The NHLBI Lymphangioleiomyomatosis Registry:

Characteristics of 230 Patients at Enrollment

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Online Data Supplement

METHODS

Study design

A wide array of data was collected in the Registry predominantly at the time of enrollment and at annual follow-up visits. Baseline data included demographics, socioeconomic features, functional status and quality of life, signs and symptoms, past medical/surgical, family medical, and medication histories, diagnosis and treatment for LAM and sequelae, pulmonary function tests, radiologic studies, transplantation data, and tissue specimens.

An Imaging Core of radiologists reviewed the radiologic studies to assure accuracy in the diagnosis and score the type, distribution, and extent of abnormalities. A Tissue Core of pathologists reviewed pathological specimens from Registry patients in order to both verify the accuracy of the diagnosis and characterize specific pathologic features. A Pulmonary Function Core analyzed the pulmonary physiology studies and verified the quality of studies across centers.

Study subjects

Over a 3-year period, 264 subjects with LAM were referred for enrollment into the Registry. Twenty-one subjects did not meet the inclusion criteria and were excluded. Thirteen patients had already undergone lung transplantation at the time of enrollment. For the purposes of this study, these 13 lung transplant recipients were also excluded. The remaining 230 subjects were analyzed for this report.

Each subject fully participated in the informed consent process and signed a consent form. All patients seen with a diagnosis of LAM at each of the six clinical centers were

offered the opportunity to enroll in the Registry. Of the 230 subjects enrolled, 210 were from the United States or its territories, with at least 1 subject enrolled from each of 41 states. Eighteen subjects resided in Canada. Two other foreign subjects were from continental South America and Africa, respectively.

Diagnostic criteria

The diagnosis of LAM was confirmed by at least one of the following criteria: (1) lung biopsy (n = 125) judged to be diagnostic of LAM by Tissue Core pathologists, (2) biopsy of lymph node or other mass judged to be diagnostic of LAM by Tissue Core pathologists (n= 21), or (3) high-resolution computed tomographic (HRCT) scan of the chest judged to be diagnostic of LAM with a high degree of certainty by two of the expert radiologists making up the Imaging Core (n= 84).

The diagnosis of LAM by HRCT required the presence of typical cystic changes diffusely throughout both lungs without relative sparing of the bases.[E1]

Pulmonary function methodology

Acceptability and reproducibility criteria from the American Thoracic Society's (ATS) latest recommendations for standardization were used to judge the validity of each testing session.[E2-E5] Pulmonary function personnel from the Clinical Centers were encouraged to submit sufficient information to allow determination of the acceptability of the testing session. Results from tests that failed to meet these standards were still collected and analyzed by the Registry.

ATS standards for acceptability and reproducibility criteria were also used for the single-breath diffusing capacity test.[E3] Clinical centers were encouraged to apply their own standards for acceptability for lung volumes, cardiopulmonary stress testing, arterial blood gases and six-minute walk tests.

Quality of life instruments

SF-36 Health Survey: The SF-36 is a multipurpose, short-form health survey with 36 questions.[E6] It is a general quality of life instrument which assess eight dimensions of health: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. The survey's standardized scoring system yields a profile of eight health scores, two summary measures (physical and mental health), and a self-evaluated change in health status. Scores range from 0-100, higher scores indicate better health-related quality of life. The survey was constructed for self-administration by persons 14 years of age and older, and for administration by a trained interviewer in person or by telephone.

The St. George's Respiratory Questionnaire (SGRQ): The SGRQ is a self-administered health-related quality of life measure for patients with respiratory disease.[E7] It contains 50 items and 76 weighted responses divided into three components: Symptoms, Activity, and Impacts. The Symptoms component contains items concerned with the level of symptomatology, including frequency of cough, sputum production,

wheeze, breathlessness, and the duration and frequency of breathlessness or wheeze. The Activity component is concerned with physical activities that either cause or are limited by breathlessness. The Impacts component covers such factors as employment, being in control of health, panic, stigmatization, the need for medication and its side effects, expectations for health and disturbance of daily life. Scores ranging from 0 to 100 are calculated for each component, as well as a total score which summarizes the responses to all items. A zero score indicates no impairment of quality of life, hence a lower score indicates better quality of life (the opposite of the SF-36)

RESULTS

Demographic data

The subjects in this Registry were highly educated with 78% having attended at least one year of college and 56% being college graduates. Fifty-four per cent of the subjects were employed; 15% were unemployed for medical reasons.

