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Bronchoalveolar Lavage Cellular Profiles in Patients With Systemic Sclerosis–Associated Interstitial Lung Disease Are Not Predictive of Disease Progression

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Objective. **To evaluate the prognostic value of bronchoalveolar lavage (BAL) cellular profiles in patients with systemic sclerosis–associated interstitial lung disease (SSc-ILD).**

Methods. **BAL cellularity was examined in relation to mortality (n = 141), serial pulmonary function findings (n = 134), and "progression-free survival" (n = 134), by proportional hazards analysis. Baseline severity was quantified according to the extent of disease on high-resolution computed tomography, the diffusing capacity for carbon monoxide, and the presence or absence of pulmonary hypertension. Mortality was subclassified into overall mortality (during 10 years of followup), early mortality (occurring within 2 years of presentation), and late mortality (occurring 2–10 years after presentation).**

Results. **Overall mortality was associated with neutrophilia on BAL (hazard ratio 2.23 [95% confidence interval 1.20–4.14], $P = 0.01$), but this effect was lost when disease severity was taken into account. Early mortality was associated with neutrophilia on BAL (hazard ratio 8.40 [95% confidence interval 1.91–36.95], $P = 0.005$), independent of disease severity. Late mortality was not associated with neutrophilia on BAL. The presence of neutrophilia on BAL was not associated with time to decline in pulmonary function or progression-free survival. Neither eosinophilia nor lymphocytosis on BAL was associated with mortality, rapidity of functional deterioration, or progression-free survival. These findings were unaltered when treatment status was taken into account.**

Conclusion. **BAL findings provide only limited prognostic information in SSc-ILD. Neutrophilia on BAL is linked to early mortality, but BAL findings are not linked to long-term survival or the rapidity of progression of lung disease. The usefulness of BAL to define alveolitis in SSc is questionable.**

Lung involvement is common in systemic sclerosis (SSc) and is the leading cause of death among patients with this disease. However, the course is highly variable. There is increasing evidence that cyclophosphamide is partially effective in the treatment of SSc–associated interstitial lung disease (SSc-ILD) (1). Because of the toxicity of immunosuppressive therapy, accurate prognostic evaluation is needed to identify patients who are at higher risk of deterioration and who may benefit from therapeutic intervention.

The prognostic value of bronchoalveolar lavage (BAL) in patients with SSc-ILD has been explored, and granulocytosis on BAL has been shown to be associated with greater risk of deterioration (2–5). This observation does not exclude the possibility that "BAL alveolitis" is a marker of disease severity, rather than an independent prognostic factor (6). A protocol of routine serial monitoring of pulmonary function during extended followup

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Table 1. Baseline characteristics of the SSc-ILD patients who did and those who did not undergo BAL*

Variable	BAL (n = 141)	No BAL (n = 71)	*P*
Age, years	47.3 ± 12.2	54.2 ± 15.3	0.0005
No. male/no. female	27/114	13/58	0.88
Smoking, no. never/no. former/no. unknown	96/45/0	35/31/5	0.04
FEV_1, % predicted	77.7 ± 17.0	73.2 ± 22.7	0.10
FVC, % predicted	78.4 ± 18.9	74.3 ± 26.7	0.20
DLCO, % predicted	56.2 ± 15.7	49.5 ± 20.0	<0.01
Extent of disease on HRCT, median (range) %	12.0 (1.0–84.0)	16.5 (1.0–77.5)	<0.01

* Except where indicated otherwise, values are the mean ± SD. SSc-ILD = systemic sclerosis–associated interstitial lung disease; BAL = bronchoalveolar lavage; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; HRCT = high-resolution computed tomography.

provided a unique opportunity to evaluate longer-term outcome, as judged by the rapidity of decline in pulmonary function indices, in a large SSc cohort. The aim of this study was to evaluate BAL as a prognostic tool with regard to mortality, subsequent disease progression, and "progression-free survival" in patients with SSc-ILD, with and without adjustment for baseline disease severity.

