University of Cincinnati

Date: 1/6/2011

I, Brent W Kinder M.D., hereby submit this original work as part of the requirements for the degree of Master of Science in Clinical and Translational Research

It is entitled:

Clinical Predictors of Survival in Lymphangioleiomyomatosis

Student's name: **Brent W Kinder M.D.**

This work and its defense approved by:

Committee chair: Erin Nicole Haynes, Dr.PH

Committee member: Francis McCormack, MD

1285

Clinical Predictors of Survival in Lymphangioleiomyomatosis

A thesis submitted to the
Graduate school
of the University of Cincinnati
in partial fulfillment of the
requirements for the degree of

Master of Science
in Environmental Health - Epidemiology

Division of Epidemiology & Biostatistics

Department of Environmental Health

College of Medicine

by

Brent Kinder

January 7, 2011

M.D. Emory University (May 2000)

B.S. West Virginia Wesleyan College (May 1996)

Committee Chair: Erin Haynes, DrPH, MS

Abstract

RATIONALE: Lymphangioleiomyomatosis (LAM) is a rare, progressive, cystic lung disease that almost exclusively affects women. Prognostic information in LAM has been limited by heterogeneous study methodology.

OBJECTIVES: We sought to establish which clinical characteristics are associated with survival and to determine cause of death in patients with LAM.

METHODS: The LAM Foundation maintains a population-based registry of self-identified LAM patients who completed a questionnaire with demographic and clinical data at enrollment. Vital status was obtained on all participants. Cox proportional hazard analysis evaluated the association of demographic and clinical features with survival.

RESULTS: Among the 401 subjects, there were 50 deaths and 55 lung transplantations during a median of 10 years of observation time. The estimated median survival time for LAM patients in the US is 29 years from symptom onset and 23 years from diagnosis. Age at diagnosis (HR per decade 0.80, CI 0.64-0.99, $p=0.04$), supplemental oxygen use (HR 3.13, CI 1.90-5.18, $p<0.001$), and reported weight loss (HR 1.93, CI 1.23-3.04, $p=0.004$) were strong independent predictors of time to death or transplant. Neither mode of presentation, history of pregnancy, nor hormonal treatment was found to be associated with survival after adjustment for covariates. Among decedents, the most common cause of death was respiratory failure.

CONCLUSIONS: Median survival in a population-based cohort of patients with LAM in the United States is longer than previously estimated. Demographic and clinical predictors are useful for prognostic determination. Patients with LAM frequently die from complications directly related to their lung disease.

TABLE OF CONTENTS

Introduction	page 1
Methods and Materials	page 3
Results	page 5
Discussion	page 8
Bibliography	page 14

Tables

Table 1	page 16
Table 2	page 17

Figures

Figure 1	page 18
Figure 2	page 19
Figure 3a and b	pages 20-21
Figure 4	page 22
Figure 5	page 23
Figure 6	page 24

Introduction

Lymphangioleiomyomatosis (LAM) is a rare, progressive, cystic lung disease that almost exclusively occurs in women (1, 2). It affects up to 40% of women with the tuberous sclerosis complex (TSC-LAM), and can also arise in a sporadic (S-LAM) form that involves only the lung, lymphatics, and kidney(3). There are no proven therapies for LAM; however an improved understanding of the molecular pathogenesis of the disease has identified targets for clinical trials. Clinically, LAM is characterized by progressive dyspnea on exertion, recurrent pneumothoraces, abdominal and thoracic lymphadenopathy, and abdominal tumors, including angiomyolipomas and lymphangiomyomas. The pulmonary manifestations of LAM usually predominate, but occasionally LAM presents exclusively in the abdomen (3). Clinicians who care for patients with this often lethal disease are hampered by an incomplete understanding of the pathogenesis and natural history and lack of proven effective therapies. In addition, the rarity of this serious disease in the practice of individual clinicians has made developing large cohorts of patients difficult, thereby further limiting clinical and scientific progress in this field.