Lung function

When lung volumes were assessed using gas dilution, the residual volume (RV) and total lung capacity were within the normal range in 73.3% of the subjects (see Table E1). However, the average residual volume determined plethysmographically was elevated, especially in the sporadic LAM patients.

Quality of life

The physical and mental component scores (mean ± SE) of the SF-36 quality of life for LAM Registry patients were 39.7 ± 0.82 and 50.2 ± 0.66, respectively, at baseline (see Figure E1 in the online data supplement). The SF-36 physical component was positively correlated with baseline spirometry and diffusion capacity (FVC % predicted r=0.25, p<0.0002; FEV_1 % predicted r=0.46, p<0.0001; FEV_1/FVC r=0.42, p<0.0001; diffusing capacity % predicted r=0.44, p<0.0001). In addition, the SF-36 physical component was significantly reduced in persons with cough (present 32.7 ± 1.42, absent 42.8 ± 0.89, p<0.001), phlegm (present 33.8 ± 1.15, absent 41.8 ± 0.91, p<0.001), wheezing (present 35.4 ± 1.16, absent 43.4 ± 1.04, p<0.001), and breathlessness (present 35.8 ± 0.87, absent 50.2 ± 1.06, p<0.001).

History of spontaneous pneumothorax or pleural effusion did not significantly affect either SF-36 component. Previous pleurodesis was associated with a reduced SF-36 physical component (present 39.0 ± 1.26, absent 43.7 ± 1.85, p=0.038.), but did not alter the mental component.

The three component scores (symptom, activity and impact) and the total score (mean ± SE) of the SGRQ for LAM registry patients at baseline were 36.1 ± 1.50, 50.3 ± 1.98, 23.6 ± 1.22 and 34.0 ± 1.37, respectively (see Figure E2 in the online data supplement). The SGRQ scores were inversely related to lung function, with component and total scores most strongly associated with FEV_1 (symptoms r=-0.32, p<0.0001; activity r=-0.63, p<0.0001; impacts r=-0.44, p<0.0001; total r=-0.53, p<0.0001). In addition, all four scores were significantly inversely associated with the presence of cough, phlegm, wheezing, and breathlessness. History of spontaneous pneumothorax or

pleural effusion did not alter any SGRQ score. Previous pleurodesis significantly increased only the symptom score (present 39.7 ± 2.17, absent 29.6 ± 3.68, p=0.028).

There was no difference in any of the SF-36 or SGRQ scores when comparing subjects with sporadic LAM to those with TSC-LAM (se Figure E3 and E4).

References

E1. Bonelli FS, Hartman TE, Swensen SJ, Sherrick A. Accuracy of high-resolution CT in diagnosing lung diseases. AJR Am J Roentgen 1998;170:1507-1512.

E2. American Thoracic Society (ATS). 1994 Update on standardization of spirometry. Am J Respir Crit Care Med 1995. 152:1107-1136.

E3. American Thoracic Society (ATS). 1995 Update on single-breath carbon monoxide diffusing capacity (transfer factor); recommendations for a standard technique. Am J Respir Crit Care Med 1995;152:1299-1307.

E4. American Thoracic Society (ATS). Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis 1991;44:1202-1218.

E5. Johnson DC. Importance of adjusting carbon monoxide diffusing capacity (DLCO) and carbon monoxide transfer coefficient (KCO) for alveolar volume. Respir Med 2000;94:28-37.

E6. Ware JE, Kosinski M, Keller SD. SF-36 Physical & Mental Health Summary Scales: A User's Manual. The Health Institute, New England Medical Center, Boston, MA. 1994.

E7. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992,145:1321-1327.

Table E1. Additional pulmonary function data at the time of enrollment

	All patients (n=230)		Sporadic LAM (n=196)		TSC-LAM (n=34)		P Value*
Characteristic	**n**[†]	**Mean ± SE**	**n**[†]	**Mean ± SE**	**n**[†]	**Mean ± SE**	
TLC, % predicted (Gas)	190	95.8 ± 1.11	160	95.4 ± 1.22	30	97.7 ± 2.68	0.44
TLC, % predicted (Plethysmography)	85	103.1 ± 1.66	69	103.8 ± 1.89	16	99.8 ± 3.33	0.30
RV, % predicted (Gas)	190	103.2±2.33	160	103.6±2.43	30	101.4±5.33	0.72
RV, % predicted (Plethysmography)	87	125.4±4.57	71	129.6±5.30	16	106.4±6.30	0.008
FRC, % predicted (Gas)	190	94.7±1.56	160	95.0±1.71	30	92.5±3.85	0.55
FRC, % predicted (Plethysmography)	44	109.9±4.96	34	113.2±6.19	10	98.9±4.71	0.073

Definition of abbreviations: FRC = functional residual capacity, LAM = pulmonary lymphangioleiomyomatosis, RV = residual volume, TLC = total lung capacity, TSC = tuberous sclerosis complex.

