

Prognostic Significance of Pulmonary Lymphangiomyomatosis Histologic Score

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Correlations were made between clinical and follow-up data and histopathologic findings in 105 women (mean age \pm standard deviation, 38.3 ± 9.0 years) with pulmonary lymphangiomyomatosis (LAM). The actuarial survival (to pulmonary transplantation or death) of the patients from the time of lung biopsy was 85.1% and 71.0% after 5 and 10 years respectively. The histologic severity of LAM, graded as a LAM histologic score (LHS), was determined on the basis of semiquantitative estimation of the percentage of tissue involvement by the two major features of LAM: the cystic lesions and the infiltration by abnormal smooth muscle cells (LAM cells) in each case: LHS-1, <25%; LHS-2, 25% to 50%; and LHS-3, >50%. Analysis using the Kaplan-Meier method revealed significant differences in survival for patients with LHS-1, -2, and -3 ($p = 0.01$). The 5- and 10-year survivals were 100% and 100% for LHS-1, 81.2% and 74.4% for LHS-2, and 62.8% and 52.4% for LHS-3. Increased degrees of accumulation of hemosiderin in macrophages also were associated with higher LHS scores ($p = 0.029$) and a worse prognosis ($p = 0.0012$). Thus, the current study suggests that the LHS may provide a basis for determining the prognosis of LAM.

Key Words: Lymphangiomyomatosis—Lung—Prognosis—Smooth muscle—HMB-45.

Am J Surg Pathol 25(4): 479–484, 2001.

Our knowledge of the clinical and histopathologic characteristics of pulmonary lymphangiomyomatosis (LAM) has increased considerably during the past decade. However, the early diagnosis of LAM continues to present difficult problems because of the insidious

nature of the disorder and the nonspecificity of its initial manifestations.¹²

The pathologic changes in pulmonary LAM are characterized by nodules of abnormal smooth muscle cells (LAM cells), which are distinguished from other types of smooth muscle cells by their reactivity with HMB-45, a mouse monoclonal antibody against a melanosomal antigen,¹ and by the presence of multiple cysts distributed diffusely throughout the lungs.^{5,7,10,13} These LAM lesions produce a characteristic constellation of clinical, radiologic, and physiologic findings.^{2,4,6,8}

Most information on survival of patients with pulmonary LAM has been based on small numbers of cases. Early reports of LAM presented a pessimistic view of survival, with most patients dying within 10 years after the initial diagnosis,^{3,11} whereas recent reports suggest a more favorable prognosis.^{12,14} Kitaichi et al.⁹ suggested that patients with a predominantly cystic type of LAM had a worse prognosis than those with a predominantly muscular type of LAM, consistent with the hypothesis that the natural history of LAM differs among various patients. However, information concerning the correlation between histopathologic features and survival of the patients was limited.

In the current study, the clinical and histopathologic findings in a large series of patients with LAM were analyzed to determine possible predictors of survival. A grading system of the severity of LAM, herein referred to as the *LAM histologic score* (LHS), was developed by reviewing surgical lung specimens from 105 patients. Statistical analysis of the data obtained by the use of this score demonstrates its usefulness as a predictor of patient survival.

METHODS

Patients

The study group consisted of 105 patients in whom the diagnosis of LAM was proved histologically by surgical

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TABLE 1. Lobe sampling of lung biopsy specimens

Lobe of lung	No. of cases	Percentage
RUL	6	6
RML	10	10
RLL	6	6
RUL & RML	2	2
RUL & RLL	3	3
RU, RM, & RLL	3	3
RM & RLL	5	5
R lung, NOS	9	9
LUL	21	20
LLL	20	19
L lung, NOS	12	11
LU & LLL	8	8
RUL & LUL	2	2
L & R lung, NOS	1	1
Lung, NOS	10	10

R, right; L, left; UL, upper lobe; ML, middle lobe; LL, lower lobe; NOS, not otherwise specified.

