EXTENDED REPORT

Predictors of end stage lung disease in a cohort of patients with scleroderma

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Objectives: To estimate the incidence of severe lung disease in patients with scleroderma and identify the combination(s) of features present at first assessment which would be useful to predict future risk of severe lung disease.

Methods: Data were analysed on 561 patients with disease onset occurring on or after 1 January 1982 and disease duration of less than five years before the first assessment. Detailed clinical and laboratory assessments were undertaken at the initial visit. End stage lung disease was defined as pulmonary hypertension requiring continuous ambulatory iloprost, or pulmonary fibrosis requiring continuous oxygen, or death from a scleroderma related lung disease. Patient status was determined at 31 December 1997. The best subset of predictors was identified by Cox regression analysis.

Results: In all, 24 patients reached end stage lung disease. The cumulative incidences were 4%, 6%, and 12% at five, seven, and 14 years respectively. As expected, the lung function tests at baseline, including being in the lowest third of either diffusing lung capacity (hazard ratio (HR) = 18.2, 95% confidence interval (CI) 3.5 to 93.8) or of forced vital capacity (HR=4.1, 95% CI 1.1 to 15.2), were highly significant predictors of end stage lung disease. Interestingly, apart from the presence of proteinuria, none of the other baseline variables, including the extent of skin disease and serological markers, were predictive of severe lung disease.

Conclusion: End stage lung disease was infrequent in this large cohort, but the cumulative incidence increased importantly with time. The risk can be predicted from baseline assessment of pulmonary function. In particular, those with normal pulmonary function at baseline are at very low risk.

Scleroderma is a multisystem disorder whose course can vary from being relatively benign, with involvement restricted to the skin and peripheral vasculature, to a rapidly progressive disease affecting internal organs. Although the extent of skin disease is an important marker of severity,[1] the involvement of internal organs is of greater pathological significance in increasing mortality risk.[2–4]

The incidence of internal organ involvement in the course of scleroderma is well described, with the lungs being one of the most commonly affected. Steen *et al* reported abnormalities in pulmonary function in 70% of patients with scleroderma studied.[5] Similarly, in a group of 165 patients, 62% with diffuse disease and 72% in the limited/CREST syndrome group[6] showed one or more pulmonary function abnormalities.

The functional abnormalities are frequently a consequence of the distinct manifestations of pulmonary disease: interstitial fibrosis and pulmonary vascular disease.[7] The cumulative occurrence of both is high, with pulmonary fibrosis occurring in up to 80%, and pulmonary hypertension in up to 50%, of patients with scleroderma.[8] Abnormalities on chest radiographs as well as on a pulmonary function test are the early hallmarks of lung disease,[9 10] and thus such investigations are widely used as screening tests.

Scleroderma is associated with decreased survival, with lung disease being a major contributor. In an earlier study we reported that 44% of all scleroderma related deaths, were related to lung disease,[11] whereas others found an even higher proportion.[4] It is thus not surprising that early evidence of lung disease is a major risk factor for subsequent mortality. Median survival of patients with diffuse skin disease and lung disease is 78 months, with a 50% eight year mortality rate.[2]

As severe fibrosis and pulmonary hypertension emerge as the leading causes of death among patients with scleroderma, as well as being associated with severe morbidity, we examined the question: can severe lung disease be predicted in early disease? There are difficulties in undertaking such investigations. Firstly, scleroderma is a rare disease and few centres see sufficiently large numbers of patients to accumulate enough data to obtain robust estimates of outcome in a relatively short period of time. Secondly, studies should also restrict the analysis to unselected cases seen early in disease to reduce the risk of "left censorship bias". We therefore attempted to recruit a cohort of patients with scleroderma relatively early on in their disease. Our objectives were to estimate the incidence of severe lung disease in this group and quantify the influence of both lung related and lung unrelated disease features.

PATIENTS AND METHODS

Design

Patients were recruited to a prospective cohort study and followed up in order to assess the relationship between the baseline results collected at first assessment and the development of end stage lung disease. Patients were followed up from their first attendance to 31 December 1997.

Subjects

All subjects were referrals to a single scleroderma centre (CMB). Inevitably, at a specialist referral centre, many patients are referred late on in the disease for a tertiary opinion. Consequently, recruitment for the analysis was restricted to those subjects who were referred within five years of disease onset (defined as the date of first self reported skin change).