Although global estimates of the prevalence of TSC (>1 million affected) indicate that TSC-LAM may be 10-fold more common than S-LAM, women with S-LAM represent approximately 85% of the > 240 patients enrolled in the National Heart, Lung, and Blood Institute (NHLBI) LAM Registry(2). These observations suggest that TSC-LAM may be a milder disease than S-LAM, or other comorbidities in TSC patients may prevent pulmonary problems from becoming health priorities. LAM is typically discovered by high-resolution CT (HRCT) scanning of patients with progressive dyspnea on exertion,

pneumothorax, or chylous effusion, or less commonly by biopsy of an abdominal or retroperitoneal mass suspected to be lymphoma or ovarian cancer. On average, women with LAM have symptoms for 3 to 5 years and experience an average of 2 pneumothoraces before the diagnosis of LAM is made(4, 5). The average age at the diagnosis of LAM in multiple series is approximately 35 years(6).

Prognostic information in LAM has been limited by small numbers and heterogeneous study methodology in published studies. Studies of early retrospective cohorts cited 5 and 10 year mortality of 40% and 80%, respectively(7, 8). More recently, mortality at 10 years has been estimated to be approximately 10 to 20% from the onset of symptoms(9, 10)and 30% at 10 years from the time of lung biopsy(11) but varies widely in individual patients. Cases of LAM in octogenarians(12) and of >30 years in duration(13)have been reported. Given the heterogeneous disease course, it would be useful to establish which clinical characteristics are associated with survival in order to develop prediction tools for disease outcome. Pulmonary function tests at the time of presentation have been shown to be associated with prognosis. Obstructive lung disease as measured by reduction in the FEV1/FVC ratio and hyperinflation manifested as an increase in TLC are associated with a worse prognosis and reduced survival(14). In a large longitudinal cohort study of 275 patients with LAM, predictors of decline in PFTs were examined over a mean duration of 5 years(15). Initial lung function and age were found to be predictors of functional decline. The rate of decline in FEV1 was inversely correlated with the initial DLCO and age (rates of decline in FEV1 were lower in older patients and in patients with higher DLCO and FEV1). A recent report from Japan(16) suggests that presentation with

pneumothorax is associated with younger age and a much more favorable prognosis (10-year survival rate, 89%) than presentation with dyspnea (10-year survival rate, 47%), but Steagall et al (17) reported 10-year survival rates of 91.3% and 92%, respectively, for patients with and without a history of pneumothorax. However, the latter study was performed at a single center and was biased towards subjects that were thought to be clinically “stable” and could tolerate travel to the study site.

We sought to determine the clinical predictors of mortality in a population based registry in the United States. Our objective was to identify the clinical characteristics which are associated with survival in order to counsel patients regarding prognosis and to stratify patients for clinical trials. Further, we investigated the cause of death for LAM patients.

Methods and Materials

Patient Selection

Patients self-identified as having a diagnosis of LAM and enrolled in the LAM Foundation population-based registry and who had completed a medical history and disease manifestation questionnaire between 1995 and 2007 were eligible for the current study. The study was approved by the Institutional Review Board at the University of Cincinnati (protocol number 08071003). A portion of these study participants had been participants in previously reported studies (2, 4, 15, 18, 19).

Clinical and Outcome Assessment

A standardized general medical history and disease manifestation questionnaire was used to collect demographic and medical information from new enrollees in the LAM Foundation registry. Vital status was obtained in all participants through December 31, 2007, by linking patient identifiers with the National Death Index. Participants were censored if they (1) were still alive on December 31, 2007, (2) had received a lung transplant (ascertained through LAM Foundation records), or (3) died. Survival time was calculated as the time since first LAM related symptom or physician diagnosis (whichever occurred first) until censoring. The cause of death was determined by physician listed cause of death (ICD9/10 code) on death certificates through the National Death Index search.

Therapy

Patients reported varied treatment regimens including hormonal manipulation (estrogen, estrogen/progesterone, progesterone, Lupron, oophorectomy). We investigated the relationship between survival and each of these treatments as individual predictors and collectively as hormonal treatment.