lung biopsy according to established criteria.^{1,3,13} Seventy-five of these patients (74 open lung biopsies and one lobectomy specimen) were studied at the Pulmonary–Critical Care Medicine Branch and the Pathology Section of the National Heart, Lung, and Blood Institute from 1995 to 1999. The other 30 patients (all of whom underwent open lung biopsy) were studied at the Department of the Pulmonary and Mediastinal Pathology of the Armed Forces Institute of Pathology from 1972 to 1999. The mean size of the biopsy specimens was $4.5 \times 2.4 \times 1.1$ cm (range, $1.2\text{--}12.5 \times 0.2\text{--}7.0 \times 0.1\text{--}2.9$ cm). A second specimen was obtained in 39 cases with a mean size of $3.9 \times 1.7 \times 0.7$ cm (range, $1.0\text{--}9.5 \times 0.5\text{--}7.0 \times 0.2\text{--}2.0$ cm). A third specimen was obtained in 16 cases with a mean size of $4.5 \times 2.4 \times 0.9$ cm (range, $1.1\text{--}16.2 \times 0.3\text{--}16.0 \times 0.2\text{--}2.5$ cm). A fourth specimen was obtained in three cases with a mean size of $3.4 \times 1.0 \times 0.3$ cm (range, $2.1\text{--}4.5 \times 0.5\text{--}1.5 \times 0.1\text{--}0.5$ cm). Of these 105 patients, 12 (11.4%) were diagnosed as having tuberous sclerosis. The study was approved by the institutional review boards of the National Heart, Lung, and Blood Institute and the Armed Forces Institute of Pathology.

The study focused on the following features: age and major signs and symptoms at the time of initial histologic evaluation of the lung tissue for LAM, the histologic severity of LAM, and the clinical course of the patients. In each case, tissue sections were stained with hematoxylin and eosin stain, and in many cases sections stained with the Masson trichrome and the Movat pentachrome stains were also available. A range of one to 10 slides (mean, three slides) was available for review. The size of the maximum diameter of the lung biopsies ranged from 1 to 6 cm with an average of 1.5 cm. The lobe sampling of the lung biopsy specimens is summarized in Table 1. More than one lobe was sampled in 24 specimens (23%). The histologic severity of LAM (i.e., the LHS) was de-

termined on the basis of the extent of the involvement of the sampled lung tissue by the two major morphologic features of the disease; namely, the cystic lesions and the infiltration by LAM cells. Thus the LHS was based on the total percentage of lung tissue involvement by both the smooth muscle and the cystic components of the LAM lesion together, rather than an individual score for each component. The total percentage of tissue involvement by these two patterns of histologic alterations was estimated semiquantitatively, using low magnification in each case, and the LHS was graded as follows: LHS-1, <25%; LHS-2, 25% to 50%; and LHS-3, >50% (Fig. 1). We also attempted to assess semiquantitatively these two patterns separately, and to estimate the maximal size of the cystic lesions on the tissue sections. The degree of accumulation of hemosiderin-laden macrophages (hemosiderosis) in the air spaces was regarded as mild when it was seen focally or in less than 5% of the overall tissue sections, moderate when it was recognized easily at a glance in any of the tissue sections or in less than 25% of the area of the section, and marked when it was observed in many air spaces or in more than 25% of the sections. Because it was often difficult to determine the time of onset of signs and symptoms of LAM, the date of the initial surgical lung biopsy was regarded as the date of diagnosis. Follow-up data on all of the studied patients were obtained by reviewing medical records and contacting the referring physicians. Information about the current status of the patients was updated as of July 2000. Pulmonary transplantation or death was regarded as a censored event for the Kaplan-Meier survival analysis.

Analysis of Data

Values are expressed as mean \pm standard deviation or median, unless otherwise stated. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS, Inc., Chicago, IL, USA). Correlations between categorical variables were made using the χ^2 method. Survival analysis was performed using the Kaplan-Meier method, with the log rank and the Tarone Ware tests for categorical variables, and the Cox regression analysis for continuous variables. Differences were considered significant at $p \leq 0.05$.