Abbreviations: ACA, anticentromere antibodies; CI, confidence interval; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HR, hazard ratio; TLCO, carbon monoxide transfer factor (diffusing lung capacity)

Table 1 Demographic data according to sex and cutaneous disease classification

	Male (n=99)	Female (n=462)	Limited disease (n=324)	Diffuse disease (n=237)
Age at first assessment (years)				
<16	2	3	2	3
16–44	35	181	113	103
45–64	53	220	159	114
65+	9	58	50	17
Median (IQR)	49.2 (38.7–57.2)	47.9 (38.4–57.7)	49.7 (39.8–59.7)	46.0 (37.2–55.5)
Disease duration from onset to 1st visit (years)				
<1	36	170	108	98
1–2.5	36	162	110	88
2.6–5.0	27	130	106	51
Median (IQR)	1.6 (0.6–2.8)	1.4 (0.7–2.7)	1.8 (0.8–3.0)	1.2 (0.7–2.2)

IQR, interquartile range.

Subjects were eligible for inclusion in the study if the date of disease onset was on or after 1 January 1982. For the purpose of this study, additional patients to those investigated in earlier work[12] were further recruited and included in the analysis up to December 1997. In all, of 830 people referred to the scleroderma centre, 561 satisfied these inclusion criteria as well as the American Rheumatism Association criteria for scleroderma.[13]

Baseline data collection

A standardised procedure for data collection was used in order to collect the following variables at the first attendance to the clinic. A modified Rodnan skin score,[14] scale 0–3 at 17 sites, assessed the degree of skin disease, and patients were also classified into limited and diffuse cutaneous disease.[15] The presence of lung disease was assessed from lung function tests including carbon monoxide transfer factor (TLCO), forced vital capacity (FVC), and from the presence of fibrosis detected by a chest *x* ray examination. Possible cardiac disease was determined from (*a*) an ECG to ascertain rhythm and conduction abnormalities (considered by the doctor to be consistent with scleroderma) and (*b*) from the chest radiographs to determine any signs of cardiac enlargement. Renal disease was assessed from raised serum creatinine and urine protein presence (greater than trace) and raised diastolic blood pressure. Muscular abnormality was assessed by creatine kinase levels. Non-organ-specific variables, including haemoglobin, erythrocyte sedimentation rate (ESR), anticentromere antibodies (ACA), and antitopoisomerase (Scl-70), were also measured.

Follow up

Patients were followed up annually to the end of December 1997, to death or the defined lung end point. The median follow up and interquartile range for the 561 patients studied was 5.0 years (3.0–7.9). Some patients stopped follow up during the study period.

Pulmonary hypertension and pulmonary fibrosis were categorised based upon the results of standard investigations. Thus fibrosis was invariably associated with a restrictive pattern of pulmonary function test abnormality (FVC <70% predicted for age/sex), and was confirmed by high resolution computed tomography with fibrotic change. Pulmonary hypertension was defined by Doppler echocardiographic features, with resting peak pulmonary arterial pressure above 30 mm Hg (plus right atrial pressure) and associated reduction in TLCO to <70% predicted. In many cases the diagnosis was further confirmed by right heart catheterisation, with resting or exercise associated mean pulmonary arterial pressure above 25 or 30 mm Hg, respectively. Isolated pulmonary hypertension was determined by these changes in the absence of significant lung fibrosis.

Vital status at the end of December 1997 was determined for all patients. Two reviewers (CMB, AJS) inspected the death certificates obtained from the UK National Health Service Central Register. Patient death was attributed to a scleroderma related cause if the underlying cause of death on the death certificate was due to a clinically coherent consequence of scleroderma or if scleroderma itself was mentioned as the actual underlying cause. In addition, patient death was further subdivided into scleroderma related lung disease if pulmonary fibrosis, fibrosing alveolitis, pulmonary hypertension, and bronchopneumonia were also included on the death certificate as well as other mentions of lung disease, where these conditions were indicated to be a direct consequence of scleroderma.

End stage lung disease in a subject was defined in three ways: (*a*) death due to scleroderma related lung disease; (*b*) a patient with pulmonary hypertension requiring continuous ambulatory iloprost; (*c*) a patient with pulmonary fibrosis requiring continuous oxygen.