Statistical Analysis

Unadjusted analyses investigating associations between relevant demographic and clinical characteristics was performed with the use of student's t test, analysis of variance (ANOVA) or the Kruskal-Wallis test for continuous variables, and the Chi-Square test or Fisher's Exact test for categorical variables, as appropriate. We estimated cumulative survival using the Kaplan-Meier technique and performed the log-rank test, where

appropriate. Cox regression was performed for the primary analysis to evaluate the associations of demographic and clinical covariates with mortality. To evaluate the proportional hazards assumptions we used visual inspection of log-minus-log plots and plots of Schoenfeld residuals versus survival time(20). Covariates for adjustment were selected *a priori*, either because they represented important demographic variables (age and race), and/or because prior reports indicate an association with prognosis in LAM. Before inclusion, Pearson's correlation coefficient between continuous covariates was evaluated to avoid co-linearity (correlation coefficients > 0.60). The final model was selected using backwards deletion, with the retention criterion of $P < 0.05$. We also evaluated for multiplicative interactions on the basis of treatment status, which was selected as a candidate effect modifier *a priori* on the basis of prior research(15).

Results

Demographic data:

The LAM Foundation maintains a population based registry, which included 1149 registered self-identified LAM patients as of July 1st, 2008. Of these, 590 completed a "General Information/Clinical History Questionnaire" with limited demographic and clinical data, including 401 who were identified as US residents and provided date of birth. These patients formed the cohort. All study subjects were women. The mean age at enrollment was 40 and 92% were Caucasians (Table 1). Approximately two thirds (62%) of the cohort had been pregnant by the time they completed the questionnaire; and the mean number of pregnancies was 1.9. A third of the study population (36%) had a

smoking history. The median observation time was 10 years (interquartile range 6-16). There were 50 deaths and 55 lung transplants in the cohort over the observation period.

Clinical data:

The most common mode of presentation in the cohort was with respiratory symptoms including dyspnea or cough (56.8%; mean age at presentation 42), followed by pleural disease (pneumothorax/pleural effusion, 30.1%; mean age at presentation 37). A variety of other non-respiratory presentations (e.g. incidental finding on CT imaging, kidney tumors, etc.) were observed in a minority of subjects (12.9%; mean age at presentation 38) (Table 1). Forty-four subjects (11%) had tuberous sclerosis. The median time between symptom onset and diagnosis was 2 years (IQR 0.33, 6). A majority of the subjects (57%) reported that the diagnosis was established with a lung biopsy (Table 1).

Treatment:

Approximately 55% of the study cohort had received hormonal treatment: 48 % progesterone, 23% underwent oophorectomy (Table 1). Pleurodesis had been performed in 176 subjects (44%, data not shown). 124 subjects (31%) needed supplemental oxygen therapy during the course of their disease.

Survival:

The median transplant-free survival for the overall cohort was 29 years from the time of symptoms onset (Figure1), and 23 years from the time of diagnosis (data not shown). The estimated 10-year transplant-free survival was 86% (Figure 1). Patients who presented with dyspnea/cough had a worse prognosis compared with the subgroup that presented

with pneumothoraces/pleural effusion or other presentations ($p=0.03$)(Figure 2). The survival time was 23 years for the subgroup that received hormonal treatment and 39 yrs for the untreated subgroup ($p=0.006$.) (Figure 3a). However, when adjusted for the severity of disease (i.e. oxygen use), there was no statistically significant difference between the hormonally treated and untreated subgroup ($p=0.42$) (Figure 3b). In addition, there was no difference in survival between those who had take oral contraceptive pills and those who had not (HR 0.90, CI 0.54-1.51, $p=0.7$; data not shown).

In the multivariate analysis, the need for supplemental oxygen therapy (HR= 3.13, $p<0.001$) and reported weight loss (HR = 1.93, $p=0.004$) were the strongest predictors of earlier mortality (Table 2). A greater age at diagnosis (HR = 0.80 per additional decade, $p=0.04$) and the presence of an AML (HR=0.49, $p=0.004$) were associated with improved survival (Table 2, Figure 5). Interestingly, neither presentation type nor hormonal treatment was found to be associated with survival time after adjustment for the above covariates.

