FEV_1$, %total lung capacity (%TLC), D_{LCO} and % D_{LCO} (Table. 2). A multivariate analysis demonstrated $\%FEV_1$, PaO_2 and D_{LCO} to be inverse independent factors for survival (HR=0.898, $p<0.05$; HR=0.921, $p<0.05$; HR=0.493, $p<0.05$, respectively) (Table 3).

Discussion

This prospective study demonstrated the FEV_1 and CO diffusing capacity to be closely correlated with the survival in patients with COPD. Most studies on mortality among patients with COPD

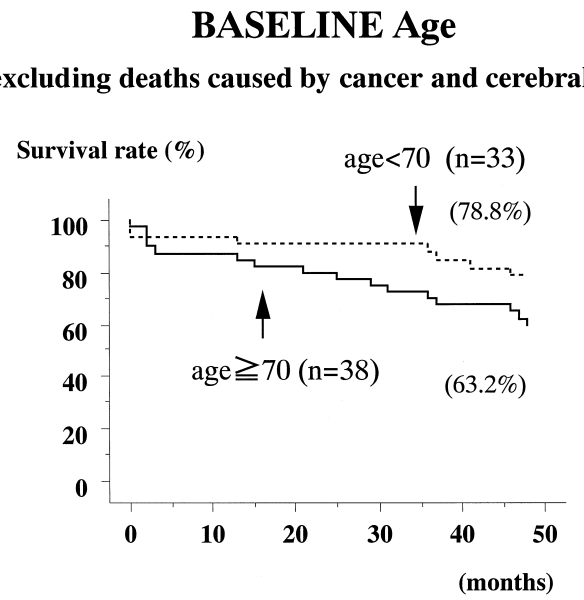

Fig. 2. Kaplan-Meier survival curves in the patients excluding the cases that died of malignancy and cerebral events based on age (cutoff point 70 yrs).

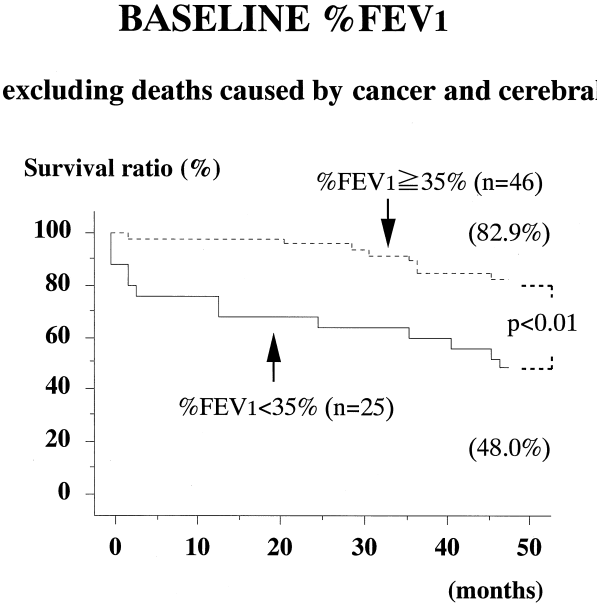

Fig. 3. Kaplan-Meier survival curves in the patients after excluding the cases who died of malignancy or cerebral events based on the % forced expiratory volume at one second (%FEV_1) (cutoff point 35%).

have reported FEV_1 to be the strongest factor related to survival[2] while other factors, with the exception of age, tend to be minor. The mortality rate of patients with severe emphysema (FEV_1 of 0.75l or 30% predicted) is 40% to 50% at 3 yr.[2)10)11)12)] The mortality rate of our patients was similar with that reported when the FEV_1 was below 600 ml after being treated by a bronchodilator.

We set cutoff points of variance to compare the long-term survival outcome excluding the cases that died of extra pulmonary events. We hypothesized that patients with a lesser degree of COPD would be able to survive for longer periods of time. In the patients, younger patients and those with milder diseased patients are able to survive for longer periods. Five cases in these groups died