Analysis

For the purpose of the analysis, results from an electrocardiogram, creatine kinase, urine protein, presence of ACA and antitopoisomerase (Scl-70) were entered dichotomously. Skin score, TLCO, FVC, pulmonary diastolic pressure, haemoglobin, packed cell volume, and ESR were analysed after division into tertiles.

Univariate analysis of the relation between risk factors considered and the development of end stage lung disease was undertaken using a Cox proportional hazard regression approach.[16] This approach assumes the effect of the different variables on the event-free time was constant over time. The hazard ratios for the baseline data were adjusted for age and sex.

All baseline variables showing any influence ($p<0.1$) on lung end point in this univariate analysis were entered into a multivariate model, with the addition of age, sex, and disease subtype. Separate multivariate modelling was also undertaken. All hazard ratios (HRs), which can be interpreted as the relative risk of developing end stage lung disease during follow up, are presented with their 95% confidence intervals (CI). All analyses were undertaken using STATA version 6.0.[17]

RESULTS

In all, 561 patients were included in the analysis, 99 male and 462 female. The median age at first assessment of the whole group was 48 years, with 25% of patients being 57 years or older. Patients, on average were seen within 18 months of the first skin change in both the male and female groups. The median age of the 324 (58%) patients with limited cutaneous disease, was significantly greater than the median age of the 237 (42%) patients with diffuse disease (49.7 years *v* 46.0 years, $p=0.0012$) (table 1).

Table 2 Demographic data by severe lung disease status

	No lung end points (n=537)	Lung end points (n=24)
Female (n=462) (No (%))	444 (82.7)	18 (75)
Mean age at first assessment (SD)	48.2 (13.8)	51.0 (13.1)
Mean disease duration (SD)	1.7 (1.5)	1.2 (1.4)

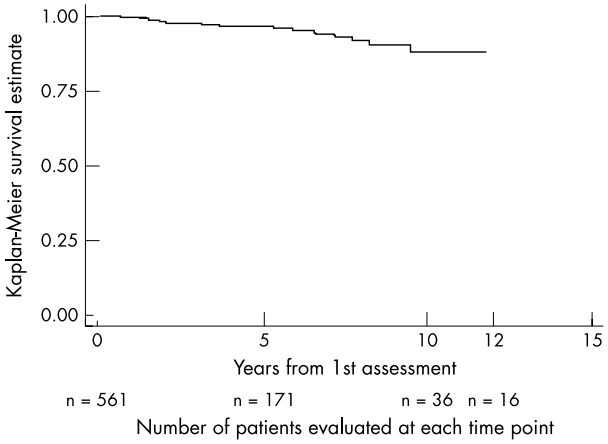

Figure 1 Kaplan-Meier curve indicating end stage lung disease events from the first assessment.

Twenty four (4.3%) patients had end stage lung disease, 16 of whom subsequently died. The lung end points occurred evenly during follow up. Thus, by the end of the third year of follow up, 8/24 (33%) of the lung end points had already occurred with 15/24 (63%) occurring by the fifth year. Table 2 shows the distribution of age and disease duration at baseline, and between those with and without a lung end point.

Figure 1 shows the Kaplan-Meier survival curve for the group from the first assessment. During the first five years, end stage lung disease was rare, with 0.96 of the study group being free from end stage lung disease (standard error (SE) 0.01). At seven and 14 years from the first assessment, the cumulative morbidity rates increased with time from 0.06 (SE 0.02) to 0.12 (SE 0.03), respectively.

Table 3 shows the results from the univariate analysis, using Cox regression. For every increase in year of age, there was a 2% increase in end stage lung disease. Women were 30% less likely to develop end stage lung disease.

As expected, being in the lowest third for lung function tests: diffusing lung capacity (TLCO) at ⩽60% predicted or FVC at ⩽80%, was highly significantly associated with increased end stage lung disease (table 3). By contrast only 2/172 (1%) of those in the top third of TLCO had developed severe lung disease during follow up. However, a number of non-lung assessment variables were also found to be important. Positive urine protein (greater than trace) was found to be significantly predictive of increased risk of the development of severe lung disease. Subjects with a skin score >14 and with cardiac abnormality from the ECG results at first assessment, had an increased risk, although not significant. There was a slight but non-significant reduction in risk in those patients who were ACA positive and a similar non-significant increase in risk in those who were antitopoisomerase positive.