Neither a history of pregnancy nor the number of pregnancies influenced survival time (Figure 4, $p=0.42$). Also, the number of pneumothoraces ($p=0.72$) and treatment with pleurodesis ($p=0.72$) were not associated with survival (data not shown). Smoking did not influence survival ($p=0.28$); neither did self reported exposure to dust/fumes ($p=0.48$) (data not shown). The presence of underlying TSC was not associated with survival time (Figure 6, $p=0.38$).

In sensitivity analyses, we restricted the analysis to those with a reported surgical lung biopsy, AML, or underlying TSC to investigate the influence of case definition and address the issue of a self-identified patient population. We found the above results to be robust with no substantial changes in the associations or effect estimates outlined above.

Cause of death:

There were 50 deaths in the cohort during the study period. The cause of death was identified in 33 patients (14 in patients that underwent lung transplant). The median age at death was 48 (IQR, 44-54). Among those subjects who had not undergone lung transplantation (n=24), the most common cause of death was respiratory failure (58%) followed by malignancy (21%) and cardiac/CHF (8%). Among those subjects who had undergone lung transplantation (n=9), the most common cause of death was respiratory failure (44%) followed by infection (33%), cardiac/CHF (33%) and malignancy (11%) (data not shown). The malignancies listed as cause of death were breast (n=2), cervical (n=1), acute promyelocytic leukemia (n=1), and soft tissue (n=1). Five subjects overall (15%) had pneumothorax listed as a cause of death (though not necessarily the primary).

DISCUSSION

This study examined the association of clinical characteristics with survival in a large, self-identified population-based cohort of LAM patients with long term and comprehensive follow-up. We showed that the median survival time from symptom onset in LAM approaches three decades. The data demonstrates that age at diagnosis, use of

supplemental oxygen and weight loss among persons with LAM are independent predictors of time to death or transplant. These associations remained essentially unaltered after statistical adjustment for other clinical predictors of mortality. There was no association between mortality and hormonal treatment or mode of presentation, after adjustment for the above predictors. Our findings confirm some results from prior studies regarding the “natural history” of subjects with LAM and contradict others.

The 10 year-survival in our cohort (86%) is consistent with the estimates from the most recent LAM natural history studies in Europe and Asia. The United Kingdom LAM registry reported 10 year-survival rates of 91% in a cohort of 57 patients (9). In Japan a nationwide survey including 173 patients, estimated 10-year survival was 76%(16). These data collectively demonstrate a far better short to medium term survival than in early retrospective cohorts (80% mortality at 10 years)(7, 8). With the lack of proven effective therapies, the most likely explanation of the divergent results in observed survival rates between the most recent studies and older studies is a lead time bias from earlier diagnosis in the modern era with an increased availability and use of CT scans. In addition, our study results may be different because of the larger and population based cohort. Similar to the Japanese study suggesting that presentation with pneumothorax is associated with a more favorable prognosis(16), we found that patients who present with dyspnea or cough have a shorter time to death or transplant. However, we found that presentation type was no longer associated with survival after adjustment for disease severity (supplemental oxygen use) and age at presentation. It is possible that patients with pneumothoraces present clinically at an earlier stage of the disease, which would be consistent with our results.

The risks associated with pregnancy in patients diagnosed with LAM are frequently debated. Based on case reports that pregnancy exacerbates LAM, patients are frequently advised to avoid pregnancy(21). In our study, neither a reported prior pregnancy nor the number of prior pregnancies was associated with survival. These results should be interpreted with caution. Our study was a retrospective cohort study with limited information regarding the specific timing of pregnancies, in particular in relation to the diagnosis of LAM. Many of the patients likely had their pregnancies before the onset or diagnosis of LAM. A recent survey reported that women diagnosed with LAM (n=15) during pregnancy had high rates of pneumothorax (67%), miscarriage (7%) and premature birth (47%)(21). Thus, it remains possible that pregnancy could adversely impact the prognosis of patients with pre-existing LAM.