TLC values are pre-bronchodilator.

* P values are for comparison between the two subgroups.

[†] Number of subjects with information available.

Figure Legends

Figures E1. SF-36 Score for All Patients with LAM. Box plots illustrate 10th, 25th, 50th, 75th and 90th percentiles.

Figure E2. St. George's Score for All Patients with LAM. Box plots illustrate 10th, 25th, 50th, 75th and 90th percentiles.

Figures E3. Comparison of SF-36 Score for Patients with Sporadic LAM versus TSC-LAM. Box plots illustrate 10th, 25th, 50th, 75th and 90th percentiles.

Figures E4. Comparison of St. George's Score for Patients with Sporadic LAM versus TSC-LAM. Box plots illustrate 10th, 25th, 50th, 75th and 90th percentiles.

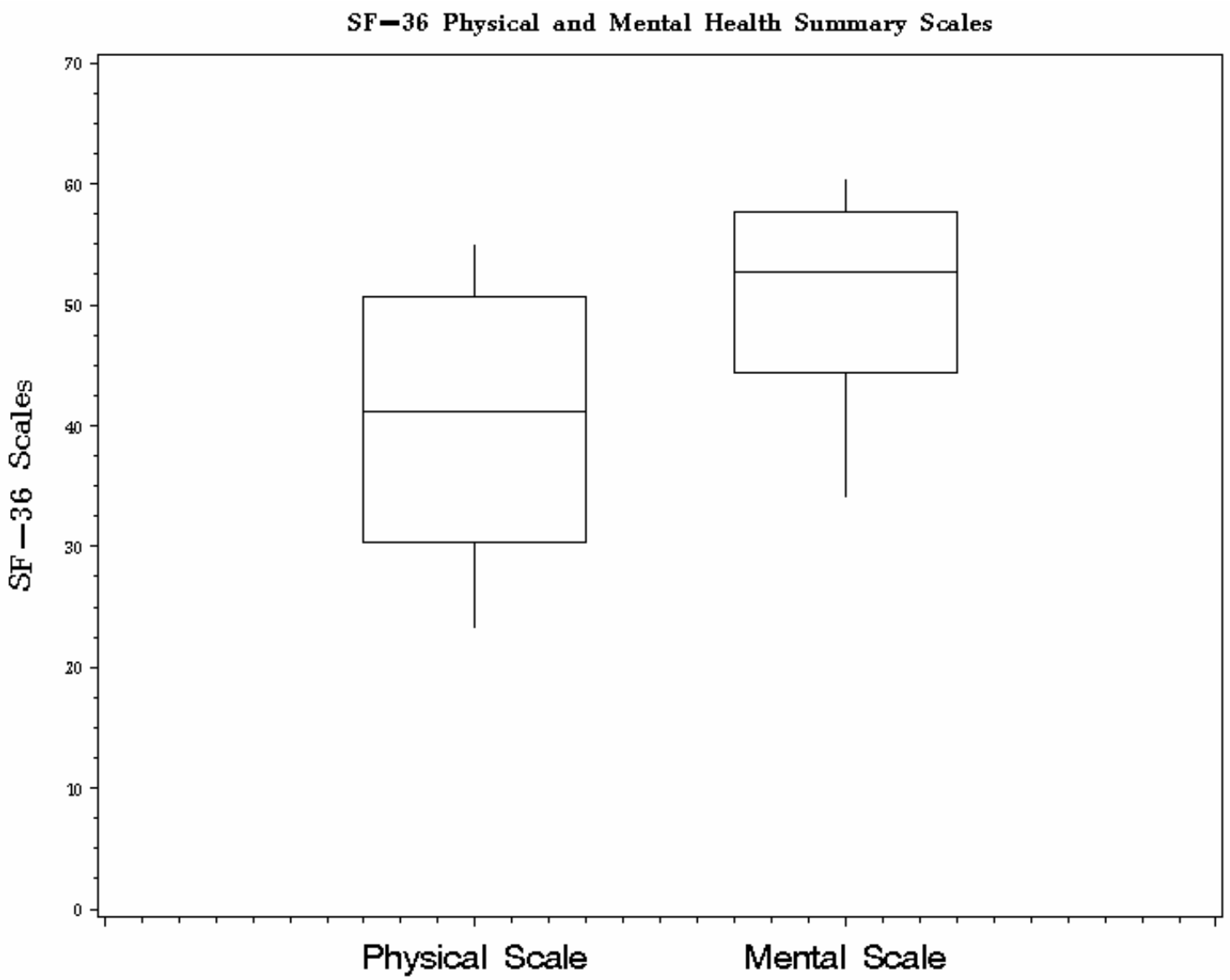
SF−36 Physical and Mental Health Summary Scales
SF−36 Scales
70
60
50
40
30
20
10
0
Physical Scale
Mental Scale