On multivariate analysis the influence of reduced FVC was attenuated after adjusting for TLCO. Thus the presence of both a reduced FVC and TLCO was not associated with any greater increased risk of a lung end point, than having a reduced TLCO alone. After adjusting for TLCO the effect of proteinuria was also attenuated and became non-significant.

DISCUSSION

This study has thus quantified the risk of developing severe lung disease over time in a large cohort presenting with scleroderma and shown that the cumulative probability of lung disease by 14 years had reached 12%. The study has also measured the predictive value of disease variables, particularly abnormalities in diffusing lung capacity (TLCO) measured at baseline, as well as demonstrating a limited role for non-pulmonary predictors. However, a number of methodological issues should be considered. Firstly, despite the large sample size there were only 24 lung end points, which limited the power to detect modest effects in some of the predictors investigated. Secondly, follow up was relatively short with only a quarter having more than eight years of follow up. This is important as primary pulmonary hypertension—that is, not developing on a background of interstitial fibrosis, is increasingly common with longer follow up.[18] Indeed in the current study, as discussed above, the cumulative event rate of 12 continued to increase uniformly throughout the study. It would, therefore be necessary to follow up patients for a longer period to ascertain their total lifetime risk of severe lung disease. Indeed only one in 10 of those with a TLCO below 60% at baseline, developed end stage lung disease on follow up. Although this is reassuring, given the short follow up, extrapolation to the longer term would be hazardous.

The ascertainment and case definition of "end stage" lung disease was somewhat arbitrary. Our definition was based on the need for specific interventions—interstitial disease that was sufficiently advanced to require continuous oxygen or pulmonary hypertension that was so raised as to justify treatment with prostaglandins—or death. Clearly, several other subjects had substantial deterioration in lung function but had not reached "end stage". We also did not separate the different causes of end stage lung disease. Rapidly progressive fibrosis almost certainly has a different pathogenesis from the more slowly progressive pulmonary hypertension that develops in those with limited skin disease.[7 19]

Of the 17 lung related deaths, two were listed on the death certificate as bronchopneumonia. Although clearly a lung cause of death it might not represent the consequence of scleroderma on the lung. Excluding these two people, however, and repeating the analysis did not alter the findings.

The patients studied were those recruited early in their disease in an attempt to reduce the left censorship bias inherent in follow up studies of prevalent cohorts. Dating disease onset is always difficult and although we used recalled onset of skin disease, this is clearly subject to error, particularly in limited disease when it is unlikely to be the first manifestation of disease. Our subjects inevitably came from a large referral centre and thus cannot claim to be extrapolatable to disease managed by non-specialist doctors.

Proteinuria (greater than "trace") on "dip stick" testing was the only non-lung variable that was predictive of lung disease, although it was not significant on multivariate analysis. This finding is, however, consistent with our previous observation that this was also predictive of all cause mortality rather than of renal deaths themselves.[12] The numbers were small and this univariate result might reflect random error. We also have no explanation as to why early proteinuria might predict non-renal severe disease.

Other factors in a subset of this cohort that were found significantly to increase the risk of all cause mortality from scleroderma, such as a raised ESR and low haemoglobin,[12] had little influence on the development of end stage lung disease.

The extent and severity of cutaneous disease were not significantly associated in this study with severe lung disease as has also previously reported.[20 21] This lack of effect might

Table 3 Assessing the relationship between end stage lung disease and risk factors. Results from univariate analysis

Variable		Hazard ratio*	95% CI
Age at 1st assessment (years)		1.02	0.99 to 1.06
Sex	Male	1.00	
	Female	0.68	0.27 to 1.74
Duration of disease from onset to 1st assessment (years)		0.89	0.71 to 1.11