PATIENTS AND METHODS

Patients. Three hundred thirty consecutive SSc patients referred to our unit with overt or suspected pulmonary involvement (261 female and 69 male; mean ± SD age 49.1 ± 13.0 years) were identified between January 1990 and December 1999. All fulfilled the American College of Rheumatology (formerly, the American Rheumatism Association) criteria for SSc (7), without evidence of overlap connective tissue disorders. Fifty-two patients (16%) without evidence of ILD on high-resolution computed tomography (HRCT) were not evaluated further. All investigations were performed as part of a prospective routine clinical protocol. The study was approved by the Royal Brompton Hospital Ethics Committee.

Current smokers (n = 25) and patients with incomplete data (n = 41) were excluded, reducing the study population to 212 patients. Data were considered incomplete either if HRCT was performed elsewhere and the scans were unavailable for scoring (n = 30) or if baseline investigations were separated by >90 days (n = 11). The 41 patients who were excluded because of missing or incomplete data did not differ from the remaining patients in age ($P = 0.94$), male:female ratio ($P = 0.25$), smoking status ($P = 0.57$), forced expiratory volume in 1 second (FEV_1) ($P = 0.65$), forced vital capacity (FVC) ($P = 0.79$), or diffusing capacity for carbon monoxide (DLCO) ($P = 0.49$). Furthermore, mortality did not differ between the patients who were excluded and the remaining patients, either with ($P = 0.60$) or without ($P = 0.53$) adjustment for baseline DLCO levels.

BAL was performed except when contraindicated based on severe pulmonary involvement, significant comorbidity, or patient aversion to the procedure; 141 of the 212 patients (67%) underwent BAL. As shown in Table 1, the group of patients in whom BAL was performed were younger ($P = 0.0005$) and had less severe disease as judged by the extent of abnormality seen on HRCT ($P < 0.01$) and by the DLCO ($P < 0.01$), compared with the group of patients who did not undergo BAL. On multivariate analysis, younger age and less severe disease (extent of disease on HRCT and DLCO examined in separate models) were both associated with the performance of BAL.

Patients not undergoing BAL were not evaluated further. Mortality was examined in the 141 patients in whom the procedure was performed. The rapidity of functional decline during followup and progression-free survival were assessed in 134 patients in whom serial pulmonary function tests (PFTs) were performed.

Clinical information. Demographic data, smoking status, baseline treatment data, echocardiography results, PFT results at the time of the BAL, and serial PFT results were extracted from hospital records. Vital status as of May 1, 2006 and results of serial PFTs performed up to the same date were recorded, with survival analysis extended to 10 years. Patients were considered ever smokers if they had smoked >1 cigarette per day for >1 year. Current smokers were defined as smoking or having stopped smoking <6 months before the time of BAL. Treatment was defined as corticosteroid (prednisolone >1 mg/day) and/or immunosuppressive (cyclophosphamide, azathioprine, or mycophenolate mofetil) therapy at the time of, or introduced within 3 months after, BAL.

Pulmonary function testing. FVC was measured using either a PKM Spiroflow spirometer (P. K. Morgan, Kent, UK) or the Jaeger Compact system (Viasys Healthcare, Warwickshire, UK). DLCO was measured by either a rebreathing technique (PKM Spiroflow) or a single-breath technique (Jaeger Compact system). Results were expressed as the percent of predicted values (8).

High-resolution computed tomography. For HCRT, 1.5-mm or 3-mm sections were acquired at 10-mm intervals (window center −550 Hounsfield units [HU]; window width 1,500 HU) using an electronic beam CT scanner (Imatron, San Francisco, CA), with the patient in a supine position at full inspiration. An additional limited number of sections through the lower zones of the lungs were acquired with the patient in a prone position, to evaluate the effects of gravity-dependent opacification in the posterobasal segments. Scans were scored (9–13) independently by 2 experienced observers (SRD and AUW), who were blinded with regard to clinical and lung function information. HRCT images were scored at 5 levels: 1)

origin of the great vessels, 2) carina, 3) pulmonary venous confluence, 4) between levels 3 and 5, and 5) 1 cm above the right hemidiaphragm. Sections were scored at each level for the total extent of disease (reticular and ground-glass opacity patterns), to the nearest 5% (14–17). Discrepancies of >20% were resolved by consensus. Mean values were computed, to provide a total disease extent score.