Figure E1.

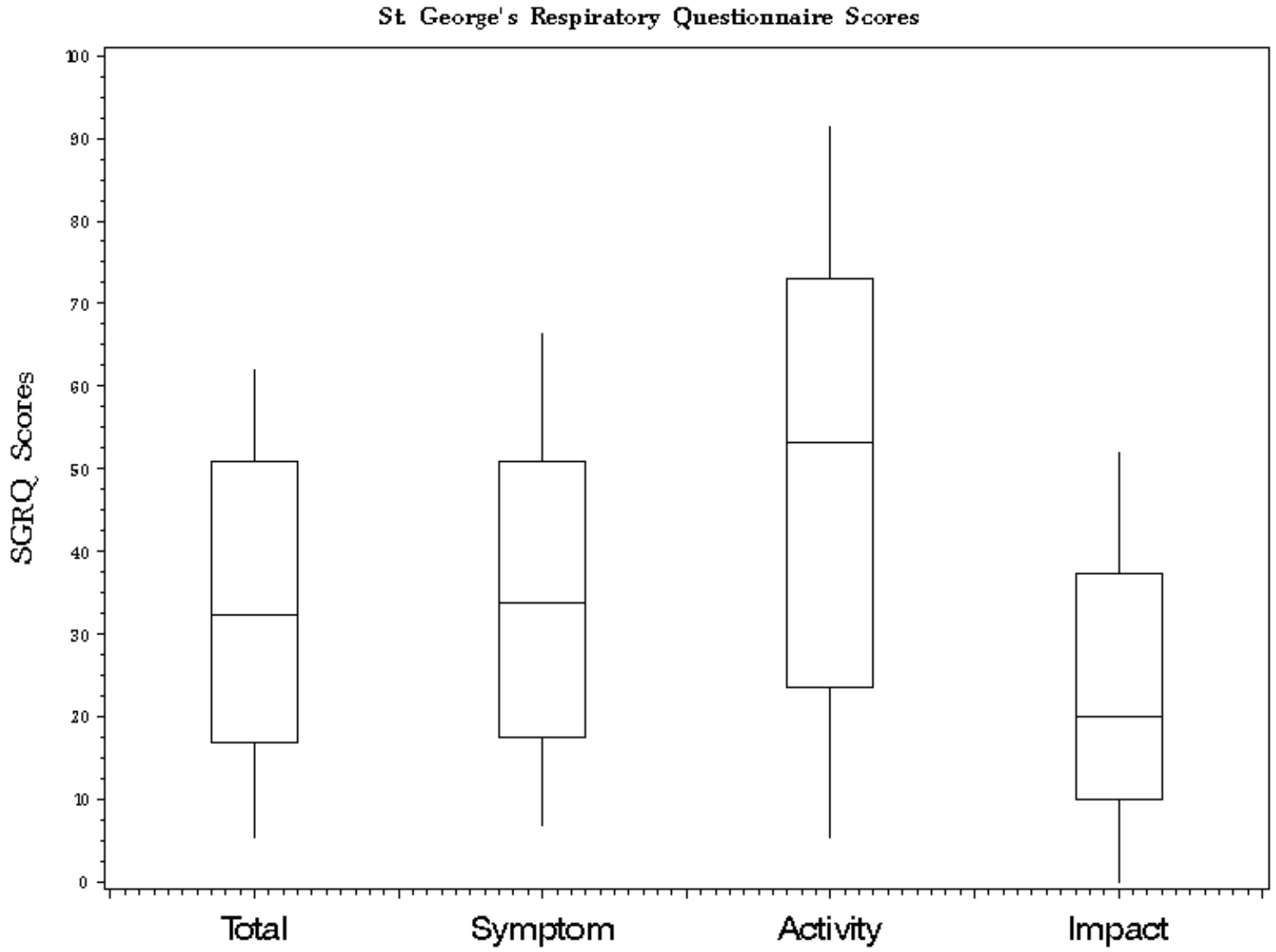
St. George's Respiratory Questionnaire Scores
SGRQ Scores
100
90
80
70
60
50
40
30
20
10
0
Total
Symptom
Activity
Impact

Figure E2.