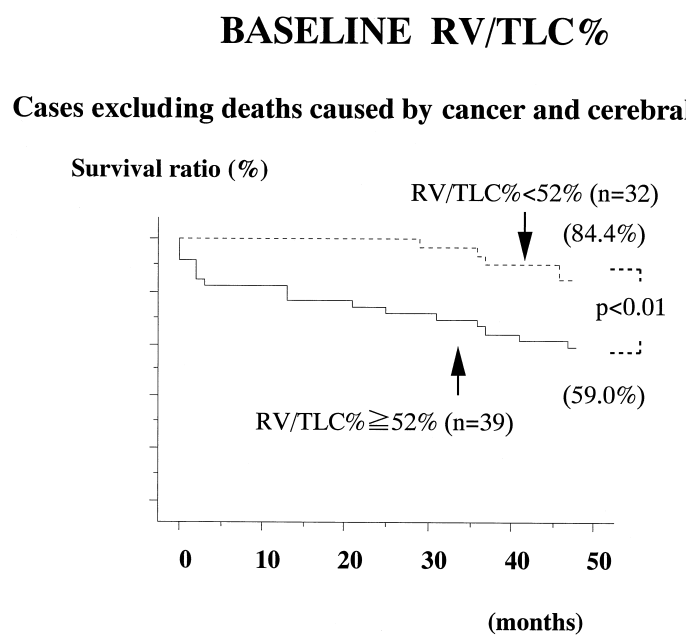

Fig. 4. Kaplan–Meier survival curves in the patients after excluding the cases who died of malignancy or cerebral events based on the residual lung volume/ total lung capacity% (RV/TLC%) (cutoff point 52%).

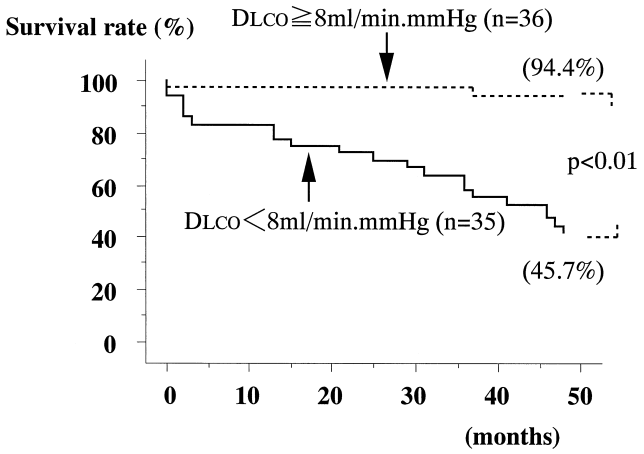

Fig. 5. Kaplan–Meier survival curves in the patients after excluding the cases who died of malignancy or cerebral events based on the diffusing capacity for carbon monoxide (D_{LCO}) (cutoff point 8 ml/min.mmHg).

of either malignancy or cerebral events while the other patients died of respiratory failure or pneumonia. We reinvestigated the survival ratio while excluding the patients that died of malignancy or cerebral events to clarify the effect of the physical situation and the pulmonary function. In this evaluation, the 1–year, 2–year, 3–year and 4–year survival rates in the group were 90.4%, 84.9%, 75.3%, 69.9%, respectively.

In these patients we investigated the relationship between the disease severity and survival. We found that FEV_1 can sensitively predict survival in

Table 2. Univariate Analysis of Prognosis

Factor	Hazard ratio	95% Confidence Limit	p value
Age	1.048	0.976–1.126	0.194
BMI	0.851	0.750–0.966	0.012
Tp	0.767	0.341–1.736	0.522
Alb	0.419	0.125–1.412	0.161
Hb	0.898	0.678–1.190	0.456
%FVC	0.966	0.946–0.987	0.017
$\%FEV_1$	0.933	0.892–0.973	0.018
%TLC	1.031	1.004–1.059	0.025
%RV	1.004	0.996–1.012	0.334
RV/TLC%	1.071	1.019–1.126	0.068
PaO_2	0.974	0.933–1.017	0.229
$PaCO_2$	1.038	0.986–1.093	0.153
D_{LCO}	0.736	0.783–0.861	0.000
$\%D_{LCO}$	0.955	0.931–0.980	0.001
D_{LCO}/VA	0.761	0.465–1.245	0.278