Echocardiography. Transthoracic echocardiography was performed with the patient in the left lateral position, using a Sonos 2500 echocardiography apparatus (Hewlett-Packard, Andover, MA). Non-imaging continuous-wave Doppler signals were recorded with a 2.0-MHz transducer (Doptek; Southampton, UK). Tricuspid regurgitant flow was identified by continuous-wave mode at the apex. The peak instantaneous systolic pressure drop from right ventricle to atrium was calculated from the peak signal velocity of the tricuspid regurgitant signal, by the simplified Bernoulli equation. The final estimation of pulmonary arterial systolic pressure was obtained by adding the jugular venous pressure to the estimated pulmonary arterial systolic pressure. The presence of pulmonary hypertension was defined as pulmonary arterial systolic pressure of ≥35 mm Hg (18).

Bronchoalveolar lavage. BAL was performed according to recommended guidelines (19) and previous reports (20). Aliquots of 60 ml of sterile normal saline were instilled through the bronchoscope, and the fluid was retrieved by mechanical suction. Negative pressures of up to 70 mm Hg were generated, with particular attention to avoiding collapse of the airways beyond the tip of the bronchoscope and trauma to the mucosa (19,21). A standard introduction volume was 240 ml. Cells were harvested from BAL fluid by low-speed centrifugation at 300*g* for 5 minutes at 4°C. Total cell counts were obtained using a Neubauer counting chamber and expressed as the total number of cells per milliliter of aspirated fluid. Absolute cell counts of neutrophils, eosinophils, and lymphocytes were calculated. Slide preparations for differential percentage counting of cells were made with a Cytospin II cytocentrifuge (Shandon, Cheshire, UK), using 100-μl aliquots of the lavage cell suspensions, adjusted to 1.25×10^6 cells/ml in Dulbecco's modified Eagle's medium. After fixation in methanol, the preparations were stained with May-Grünwald-Giemsa. Differential counts were made from a minimum of 300 cells. BAL values considered to be abnormal were as follows: neutrophils >4%, eosinophils >2%, lymphocytes >14%, or granulocytosis (neutrophils >4% and/or eosinophils >2%). The cellular constituents were analyzed both as continuous variables (percentage cells and absolute cell counts) and as dichotomous variables (presence or absence of neutrophilia, eosinophilia, lymphocytosis, or granulocytosis).

Outcome measures. The date of the BAL was the baseline date from which mortality and progression of disease (time to decline) were evaluated. As in a previous study of idiopathic fibrotic lung disease (22), mortality was subcategorized as overall mortality (during 10-year followup), early mortality (within 2 years of presentation), and late mortality (2–10 years after presentation, in the 117 patients who were still living at 2 years).

The time to decline was determined by serial PFT. Changes in PFT results were assessed using the American Thoracic Society/European Respiratory Society criteria (23). Significant change was defined as a decrease (quantified as the percent change from baseline) of ≥10% in the FVC percent predicted or of ≥15% in the DLco percent predicted, recorded on at least 2 consecutive occasions. When functional deterioration was observed at the last followup visit, even if not observed at the preceding visit, this was taken to indicate significant decline, with the proviso that there was symptomatic or radiographic evidence of deterioration. Progression-free survival, defined as the time to disease progression or death, was also evaluated (24).

Data analysis. Analyses were performed using Stata software (Computing Resource Centre, Santa Monica, CA). Data were expressed as the mean ± SD or the median (range), depending on distribution. Group comparisons were made using Student's *t*-test, Wilcoxon's rank sum test, chi-square statistics, or Fisher's exact test, as appropriate. Correlations between BAL data and indices of disease severity were examined by Spearman's rank correlation. *P* values less than 0.05 were considered significant.

The prognostic value of BAL was examined in relation to survival and, separately, in relation to disease progression, using proportional hazards analysis (25). Baseline disease severity was quantified according to the extent of disease on HRCT, the baseline DLco level, and the presence or absence of pulmonary hypertension. Proportional hazards analysis was used to evaluate time to decline in the FVC, time to decline in the DLco, and time of progression-free survival (with progression defined as the occurrence of either decline in FVC, decline in DLco, or death in patients without prior functional decline). Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated. Univariate and stepwise multivariate analyses were performed. Variables included in multivariate analysis were those shown to be associated with outcome in univariate analysis.