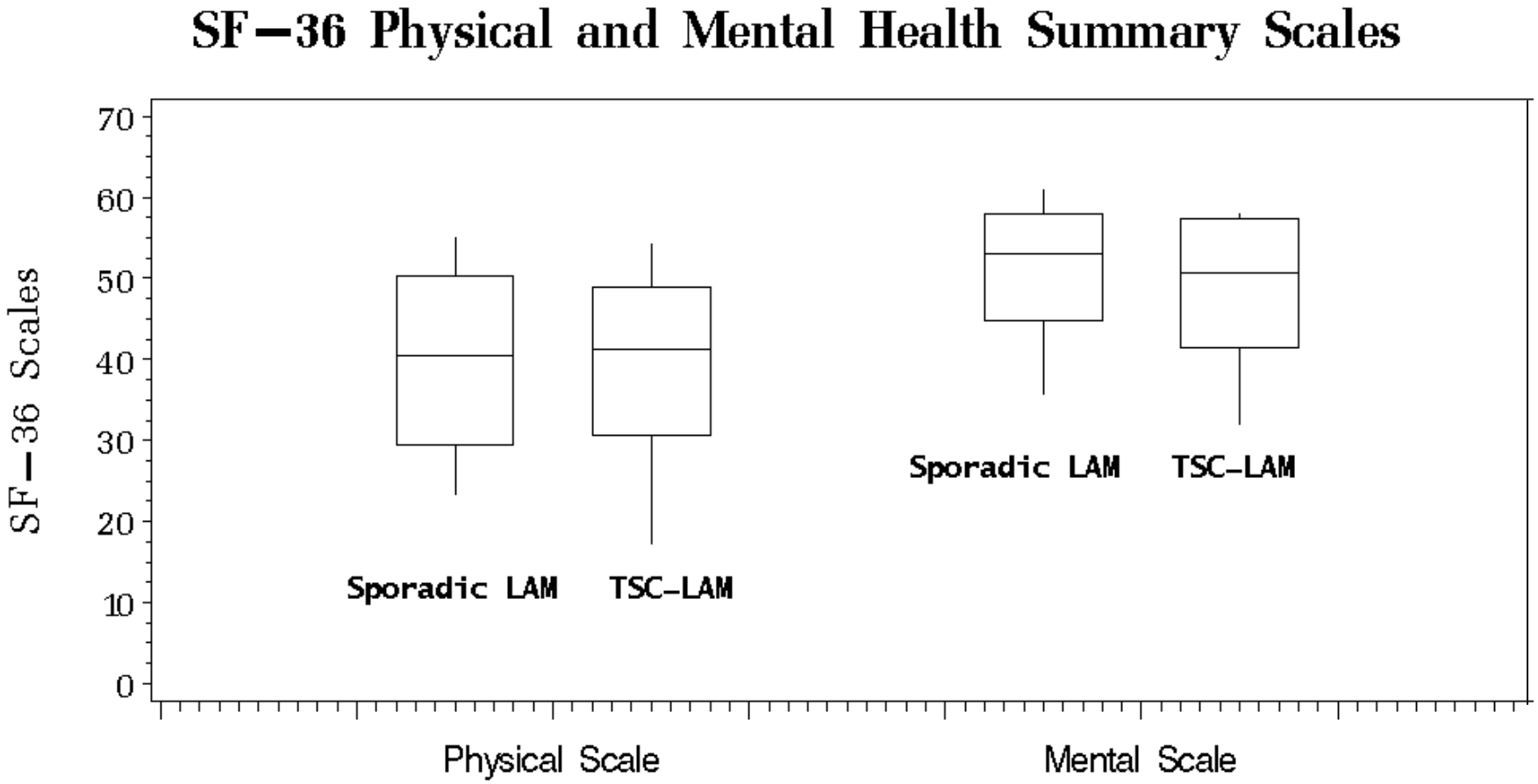
SF−36 Physical and Mental Health Summary Scales
SF−36 Scales
70
60
50
40
30
20
10
0
Sporadic LAM
TSC-LAM
Sporadic LAM
TSC-LAM
Physical Scale
Mental Scale

Figure E3.