Table 3. Multivariate Analysis of Prognosis

Factor	Hazard ratio	95% Confidence Limit	p value
Age	1.035	0.929–1.152	0.531
BMI	0.910	0.693–1.193	0.492
Alb	0.475	0.126–1.795	0.272
%FVC	0.987	0.943–1.033	0.568
$\%FEV_1$	0.898	0.823–0.980	0.015
%TLC	1.033	0.999–1.068	0.060
RV/TLC	1.041	0.946–1.145	0.409
PaO_2	0.921	0.854–0.992	0.029
$PaCO_2$	1.030	0.964–1.100	0.385
D_{LCO}	0.493	0.247–0.986	0.046
$\%D_{LCO}$	0.969	0.895–1.048	0.431

the subjects based on a multivariate analysis. Traditionally, the severity of COPD is graded according to the degree of airflow limitation, as expressed by the FEV_1 of the forced vital capacity maneuver. It is a useful predictor of mortality and the defining characteristic of FEV_1 and its change over time in patients with COPD have been well studied.[13] Martinez[14] and coworkers explored the factors predicting mortality in the patients participating in the National Emphysema Therapy Trial (NETT) who were randomized according to the optimal medical treatment. The study concluded that FEV_1 was a significant predictor of mortality based on a univariate analysis, but not based on a multivariate analysis. This result was different from our findings. The important difference is that our study did not include a distance walk of 6 min. Pinto－Plata[15] et al reported that a distance walk of 6 min predicts mortality better than other traditional markers of disease severity, such as FEV_1. FEV_1 most likely expresses the respiratory system involvement and it does not reflect any systemic manifestations.[16]

We also found D_{LCO} to be a independent predictor of survival in the subjects. D_{LCO} as a predictor for survival in the patients with COPD has not yet been well described. The single-breath diffusing capacity for carbon monoxide has been widely used in population surveys. It is used as a noninvasive test of pulmonary gas exchange in the respiratory system.[17] However, a severe obstructive ventilatory defect decreases accuracy of the test. We measured D_{LCO} three times to evaluate its reliability. The difference of each values existed within a 10% difference and the mean value of three measurements was used for a survival analysis. A multivariate analysis demonstrated the $\%FEV_1$ and D_{LCO} to be inverse independent fac-

tors for survival (HR＝0.898, $p<0.05$; HR＝0.493, $p<0.05$, respectively). This finding suggests that D_{LCO} is more sensitive than $\%FEV_1$ in order to predict the survival in patients with moderate to severe COPD. The D_{LCO} has been shown to be related to the nutritional status.[18] This finding may suggest that D_{LCO} may possibly be related with survival in patients with COPD.

PaO_2 also remained significantly associated with mortality in the patients based on a multivariate analysis (HR＝0.921, $p<0.05$). Schols[19] et al reported the PaO_2 to be a significant predictor of survival in addition to the BMI and age based on a multivariate analysis. In addition, $PaCO_2$ was not selected as an independent contributor. These findings were similar to our results. PaO_2, as a functional summary of respiratory and circulatory system, could therefore significantly affect the mortality of COPD.

In this study, the age and BMI were not significant prognostic factors based on a multivariate analysis. The age of the subjects was 69.5±6.6 and the deviation was small. This homogenity of age may explain the insignificant relationship to age in this study. Landobo[20] et al reported that the association between the BMI and mortality was especially significant in severe COPD and it differed according to the severity of airflow limitation. In this study, moderate COPD patients were included, as a result, the BMI did not remain as an independent factor for survival. Schols[19] et all reported that after the stratification of the patients with COPD into BMI quintiles a threshhold value of 25 kg/m^2 was identified below in which the mortality risk clearly increased. In this study, 7 patients had a BMI above 25 kg/m^2 while most patients showed significant emaciation. This finding may explain that the BMI does not remain an independent factor for survival.

The chief weakness of this study was the small number of patients enrolled. Second, it may be argued that the baseline predictors were taken over a long period of time, without taking into account other changes occurring during the follow-up. Third, as the entry criteria excluded the major comorbities that might affect mortality, we did not investigate the significance of such comorbidity factors. Cormorbidities have been reported to play an important role in the prediction of survival of COPD patiemts.[21] Therefore, we should have searched for a better way to investigate the relationship between cormorbities and survival. Fourth, only patients who could perform spirometry were enrolled. Although we were thus able to guarantee that all enrolled patients had a confirmed diagnosis of COPD, in doing so we thereby possibly excluded the most severely affected patients. These limitations, however, do not change the main findings of the present study.

In conclusion, we herein demonstrated a significant relationship between the D_{LCO} and mortality in COPD patients independent of FEV_1. Although an airflow limitation has been traditionally used as the index of disease severity in COPD, as it is also regarded as a significant predictor of mortality, the D_{LCO} may therefore potentially have an impact on the multidimensional evaluation of COPD from the standpoint of mortality.

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