RESULTS

Patient characteristics. Demographic and clinical data are presented in Tables 1 and 2. There were 43 deaths (30%) during a median followup of 95.3 months. Seventy-nine of 134 patients (59%) had a decline in the FVC (median time to decline 64.5 months). Eighty of 134 patients (60%) had a decline in the DLco (median time to decline 65.1 months). One hundred six of 134 patients (79%) had a functional decline, or died without having prior functional deterioration (median time of progression-free survival 35.6 months). Seventeen patients (12%) died within 2 years of presentation, and 26 patients (18%) died 2–10 years after presentation. Compared with the patients who did not develop pulmonary hypertension, the 18 patients with pulmonary hypertension (13%) were characterized by older age (mean ± SD 53.7 ± 10.4 years versus 46.4 ± 12.2 years; $P = 0.02$), lower DLco (% predicted 44.0 ± 13.8 versus 58.0 ± 15.2; $P < 0.0005$), more extensive disease seen on HRCT (median [range] 24.0% [4.5–70.0%] versus 11.5% [1.0–84.0%]; $P = 0.03$), and a higher likelihood of neutro-

Table 2. BAL results in 141 patients with SSc-ILD*

BAL differential cell count, median (range)	
% neutrophils	4.0 (0–72.0)
% eosinophils	2.0 (0–20.0)
% lymphocytes	9.0 (1.0–67.0)
Presence of neutrophilia (>4% neutrophils)	66 (47)
Presence of eosinophilia (>2% eosinophils)	61 (43)
Presence of lymphocytosis (>14% lymphocytes)	36 (26)
Presence of granulocytosis	89 (63)
BAL absolute cell count ($\times 10^6$/ml), median (range)	
Neutrophils	0.045 (0–1.44)
Eosinophils	0.020 (0–0.38)
Lymphocytes	0.11 (0.0012–0.48)

* Except where indicated otherwise, values are the number (%) of patients. BAL = bronchoalveolor lavage; SSc-ILD = systemic sclerosis–associated interstitial lung disease.

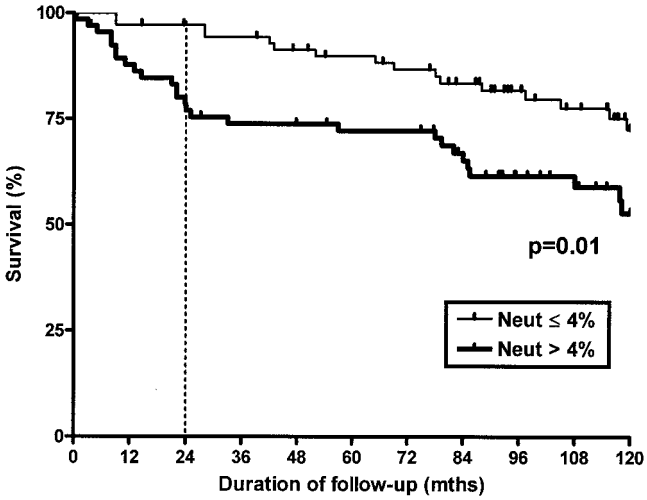

Figure 1. Survival of patients with systemic sclerosis–associated interstitial lung disease with neutrophilia and those without neutrophilia on bronchoalveolar lavage (defined as neutrophils [Neut] >4%). Survival at 24 months is indicated by the vertical dashed line.

philia on BAL (13 of 18 patients versus 53 of 123 patients; $P = 0.02$).