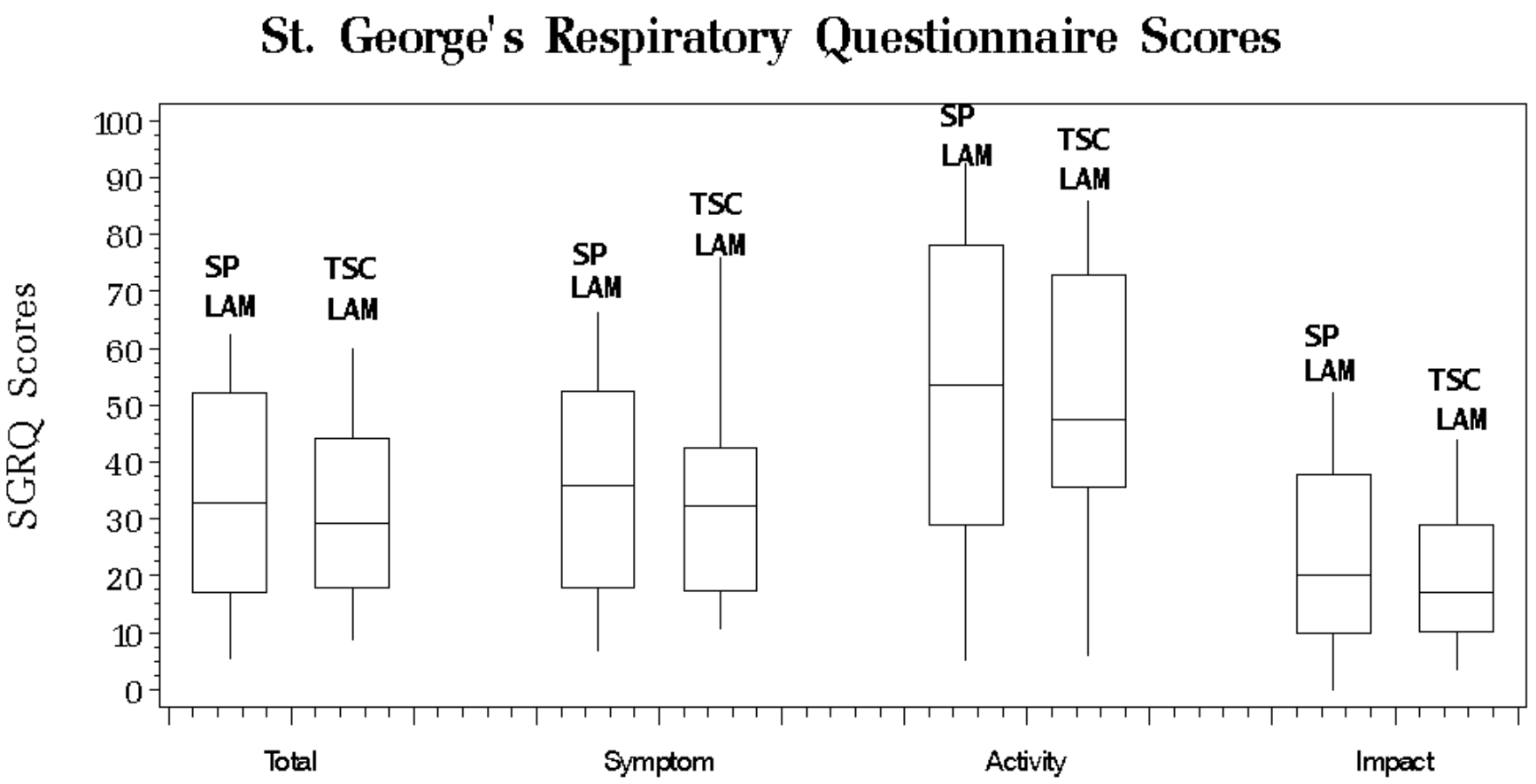
St. George's Respiratory Questionnaire Scores
SGRQ Scores
100
90
80
70
60
50
40
30
20
10
0
SP LAM
TSC LAM
SP LAM
TSC LAM
SP LAM
TSC LAM
SP LAM
TSC LAM
Total
Symptom
Activity
Impact

Figure E4.