Our results indicate that hormonal treatment does not improve survival. On unadjusted analysis we found that hormonal treatment, progesterone in particular, was associated with a shorter survival time. However, in multivariate analysis adjusted for severity of disease (e.g. use of supplemental oxygen) there was no longer an observed association between hormonal treatment and mortality. The most plausible explanation is confounding by indication (i.e. sicker patients were offered treatment and sicker patients were most likely to have a worse outcome). Our results suggest that self-reported history of hormonal treatment does not substantially improve outcomes in LAM.

We also report a strong association between reported weight loss and increased mortality in patients with LAM. The mechanism for this association is unclear, but does replicate the findings in chronic obstructive pulmonary disease, another chronic lung disease that may develop cyst-like structures in the lung, in which reductions in body mass index are associated with mortality (i.e., mBODE index)(22). Weight loss in itself has not previously been reported as a significant prognostic factor for patients with LAM. Another notable finding was that older age at diagnosis of LAM conferred a better survival time. These results are complementary to the prior finding that patients diagnosed later in life have a less pronounced decline in lung function(15). These observations could be a reflection that patients presenting at later ages may have a less aggressive form of disease that may lead to a delay in symptom onset and thus diagnosis. Interestingly, the presence of angiomyolipomas also conferred a survival advantage in our cohort. It is unclear if this is a reflection of a different phenotype of the disease in these patients or just a consequence of an earlier diagnosis due to their AML related symptoms (lead time bias).

Several limitations should be considered when interpreting our results. First, given the median survival time of more than two decades, the length of observation necessary to accrue the number of events (death or transplant) required for sufficient statistical power may have resulted in influences by secular trends in the management of disease. However, it is unlikely that these trends affected the associations reported here, as effective therapy has not been demonstrated in patients with LAM during the timeframe of the study. Second, there is the potential for residual confounding by unmeasured but important variables. The lack of reliable PFTs as means of objectively assessing the

severity of the disease is a weakness of our study. We attempted to mitigate this potential weakness by using need for supplemental oxygen therapy as a surrogate for severity of disease. In addition, we evaluated clinical parameters measured at a single baseline time point and did not have serial measurements of these predictors. Studies of other chronic lung diseases have demonstrated that longitudinal changes in important clinical parameters can provide powerful predictive information(22-24).The relationship between serial changes in pulmonary function tests, such as FEV1, and survival in LAM is an important question that will require evaluation in future studies. Although our cohort is comprised of self-identified LAM patients, we attempted to address any potential misclassification by performing comprehensive sensitivity analyses utilizing a restricted case definition (limiting to only those patients with reported lung biopsy or other clinical evidence of a definitive LAM diagnosis such as presence of AML or underlying TSC). These complementary analyses confirmed the associations found in the larger study cohort. Further, the baseline clinical characteristics of our cohort closely mimic those of the very well characterized NHLBI LAM Registry(2).

To our knowledge, this is the first study to systematically investigate and report on cause of death in patients with LAM. The increased occurrences of respiratory failure, pneumothorax and respiratory infections as listed cause of death represent the main differences seen in this population versus the general United States female population in the same age group (35-54). In the 2006 CDC report (www.cdc.gov), chronic lower respiratory disease was reported as a cause of death in only 1.4% of women in the 35-44 year of age range and 2.8% in the 45-54 year of age range. The incidence of death due to malignancies or heart diseases reproduces the trends in the general population.

In summary, we demonstrate that age at diagnosis, supplemental oxygen use, and reported weight loss are strong independent predictors of time to death or transplant among patients with LAM. Further, LAM patients frequently die from complications directly related to their lung disease. In spite of recent efforts and progress toward a better understanding and characterization of the disease, LAM remains an incompletely understood clinical entity. The recently completed enrollment of the first placebo-controlled trial to evaluate a therapeutic agent in LAM underscores the need for better clinical prediction tools in LAM. Once effective therapies are discovered, appropriate management will require tools for determining prognosis(19). On a population level, the benefits of prognostic information include better planning and distribution of health-care resources(25). At the patient level, prognostic information could be used to estimate the absolute benefit of therapeutic strategies. In the future, integration of longitudinal pulmonary function tests and novel biomarkers(26, 27) with clinical and demographic data may allow for more comprehensive and explanatory prediction models for disease outcome among LAM patients.