Overall mortality (n = 141). By univariate analysis, the presence of neutrophilia on BAL was associated with increased mortality (HR 2.23 [95% CI 1.20–4.14], $P = 0.01$) (Table 3). Figure 1 shows Kaplan-Meier curves illustrating survival among patients with and those without neutrophilia on BAL. The association between mortality and neutrophilia on BAL diminished after adjustment for extent of disease seen on HRCT (HR 2.02 [95% CI 1.07–3.82], $P = 0.03$), DLco (HR 1.84 [95% CI 0.97–3.48], $P = 0.06$), and presence or absence of pulmonary hypertension (HR 1.79 [95% CI 0.94–3.41], $P = 0.08$). After adjustment for baseline DLco and presence or absence of pulmonary hypertension in combination, the presence of neutrophilia on BAL was not associated with increased mortality (HR 1.54 [95% CI 0.80–2.99], $P = 0.20$). In the same model, baseline DLco and presence or absence of pulmonary hypertension were independently associated with increased mortality (HR 0.97 [95% CI 0.94–0.99], $P = 0.004$ and HR 2.73 [95% CI 1.29–5.79], $P = 0.009$, respectively).

There were no statistically significant associations between overall mortality and eosinophilia, lymphocytosis, or granulocytosis on BAL. As shown in Table 3, BAL findings were not found to be related to mortality when cell counts were expressed as continuous variables (cell differential percentages and absolute cell counts in separate analyses).

Early mortality (n = 141). By univariate analysis, the presence of neutrophilia on BAL was associated with increased mortality (HR 8.40 [95% CI 1.91–36.95], $P = 0.005$) (Table 4), and this finding remained significant after adjustment for extent of disease seen on HRCT, baseline DLco, and presence or absence of pulmonary hypertension, in separate models ($P = 0.01$, $P = 0.02$, and $P = 0.02$, respectively). There were no statistically significant associations between early mortality and eosinophilia, lymphocytosis, or granulocytosis (Table 4). BAL results were not found to be related to mortality when cell counts were expressed as continuous variables (cell differential percentages and absolute cell counts in separate analyses).

Table 3. Relationship between overall mortality and individual BAL findings*

BAL feature	HR (95% CI)
Dichotomous variables	
Neutrophilia	2.23 (1.20–4.14)†
Eosinophilia	1.06 (0.58–1.93)
Lymphocytosis	0.77 (0.37–1.60)
Granulocytosis	1.92 (0.97–3.82)
Cell differential percentages	
Neutrophils	1.01 (0.98–1.04)
Eosinophils	1.00 (0.92–1.08)
Lymphocytes	0.99 (0.96–1.02)
Absolute cell counts	
Neutrophils	2.51 (0.77–8.23)
Eosinophils	0.97 (0.01–78.62)
Lymphocytes	0.49 (0.03–9.00)

* BAL = bronchoalveolar lavage; HR = hazard ratio; 95% CI = 95% confidence interval.
† $P = 0.01$.

Table 4. Relationship between early mortality and individual BAL findings*

BAL feature	HR (95% CI)
Dichotomous variables	
Neutrophilia	8.40 (1.91–36.95)†
Eosinophilia	1.25 (0.47–3.33)
Lymphocytosis	0.41 (0.09–1.80)
Granulocytosis	4.24 (0.96–18.65)
Cell differential percentages	
Neutrophils	1.01 (0.98–1.05)
Eosinophils	1.05 (0.93–1.17)
Lymphocytes	0.94 (0.87–1.02)
Absolute cell counts	
Neutrophils	1.87 (0.29–12.11)
Eosinophils	2.31 (0.003–2,044.72)
Lymphocytes	0.50 (0.004–69.47)

* BAL = bronchoalveolar lavage; HR = hazard ratio; 95% CI = 95% confidence interval.
† $P = 0.005$.

Late mortality (n = 117). BAL findings, expressed as either dichotomous or continuous variables, were not predictive of late mortality, in either univariate or multivariate analyses ($P > 0.10$).

Deterioration in pulmonary function (n = 134). There were no significant or marginal relationships between the time to decline in either the FVC or the DLCO and 1) the presence of neutrophilia, eosinophilia, lymphocytosis, or granulocytosis on BAL (Table 5) or 2) BAL findings expressed as cell differential percentages or absolute cell counts (data not shown). Similarly, in patients undergoing PFT at 1 year (n = 113) and at 2 years (n = 99), BAL findings were not significantly or marginally related to the amplitude of change in either the FVC or the DLCO (data not shown).

Progression-free survival (n = 134). There were no significant or marginal relationships between progression-free survival and BAL findings, whether expressed as dichotomous variables, cell differential percentages, or absolute cell counts (data not shown).