RESULTS

All patients were women, ranging in age from 17 to 70 years (mean age, 38.3 ± 9.0 years). Eight of the patients (7.6%) were older than 50 years of age. The major clinical signs and symptoms at the time of histologic evaluation were pneumothorax in 57 patients (54.3%), abnormalities on routine radiographic examination and/or high-resolution computed tomography (HRCT) of the chest in 21 patients (20%), dyspnea at rest in 16 patients

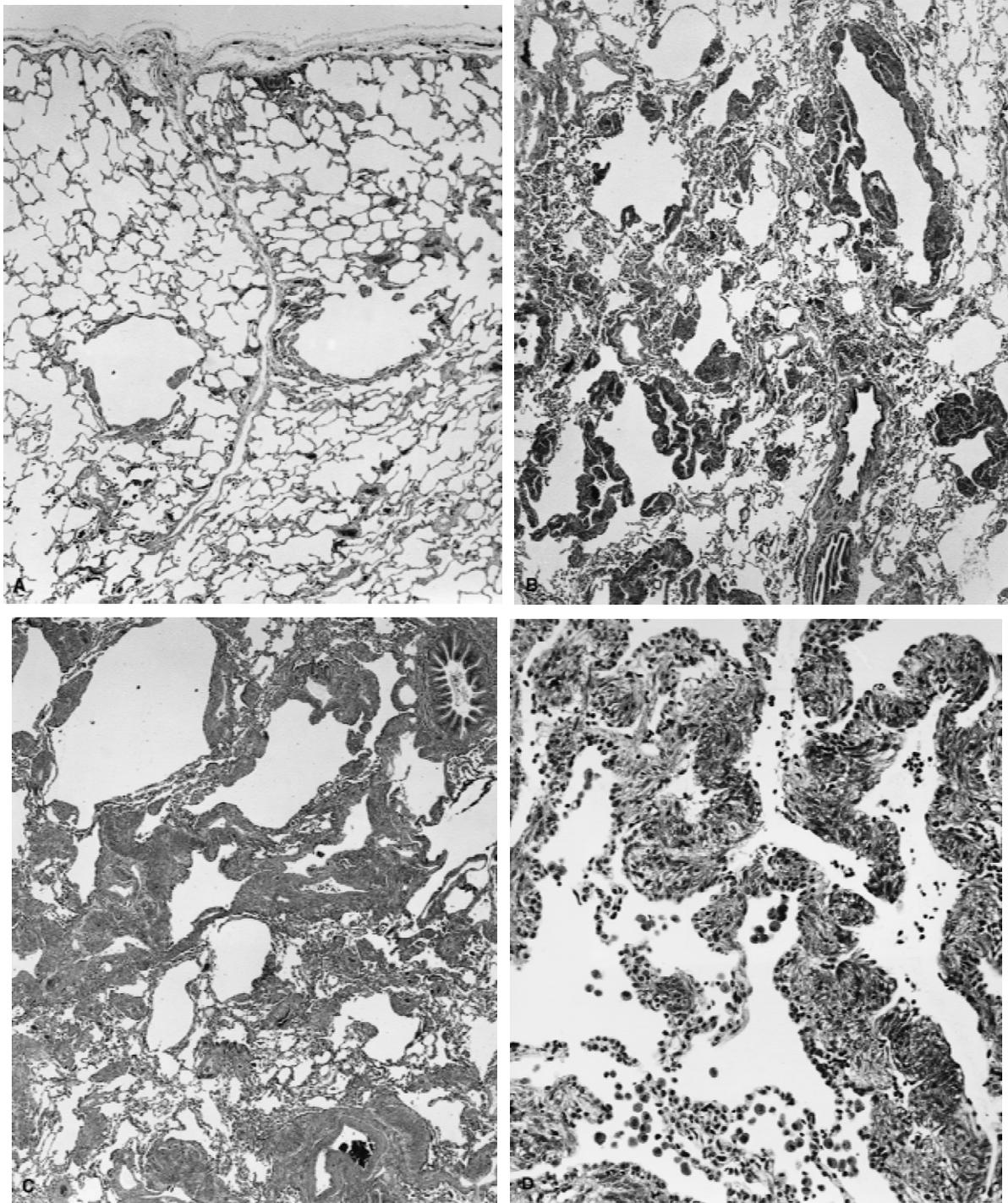


FIG. 1. (A–C) Low-magnification views of the histologic changes representative for lymphangioliomyomatosis histologic score type 1 (LHS-1) (A), LHS-2 (B), and LHS-3 (C). (D) A higher magnification of B, illustrating proliferation of abnormal smooth muscle cells.