Bibliography:

1. Juvet, S. C., F. X. McCormack, D. J. Kwiatkowski, and G. P. Downey. 2007. Molecular pathogenesis of lymphangioleiomyomatosis: lessons learned from orphans. *Am J Respir Cell Mol Biol* 36(4):398-408.
2. Ryu, J. H., J. Moss, G. J. Beck, J. C. Lee, K. K. Brown, J. T. Chapman, G. A. Finlay, E. J. Olson, S. J. Ruoss, J. R. Maurer, T. A. Raffin, H. H. Peavy, K. McCarthy, A. Taveira-Dasilva, F. X. McCormack, N. A. Avila, R. M. Decastro, S. S. Jacobs, M. Stylianou, and B. L. Fanburg. 2006. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med* 173(1):105-11.
3. Crino, P. B., K. L. Nathanson, and E. P. Henske. 2006. The tuberous sclerosis complex. *N Engl J Med* 355(13):1345-56.
4. Almoosa, K. F., J. H. Ryu, J. Mendez, J. T. Huggins, L. R. Young, E. J. Sullivan, J. Maurer, F. X. McCormack, and S. A. Sahn. 2006. Management of pneumothorax in lymphangioleiomyomatosis: effects on recurrence and lung transplantation complications. *Chest* 129(5):1274-81.
5. Hagaman, J. T., D. P. Schauer, F. X. McCormack, and B. W. Kinder. 2010. Screening for lymphangioleiomyomatosis by high-resolution computed tomography in young, nonsmoking women presenting with spontaneous pneumothorax is cost-effective. *Am J Respir Crit Care Med* 181(12):1376-82.
6. McCormack, F. X. 2008. Lymphangioleiomyomatosis: a clinical update. *Chest* 133(2):507-16.
7. Corrin, B., A. A. Liebow, and P. J. Friedman. 1975. Pulmonary Lymphangiomyomatosis: A review. *Am J Path* 79(2):348-366.
8. Silverstein, E. F., K. Ellis, M. Wolffe, and A. Jaretzki. 1974. Pulmonary Lymphangiomyomatosis. *Am J Radiol* 120:832-850.
9. Johnson, S. R., C. I. Whale, R. B. Hubbard, S. A. Lewis, and A. E. Tattersfield. 2004. Survival and disease progression in UK patients with lymphangioleiomyomatosis. *Thorax* 59(9):800-3.
10. Urban, T., R. Lazor, J. Lacronique, M. Murris, S. Labrune, D. Valeyre, and J. F. Cordier. 1999. Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). *Medicine (Baltimore)* 78(5):321-37.
11. Matsui, K., M. B. Beasley, W. K. Nelson, P. M. Barnes, J. Bechtel, R. Falk, V. J. Ferrans, J. Moss, and W. D. Travis. 2001. Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. *Am J Surg Pathol* 25(4):479-84.
12. Ho, T. B., J. H. Hull, and N. C. Hughes. 2006. An 86-year-old female with lymphangioleiomyomatosis. *Eur Respir J* 28(5):1065.
13. Moses, M. A., J. Harper, and J. Folkman. 2006. Doxycycline treatment for lymphangioleiomyomatosis with urinary monitoring for MMPs. *N Engl J Med* 354(24):2621-2.
14. Kitaichi, M., K. Nishimura, H. Itoh, and T. Izumi. 1995. Pulmonary lymphangioleiomyomatosis: a report of 46 patients including a clinicopathologic study of prognostic factors. *Am J Respir Crit Care Med* 151(2 Pt 1):527-533.