Table 5. Relationship between time to decline in FVC and DLCO and BAL findings (expressed as dichotomous variables)*

	HR (95% CI)†	
BAL feature	FVC	DLCO
Neutrophilia	1.24 (0.80–1.92)	1.29 (0.83–2.00)
Eosinophilia	1.30 (0.83–2.02)	0.91 (0.59–1.42)
Lymphocytosis	1.16 (0.71–1.89)	1.03 (0.63–1.70)
Granulocytosis	1.35 (0.84–2.16)	1.12 (0.71–1.75)

* FVC = forced vital capacity; DLCO = diffusing capacity for carbon monoxide; BAL = bronchoalveolar lavage.
† None of the hazard ratios (HRs) were statistically significant. 95% CI = 95% confidence interval.

Treatment effects. Thirty-six patients (26%) were receiving treatment at the time of BAL (prednisolone n = 23, azathioprine n = 1, mycophenolate mofetil n = 1, prednisolone and azathioprine n = 5, prednisolone and cyclophosphamide n = 6). Treatment was introduced within 3 months after BAL in 26 patients (18%) (prednisolone n = 4, cyclophosphamide n = 1, prednisolone and azathioprine n = 4, prednisolone and cyclophosphamide n = 17). Relationships between BAL findings and outcome (mortality and disease progression) were not altered with adjustment for treatment status (treatment versus no treatment) either at the time of BAL or 3 months after BAL.

Presence of neutrophilia on BAL in relation to disease severity. The presence of neutrophilia on BAL was associated with more extensive disease seen on HRCT (median [range] extent of disease 15.0% [1.0–84.0%] versus 10.0% [1.5–53.5%]; $P < 0.005$) and a greater reduction in the DLCO (mean ± SD % predicted 53.4 ± 16.6 versus 58.7 ± 14.5; $P < 0.05$). Increasing percentage of neutrophils on BAL, expressed as a continuous variable, was associated with increasingly extensive disease on HRCT ($r_s = 0.31$, $P < 0.0005$), but not with DLCO ($r_s = -0.14$, $P = 0.11$).

DISCUSSION

Bronchoalveolar lavage findings are widely used to guide treatment decisions in patients with SSc-ILD, based on accumulated clinical experience and expert opinion (2–5,26). However, the current data, from a large patient cohort managed using a standardized approach, indicate that after adjustment for baseline disease severity, BAL cellularity does not predict overall or late mortality, disease progression (as judged by the rapidity of decline in pulmonary function indices), or progression-free survival.

Our results highlight the importance of controlling for baseline disease severity when assessing the implications of findings seen on BAL. The presence of granulocytosis on BAL reportedly identifies a higher likelihood of disease progression (2–5), except in treated patients (2,4), but is also associated with severe disease, as judged by pulmonary function impairment (2–5), chest radiography (3), or HRCT (27). Thus, we postulated that with measurement of disease severity using PFT and HRCT, BAL information might become redundant for prognostic purposes.

In support of this hypothesis, an initial association between overall mortality and neutrophilia on BAL was lost when baseline disease severity was taken into

account. However, there was a modest but statistically significant link between early mortality and the presence of neutrophilia on BAL, which was independent of other measures of severity. This was not explained by more rapid progression of lung disease ("disease activity"), as judged by trends seen on serial PFT. A more plausible explanation is that neutrophilia on BAL is itself a marker of disease severity and is linked to mortality for that reason. The finding that neutrophilia on BAL was associated with more extensive disease seen on HRCT and with greater functional impairment provides evidence in support of this.

In the absence of a "reference standard," the optimal method for quantifying disease in SSC-ILD is uncertain, and this prompted us to examine both disease extent and disease severity, using HRCT and PFT in separate multivariate models. The selection of DLCO as the primary severity variable was based on its reported strong correlation with the extent of ILD in SSc (28). Pulmonary hypertension, an important clinical marker of the severity of disease, was also taken into account in the analyses.