(15.2%) or on exertion in four patients (3.8%), chylothorax in two patients (1.9%), hemoptysis in two patients (1.9%), and various other symptoms in three patients (2.9%). Pneumothorax was recurrent in 36 of the 57 patients (63.2%) in whom this abnormality developed.

Of the 105 patients, seven died of the disease (respiratory insufficiency) and nine underwent pulmonary transplantation. Mean follow-up was 54.4 months (range, 1–264 months) for the overall group of patients. Two patients included in the study died after 1 and 2 months

TABLE 2. Percentage of total area of lung biopsy affected by cystic lesions, abnormal smooth muscle cells (LAM cells), or both (LAM histologic score): correlation with numbers of deaths and lung transplantation

Percentage	LHS (cystic lesions + LAM cells)		Cystic lesions		LAM cells	
	No. of patients (%)	DOD/LT	No. of patients (%)	DOD/LT	No. of patients (%)	DOD/LT
1-25	30 (28.6)	0/0	67 (63.8)	1/4	88 (83.8)	6/7
26-50	49 (46.7)	4/5	24 (22.9)	2/4	12 (11.4)	1/1
>50	26 (24.8)	3/4	14 (13.3)	4/1	5 (4.8)	0/1

DOD, died of disease; LHS, LAM histologic score; LT, lung transplantation.

of follow-up. Mean follow-up for patients with LHS-1, -2, and -3 was 49, 63, and 54 months respectively. The 5- and 10-year survival for all patients was 85.1% and 71.0% respectively.

According to the classification system outlined earlier, the histologic severity of LAM was graded as LHS-1 in 30 patients (28.6%), LHS-2 in 49 (46.7%), and LHS-3 in 26 (24.8%; Table 2, Fig. 1). The LHS showed a strong correlation with the overall survival of the patients (Fig. 2; $p = 0.01$). Survival at 5 and 10 years after biopsy was 100% in patients with LHS-1, 81.2% and 74.4% in the patients with LHS-2, and 62.8% and 52.4% in the patients with LHS-3. Mean survival times were 190 months in the patients with LHS-2 and 109 months in the patients with LHS-3. The lung tissues from all three patients who died of the disease were classified as LHS-3.

The frequency distribution of the maximal size of the cysts and the percentage of cystic lesions and LAM cells on the tissue sections are shown in Tables 2 and 3 respectively. The percentage of the area of the lung biopsy affected by the cystic lesions (Table 2) showed a correlation with the overall survival of the patients ($p = 0.038$). The correlation between the maximal size of the cysts (Table 3) and the survival of the patients was very close to significant ($p = 0.0508$). The maximal size of the cysts was larger than 5 mm in seven of 12 patients (58.3%) who died of the disease or who underwent pul-

monary transplantation. The percentage of lung tissue occupied by LAM cells (Table 2) did not show a correlation with survival of the patients ($p = 0.399$).

Table 2 allows for comparison of three different methods of assessing the percentage of lung affected by LAM, according to the involvement by either cysts or infiltrates of LAM cells alone, or the LHS, which is based on the combined extent of these two histologic patterns. It also allows for comparison of the number of patients who died or who underwent transplantation in each category of severity. The observations showing that one death and four transplants occurred in the group with cysts affecting 1% to 25% of the lung, and that six deaths and seven transplants occurred in the group in which LAM cells affected 1% to 25% of the lung are in stark contrast to those based on the LHS scores, which showed that no patients with LHS-1 either died or required transplantation (Table 2). This underscores the need to include both the cysts and the LAM cell infiltrates in the LHS, which assesses the severity of lung involvement by the two LAM lesions.