System	Variable	Category	No (%)	Lung end point (n=24)	No lung end point (n=537)	Hazard ratio	95% CI
Skin	Cutaneous type	Limited	324 (57.8)	11	313	1.00	
		Diffuse	237 (42.2)	13	224	1.65	0.71 to 3.85
	Skin score	⩽6	167 (29.8)	3	164	1.00	
		6–14	168 (29.9)	8	160	1.95	1.50 to 7.59
		>14	226 (40.3)	13	213	2.68	0.74 to 9.71
Lung	Diffusing lung capacity (TLCO) (%)	⩽60	151 (30.8)	15	136	18.19	3.53 to 93.82
		60–77	168 (34.2)	4	164	2.97	0.47 to 18.39
		>77	172 (35.0)	2	170	1.00	
	Forced vital capacity (%)	1–80	165 (32.9)	11	154	4.09	1.10 to 15.19
		81–100	173 (34.5)	9	164	2.36	0.62 to 9.00
		>100	163 (32.5)	3	160	1.00	
Heart	ECG	Normal	533 (97.1)	22	511	1.00	
		Abnormal	16 (2.9)	2	14	3.22	0.70 to 14.90
	Diastolic blood pressure (mm Hg)	1–70	172 (35.4)	9	163	1.53	0.59 to 3.96
		71–80	212 (43.6)	9	203	1.00	
		>80	102 (21.0)	1	101	0.21	0.03 to 1.64
Kidney	Serum creatinine (mg/l)	⩽8.2	154 (33.9)	8	146	1.00	
		8.3–9.0	153 (33.7)	5	148	0.74	0.23 to 2.30
		>9.0	147 (32.4)	8	139	0.80	0.26 to 2.50
	Urine protein	Absent	536 (95.5)	21	515	1.00	
		Present	25 (4.5)	3	22	3.91	1.14 to 13.35
Muscle	Creatine kinase	Normal	508 (91.7)	22	486	1.00	
		Raised	46 (8.3)	2	44	1.43	0.33 to 6.21
General	Haemoglobin (g/l)	⩽123	170 (33.5)	6	164	0.85	0.29 to 2.54
		124–134	165 (32.5)	7	158	0.80	0.25 to 2.51
		>134	173 (34.1)	8	165	1.00	
	Packed cell volume	0.01–0.36	165 (32.5)	8	157	0.74	0.26 to 2.10
		0.37–0.40	204 (40.2)	4	200	0.24	0.07 to 0.82
		>0.40	139 (27.4)	9	130	1.00	
	ESR (mm/1st h)	⩽10	172 (36.6)	8	164	1.00	
		11–24	155 (33.0)	4	151	0.67	0.20 to 2.25
		⩾25	143 (30.4)	7	136	1.52	0.54 to 4.31
Antibody markers	ACA	Negative	442 (78.8)	20	422	1.00	
		Positive	119 (21.2)	4	115	0.57	0.19 to 1.74
	Antitopoisomerase	Negative	462 (82.4)	19	443	1.00	
		Positive	99 (17.7)	5	94	1.54	0.56 to 4.23

*Hazard ratios from Cox regression analysis adjusted for age, sex, and disease duration.

have concealed a disease subgroup specific influence. Thus, restrictive lung disease is more often found among patients with diffuse scleroderma and a higher prevalence of pulmonary hypertension among patients with limited scleroderma.[20] Unfortunately, owing to the small numbers, we were unable to analyse the two groups separately.

There are limited published data on additional—that is, non-lung, predictors of severe lung disease. Although a raised ESR was not indicative of an increased risk of developing end stage lung disease in our study, Steen *et al* did show that an increased ESR was associated with increased severity of, and mortality from, restrictive disease.[21] That observation suggests that a raised ESR, as a marker for the inflammatory process in the lung, would lead to severe interstitial lung disease. Our failure to confirm this might be a consequence of combining all lung end points.

There is considerable variability in the ascertainment and interpretation of investigations of reduced diffusing lung capacity, which is clearly subject to misclassification. Despite this, several studies, in addition to the current study, have shown that such signs are associated with poor prognosis.[10 22] The latter showed that the diffusing lung capacity test was the best predictor of increased pulmonary arterial pressure and poor survival. Further, Steen *et al* identified those patients with increased risk of developing pulmonary hypertension when lung function tests were poor.[18]

We only examined the role of predictors at first presentation on the development of lung disease. It would be interesting to

investigate further whether changes in some of these measures have additional value in predicting end stage lung disease.

In summary, therefore, severe lung disease is a common end point, whose occurrence increases with increasing follow up. Not surprisingly, the strongest predictors are early lung disease with few clues from the baseline characteristics. From this study, possibly the most useful observation is that normal lung function at first presentation is associated with a very low subsequent risk of end stage lung disease.

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