In earlier studies, various criteria were used to define BAL "activity" in SSc, including the presence of granulocytosis (neutrophilia and/or eosinophilia) (2,3,5), neutrophilia and/or lymphocytosis (4), and the separate examination of all 3 cellular components (20,27). In the present study, the findings were unaltered when BAL neutrophil and eosinophil profiles were amalgamated (as the presence or absence of granulocytosis). Similarly, the results were not influenced by the expression of cellular constituents as percentage differential values, absolute numbers, or dichotomous variables (presence/absence) in separate analyses.

Bias due to patient exclusions is unlikely to have materially affected the findings of this study. Demographic features, disease severity, and mortality did not differ between patients who were excluded because of incomplete baseline data and the studied population. Patients undergoing BAL were younger and had less severe disease than those not undergoing BAL, but this finding reflected the fact that BAL is often clinically inappropriate in older patients and in patients with severe lung disease. Thus, the studied population was representative of SSc-ILD patients in whom BAL tends to be performed in routine practice.

In contrast, it was not possible to definitively exclude a degree of confounding due to treatment. Unlike previous cohorts (2–4), in the present investigation consecutive patients, including patients already receiving treatment, were enrolled when referred for overt or suspected pulmonary involvement. For analysis, treatment status was categorized as the presence or absence of treatment at the time of BAL, irrespective of agent (corticosteroids, immunosuppressive drugs), dosage, or mode of administration, because the differential effects of these factors on BAL findings have not been studied. Results were unaltered when treatment status at the time of BAL and, separately, early introduction of treatment (within the first 3 months after BAL) were taken into account in multivariate analysis.

However, the introduction of treatment during later followup could not be taken into account in outcome analyses. The choice, timing, and duration of therapy varied widely during the years of followup, with treatments often modified or withdrawn due to side effects. Therefore, the present study remains essentially a prognostic evaluation of BAL, in the context of intended "best management" of unselected patients with SSc-ILD. Further analyses of the prognostic value of BAL findings in the placebo arms of controlled treatment studies will provide important additional information.

This caveat is important because it is possible that BAL findings might have provided limited prognostic information when treatment decisions were difficult and BAL information was influential. It could be argued that the introduction of therapy prevented or delayed functional deterioration in these cases, masking the prognostic value of BAL. However, it is unlikely that this problem seriously distorted our findings. First, relationships to outcome were unaltered when treatment status in the 3 months after BAL was taken into account in subanalysis; treatment was introduced during this period in $<20\%$ of cases. More importantly, BAL findings were seldom the final determinant of management decisions in our unit, and introduction of treatment was based largely on the severity of lung disease, evidence of recent deterioration, and duration of systemic disease (6).

Our findings strongly suggest that the term "BAL alveolitis," implying pathogenetic lung inflammation in SSc, is potentially misleading. The concept of alveolitis is important because interstitial inflammation is widely believed to precede and lead to lung fibrosis in SSc (29). However, BAL neutrophil content does not provide useful insights in this regard. In SSc-ILD, although there is a high prevalence of neutrophilia and/or eosinophilia on BAL, fibrotic histology predominates on lung biopsy (30,31), and fibrotic appearances predominate on HRCT (11). The current findings indicate that neutrophilia on BAL reflects more extensive disease, rather than denoting interstitial inflammation. Consistent with

this conclusion, treatment of SSc-ILD in patients with granulocytosis on BAL is generally associated with subsequent stability of disease and, at best, minimal functional improvement (2,4).

In conclusion, the results of the present study indicate that BAL findings do not greatly refine prognostic evaluation in SSc-ILD, once disease severity has been quantified by pulmonary function testing and computed tomography. A limited role for BAL cannot be wholly discounted if there is uncertainty regarding treatment decisions following routine staging, but this applies to highly selected patient subgroups.

AUTHOR CONTRIBUTIONS

Dr. Wells had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Goh, Wells.

Acquisition of data. Goh, Veeraraghavan, Desai, Cramer, Hansell, Black, du Bois, Wells.

Analysis and interpretation of data. Goh, Desai, Cramer, Denton, Black, du Bois, Wells.

Manuscript preparation. Goh, Veeraraghavan, Desai, Hansell, Denton, Black, du Bois, Wells.

Statistical analysis. Goh, Wells.

Organization of pulmonary function testing. Cramer.

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