Lung biopsy samples with higher LHS scores had greater amounts of hemosiderosis ($p = 0.029$; Table 4). Hemosiderosis was absent or only mild in 25 patients (83.3%) with LHS-1, whereas moderate or marked hemosiderosis was observed in 31 patients (41.3%) with LHS-2 or LHS-3. The survival rates were 89.1% and 75.1% for the former group versus 67.9% and 33.9% for the latter group, at 5 and 10 years respectively ($p = 0.0012$).

There was no correlation between the age of the patient and survival ($p = 0.713$).

DISCUSSION

We report the LHS as a prognostically useful method for assessing the histologic severity of lung involvement

TABLE 3. Frequency distribution of maximal cyst size

Maximal size of cyst (mm)	No. of patients (%)	DOD/LT
<3	25 (23.8)	2/1
3-5	50 (47.6)	1/4
>5	30 (28.6)	4/4

DOD, died of disease; LT, lung transplantation.

The maximal size of the cyst was determined by direct measurement in the tissue sections.

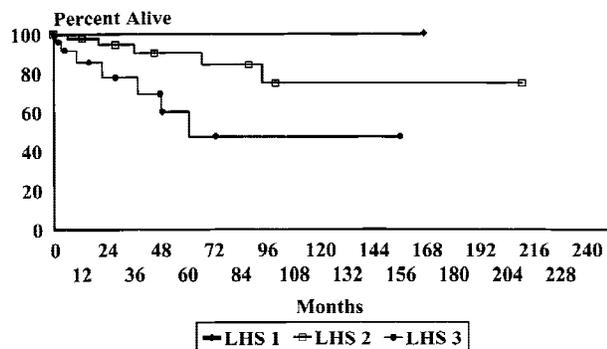


FIG. 2. Kaplan-Meier survival curves of the patients with pulmonary lymphangiomyomatosis according to the lymphangiomyomatosis histologic score (LHS). Patients with LHS-1 have an excellent survival. Patients with LHS-3 have the worst survival, and those with LHS-2 have an intermediate survival ($p < 0.002$).

TABLE 4. Relationship between LHS and degree of hemosiderosis

LHS	Hemosiderosis			
	None/mild		Moderate/marked	
	No. of patients (%)	DOD/LT	No. of patients (%)	DOD/LT
1	25 (83.3)	0/0	5 (16.7)	0/0
2	31 (63.3)	3/3	18 (36.7)	1/2
3	13 (50.0)	1/2	13 (50.0)	2/2

DOD, died of disease; LHS, LAM histologic score; LT, lung transplantation.

in LAM. The LHS was based on the total percentage of lung tissue involvement by *both* the smooth muscle and the cystic components of the LAM lesion, rather than an individual score for each component. Remarkably, none of the patients with LHS-1 died or required lung transplantation. At 5 years, but particularly at 10 years, after the open lung biopsy, patient survival was much greater in the LHS-1 group than in the groups with LHS-2 and LHS-3. Higher grades of LHS also correlated with greater degrees of hemosiderosis, which was found to be another predictor of the prognosis of patients with LAM.

The relationships between the histologic patterns and the survival of the patients with LAM were analyzed by Kitaichi et al.,⁹ who classified the histologic features of LAM into two types: a predominantly cystic type and a predominantly muscular type. Their study showed that patients with the former type had a poorer prognosis than those with the latter. Using a grading system based on the overall histologic abnormalities resulting from cystic lesions and muscle proliferation, these investigators concluded that increased amounts of abnormal areas showed a negative correlation with survival of the patients from 2 to 5 years after open lung biopsy. The basic concept of the histologic grading system of LAM used in the current study is quite similar to that proposed by Kitaichi et al.⁹ in that the two major histologic features (i.e., the extent of cystic lesions and the muscle proliferation) form the basis of both grading systems. We observed, however, that these two major histologic findings were too variable to serve as the basis for a classification into nodular and cystic types. Like Kitaichi et al.,⁹ we found that the percentage of cystic lesions by itself was a predictor of survival, whereas the extent of infiltration by LAM cells was not. Nevertheless, a combination of cystic lesions and muscle proliferation provided a grading system that correlated much more closely with survival of the patients than did grading by cystic lesions alone. Furthermore, the category of LHS-1 identified a group of patients who did not die or undergo lung transplantation. However, deaths or lung transplantation occurred in patients whose lung biopsies had a 1% to 25% involvement when cysts or LAM infiltrates were assessed separately.