15. Taveira-DaSilva, A. M., M. P. Stylianou, C. J. Hedin, O. Hathaway, and J. Moss. 2004. Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. *Chest* 126(6):1867-74.
16. Hayashida, M., K. Seyama, Y. Inoue, K. Fujimoto, and K. Kubo. 2007. The epidemiology of lymphangioleiomyomatosis in Japan: a nationwide cross-sectional study of presenting features and prognostic factors. *Respirology* 12(4):523-30.
17. Steagall, W. K., C. G. Glasgow, O. M. Hathaway, N. A. Avila, A. M. Taveira-Dasilva, A. Rabel, M. P. Stylianou, J. P. Lin, X. Chen, and J. Moss. 2007. Genetic and morphologic determinants of pneumothorax in lymphangioleiomyomatosis. *Am J Physiol Lung Cell Mol Physiol* 293(3):L800-8.
18. Young, L. R., K. F. Almoosa, S. Pollock-Barziv, M. Coutinho, F. X. McCormack, and S. A. Sahn. 2006. Patient perspectives on management of pneumothorax in lymphangioleiomyomatosis. *Chest* 129(5):1267-73.
19. Kinder, B. W., A. C. Sherman, L. R. Young, J. T. Hagaman, N. Oprescu, S. Byrnes, and F. X. McCormack. 2010. Predictors for clinical trial participation in the rare lung disease lymphangioleiomyomatosis. *Respir Med* 104(4):578-83.
20. Vittinghoff, E., D. V. Glidden, S. C. Shiboski, and C. E. McCulloch. 2005. *Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models*, First edition ed. Springer Science and Business Media, New York, NY.
21. Cohen, M. M., A. M. Freyer, and S. R. Johnson. 2009. Pregnancy experiences among women with lymphangioleiomyomatosis. *Respir Med* 103(5):766-72.
22. Martinez, F. J., M. K. Han, A. C. Andrei, R. Wise, S. Murray, J. L. Curtis, A. Sternberg, G. Criner, S. E. Gay, J. Reilly, B. Make, A. L. Ries, F. Sciurba, G. Weinmann, Z. Mosenifar, M. DeCamp, A. P. Fishman, and B. R. Celli. 2008. Longitudinal change in the BODE index predicts mortality in severe emphysema. *Am J Respir Crit Care Med* 178(5):491-9.
23. Flaherty, K. R., J. A. Mumford, S. Murray, E. A. Kazerooni, B. H. Gross, T. V. Colby, W. D. Travis, A. Flint, G. B. Toews, J. P. Lynch, III, and F. J. Martinez. 2003. Prognostic Implications of Physiologic and Radiographic Changes in Idiopathic Interstitial Pneumonia. *Am. J. Respir. Crit. Care Med.* 168(5):543-548.
24. Collard, H. R., T. E. King, Jr., B. B. Bartelson, J. S. Vourlekis, M. I. Schwarz, and K. K. Brown. 2003. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. *Am. J. Respir. Crit. Care Med.* 168(5):538-542.
25. Schunemann, H. 2009. From BODE to ADO to outcomes in multimorbid COPD patients. *Lancet* 374(9691):667-8.
26. Young, L. R., Y. Inoue, and F. X. McCormack. 2008. Diagnostic potential of serum VEGF-D for lymphangioleiomyomatosis. *N Engl J Med* 358(2):199-200.
27. Young, L. R., R. Vandyke, P. M. Gulleman, Y. Inoue, K. K. Brown, L. S. Schmidt, W. M. Linehan, F. Hajjar, B. W. Kinder, B. C. Trapnell, J. J. Bissler, D. N. Franz, and F. X. McCormack. 2010. Serum vascular endothelial growth factor-D prospectively distinguishes lymphangioleiomyomatosis from other diseases. *Chest* 138(3):674-81.