Thus, we believe that the percentage of tissue involvement by both these two major histologic features should be evaluated together to assess the overall histologic severity of LAM. This may indicate that assessment of the severity of LAM by cystic change alone, as detected by HRCT, may not be as reliable as that provided by surgical lung biopsy because our data suggest that the extent of muscle is also an important component of the LHS. Future studies comparing prognostic scores by HRCT versus surgical lung biopsy are necessary to address this issue.

There are five major reports of the survival of patients with pulmonary LAM,^{9,11,12} and data from these reports, together with those of the current study, are summarized in Table 5. Early studies consider the prognosis of LAM to be poor. In 1974, Silverstein et al.¹¹ found that death from respiratory insufficiency occurred in 11 of 31 patients (36%) within 4 years after the onset of the disease. In 1975, Corrin et al.³ found that 11 of 23 patients (48%) died within 10 years after the onset of LAM, with an overall 10-year survival rate of 30%. In 1990, Taylor et al.¹² reported that 25 of 32 patients (78%) with LAM remained alive at 8.5 years after onset of the disease. More recently, Urban et al.¹⁴ reported survivals of 91% and 79% after 5 and 10 years of the disease respectively in their series of 64 patients. In the current study, survival data derived from Kaplan-Meier plots were similar to those reported by Taylor et al.¹² and Urban et al.,¹⁴ with survival probabilities of 85% after 5 years and 71% after 10 years. However, the survival reported by Kitaichi et al.⁹ was similar to that found by Corrin et al.³ The Kaplan-Meier plot of actuarial survival of our patients with pulmonary LAM is significantly better than that of the patients reported by Corrin et al.,³ with an 85% versus a 57% 5-year survival ($p = 0.0008$; Fig. 3).

We do not know whether the improved survival in the current study as well as in two other recent reports^{9,12} is the result of earlier diagnosis, hormonal interventions, or better supportive treatments. The rate of progression of LAM varies considerably among different patients. It appears that many patients with LAM have a clinically indolent course without apparent relationship to the type of therapy,¹⁴ whereas a few undergo rapid deterioration

TABLE 5. Survival of patients with pulmonary LAM in major reports

Authors	Year	No. of patients	5-year survival (%)	10-year survival (%)
Silverstein et al. ¹¹	1974	31	61	24
Corrin et al. ¹²	1975	23	65	30
Taylor et al. ¹	1990	32	81	78
Kitaichi et al. ¹⁴	1995	46	78	40
Urban et al. ¹³	1999	64	91	79
Present study	2000	105	85	71

LAM, lymphangioleiomyomatosis.

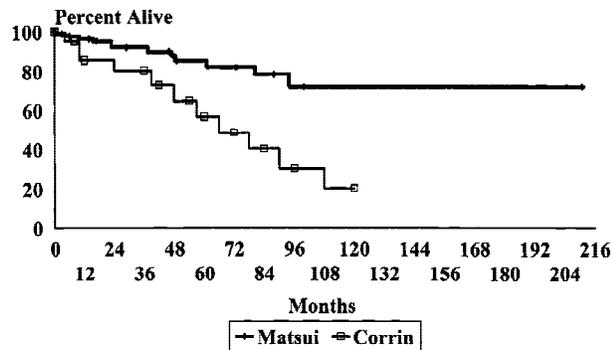


FIG. 3. Kaplan-Meier survival curve of 105 patients with pulmonary lymphangiomyomatosis included in the current study. The survival is significantly different ($p < 0.0012$) from that reported for the 23 patients of Corrin et al.³

early during the course of the disease. However, we have shown that evaluation according to the LHS can be of predictive value in assessing the prognosis of patients with this disease. The LHS may provide a basis for staging of pulmonary LAM. □

Acknowledgments

The authors express their appreciation to Richard Dreyfus and Michael Spencer for assistance with the photography.

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