Table 1. General characteristics and clinical features by presentation type among LAM subjects in the United States

Variables	Overall Study Population (N=401)	Group A (N=228)	Group B (N=121)	Group C (N=52)	p-value
Age, mean (SD)	40 (10)	42 (11)	37 (9)	38 (8)	0.0001
Caucasian, Number/measured (%)	365/398 (92)	204/227 (90)	115/119 (97)	46/52 (88)	0.04
Symptom duration at diagnosis, median years (IQR)	2 (0.33, 5)	2 (0.5, 5)	1.8 (0.2, 5)	2.3 (0.33, 9.3)	0.02
Follow-up time, median years (IQR)	10 (6, 16)	9 (3, 14)	11 (7, 18)	10 (5, 22)	0.08
Ever smoker, number/measured (%)	145/400 (36)	84/228 (37)	42/120 (35)	19/52 (37)	0.95
Tuberous Sclerosis, number/measured (%)	44/401 (11)	19/228 (8)	15/121 (12)	10/52 (19)	0.07
Diagnosis by surgical lung biopsy, number (%)	230/401 (57)	122 (54)	87 (72)	21 (40)	<0.001
Experienced a pneumothorax, number (%)	227/401 (57)	97 (43)	114 (94)	16 (31)	<0.001
Number of pneumothoraces, mean (SD)	2.5 (5)	1.6 (4.5)	4.5 (4.8)	1.8 (7)	<0.001
Angiomyolipoma, number (%)	158 (39)	80 (35)	47 (39)	31 (60)	0.005
Reported weight loss, number (%)	86 (21)	52 (23)	25 (21)	9 (17)	0.68
Ever pregnant, number (%)	248 (62)	146 (64)	69 (57)	33 (63)	0.42
Mean number of pregnancies, if ever pregnant (SD)	1.9 (0.88)	2.0 (0.97)	1.6 (0.69)	1.7 (0.61)	0.002
Received hormonal treatment, number (%)	221 (55)	127 (56)	72 (60)	22 (42)	0.11
Received progesterone treatment, number (%)	193 (48)	112 (49)	61 (50)	20 (38)	0.32
Received oophorectomy treatment, number (%)	92 (23)	55 (24)	26 (21)	11 (21)	0.85
Oxygen therapy, number/measured (%)	124/ 400 (31)	97/228 (43)	21/120 (18)	6/52 (12)	<0.001

Group A= presenting with respiratory symptoms (dyspnea or cough), Group B= presenting with pleural manifestations (pneumothorax or effusion), Group C=all other types of presentation; SD= standard deviation; IQR= interquartile range

Table 2. Cox Proportional Hazards Model for Independent Predictors of Mortality among LAM subjects in the United States

Predictor variables	Hazard Ratio	95%CI	P value
Age at diagnosis, per additional decade	0.80	0.64, 0.99	0.043
Hormonal treatment	1.25	0.69, 2.26	0.46
Presentation Type			
Type A	1.00	reference	reference
Type B	1.08	0.67, 1.7	0.75
Type C	0.56	0.23, 1.4	0.20
Presence of Angiomyolipoma	0.49	0.30, 0.79	0.004
Oxygen therapy	3.13	1.90, 5.18	<0.001
Weight loss	1.93	1.23, 3.04	0.004

Group A= presenting with respiratory symptoms (dyspnea or cough), Group B= presenting with pleural manifestation (pneumothorax or effusion), Group C=all other types of presentation.

Figure 1. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America.

Figure 2. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by presentation type. Group A= presenting with respiratory symptoms (dyspnea or cough), Group B= presenting with pleural manifestations (pneumothorax or effusion), Group C=all other types of presentation. Log-rank test $p= 0.03$.

Figure 3a. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by hormonal transplant status. Hormonal treatment included estrogens, progesterone, and chemical or surgical oophorectomy. Log-rank test $p=0.006$.

Figure 3b. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by hormonal transplant status adjusted for severity. Hormonal treatment included estrogens, progesterone, and chemical or surgical oophorectomy. Severity is approximated by need for supplemental use of oxygen. Cox proportional hazard $p=0.43$.

Figure 4. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by pregnancy status. (Please note that the pregnancies were not necessarily contemporaneous with the diagnosis of LAM). Log-rank test $p=0.42$.

Figure 5. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by weight loss status. Log-rank test $p=0.0006$.

Figure 6. Kaplan-Meier survival curve of estimated transplant-free survival among patients with LAM in the United States of America by tuberous sclerosis (TSC) status. Log-rank test $p=0.38$.