An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study

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Summary

Background Mortality in pulmonary sarcoidosis is highly variable and a reliable prognostic algorithm for disease staging and for guiding management decisions is needed. The objective of this study is to derive and test a staging system for determining prognosis in pulmonary sarcoidosis.

Methods We identified the prognostic value of high-resolution computed tomography (HRCT) patterns and pulmonary function tests, including the composite physiological index (CPI) in patients with pulmonary sarcoidosis. We integrated prognostic physiological and HRCT variables to form a clinical staging algorithm predictive of mortality in a test cohort. The staging system was externally validated in a separate cohort by the same methods of discrimination used in the primary analysis and tested for clinical applicability by four test observers.

Findings The test cohort included 251 patients with pulmonary sarcoidosis in the study referred to the Sarcoidosis clinic at the Royal Brompton Hospital, UK, between Jan 1, 2000, and June 30, 2010. The CPI was the strongest predictor of mortality (HR 1·04, 95% CI 1·02–1·06, p=0·0001) in the test cohort. An optimal CPI threshold of 40 units was identified (HR 4·24, 2·84–6·33, p<0·0001). The CPI, main pulmonary artery diameter to ascending aorta diameter ratio (MPAD/AAD), and an extent of fibrosis threshold of 20% were combined to form a staging algorithm. When assessed in the validation cohort (n=252), this staging system was strikingly more predictive of mortality than any individual variable alone (HR 5·89, 2·68–10·08, p<0·0001). The staging system was successfully applied to the test and validation cohorts combined, by two radiologists and two physicians.

Interpretation A clear prognostic separation of patients with pulmonary sarcoidosis is provided by a simple staging system integrating the CPI and two HRCT variables.

Introduction For most patients, pulmonary sarcoidosis is a somewhat benign and self-limiting disorder. Clinically occult disease and spontaneous remission occur in the majority of patients. However, for some, pulmonary sarcoidosis can be a chronic and debilitating disease associated with significant mortality. Although several studies have reported on factors that might predict prognosis in pulmonary sarcoidosis such as reduced forced vital capacity, pulmonary arterial hypertension, and the radiographic presence of pulmonary fibrosis, attempts to devise a reliable prognostic algorithm for pulmonary sarcoidosis have been largely unsuccessful, and this has impeded the development of consensus management and treatment recommendations. A major barrier to this specific research effort is that mortality due to pulmonary sarcoidosis in unselected populations is too low for the empowerment of survival analyses. Referral centre populations have a higher than expected mortality than that in unselected populations of patients with pulmonary sarcoidosis. Therefore, referral centres provide an enriched population ideal for deriving prognostic methods, using mortality as an appropriate primary endpoint.

Pulmonary fibrosis and pulmonary arterial hypertension are two important causes of death in patients with pulmonary sarcoidosis. Pulmonary arterial hypertension is a substantial issue regardless of whether there is fibrosis—more than 70% of patients with pulmonary sarcoidosis awaiting lung transplantation have substantial pulmonary arterial hypertension, which is present in almost half of patients with pulmonary sarcoidosis with dyspnoea (out of proportion to their pulmonary function abnormalities). In idiopathic pulmonary fibrosis, Wells and colleagues devised the composite physiological index (CPI), which is a weighted index of pulmonary function variables that correlates with extent of interstitial disease on high-resolution computed tomography (HRCT). CPI was a stronger predictor of mortality than any individual lung function variable. Pulmonary arterial hypertension is a frequent complication in idiopathic pulmonary fibrosis and an important cause of mortality in these patients. The prognostic strength of the CPI in the setting of idiopathic pulmonary fibrosis might be explained by its incorporation of diffusing capacity of carbon monoxide (DLCO), which might confer increased sensitivity to concurrent pulmonary arterial
hypertension, while at the same time capturing the prognostic effect of interstitial disease. Following from this finding, the CPI could be postulated to also be useful in pulmonary sarcoidosis for the identification of patients with a poor prognosis.

The CPI has not been studied in sarcoidosis, thus the aim of our study was to assess the prognostic strength of the CPI in a large cohort of patients with pulmonary sarcoidosis. Additionally, we explored whether the CPI and HRCT variables could be integrated to form a clinical staging system for identifying patients at high and low risk of mortality.

Methods

Patients and study design

In this case-cohort study, we clinically defined and did all pulmonary function tests and HRCTs in accordance with local protocols. For the purposes of a retrospective examination of these data, the institutional ethics review board waived informed patient consent.

We identified consecutive outpatients referred to the Sarcoidosis clinic at the Royal Brompton Hospital. We only included patients with a diagnosis of pulmonary sarcoidosis, synthesised from clinical, radiological, and pathological data and an HRCT within 90 days of baseline pulmonary function tests in the study population. Exclusion criteria were: diagnosis not confirmed at multidisciplinary review; no HRCT available within 90 days of baseline pulmonary function tests; and no HRCT or pulmonary function test evidence of pulmonary involvement. To exclude patients for whom a diagnosis of chronic hypersensitivity pneumonitis might have been possible, all patients with HRCT features compatible with pulmonary sarcoidosis and a lymphocytosis on bronchoalveolar lavage were required to meet at least one of the other two criteria to be included in the study (appendix). In patients for whom none of these criteria were available, the HRCT imaging was reviewed by a thoracic radiologist of 25 years’ experience in the diagnosis of interstitial lung diseases.

Procedures

We documented age, sex, smoking status, treatment at the time of baseline pulmonary function tests, follow-up time, baseline pulmonary function tests, and presence of extrapulmonary symptoms. We recorded smoking status as “current smoker”, “ever smoker”, and “never smoker.” “Ever smokers” had smoked more than one cigarette a day for more than 1 year. Treatment was recorded at the time of baseline pulmonary function testing and at 4 months follow-up (to capture patients for whom treatment was not instigated at first visit, but was begun soon after their first consultation) and consisted of one or a combination of corticosteroid (prednisolone) and immunosuppressant therapy (hydroxychloroquine, cyclophosphamide, azathioprine and methotrexate).

These data provided two separate groups for analysis based on the management strategy chosen—those who underwent observation only (intention to observe) and those who received treatment (intention to treat).

We measured the forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁) and DLCO according to established protocols. The CPI, originally derived in idiopathic pulmonary fibrosis, is a weighted index of pulmonary function that captures physiological impairment due to interstitial disease but excludes impairment due to emphysema. We calculated this index with the following formula: \( 91.0 - (0.65 \times \text{predicted DLCO}) - (0.53 \times \text{percent predicted FVC}) + (0.34 \times \text{percent predicted FEV₁}) \) for every patient.

The appendix shows a detailed discussion of HRCT scoring methods. In brief, all images were anonymised and two thoracic radiologists (DMH with 24 years’ experience and NS with 11 years’ experience) reviewed them independently. The entire lungs were assessed for the presence and extent of fibrosis (defined as criss-crossing linear opacities [reticulation] with or without honeycombing [air-filled cystic spaces with irregular walls deemed not to be distracted airways]), ground glass opacification, and other (defined as patterns of disease not covered by fibrosis or ground glass opacification). Observers also assessed the presence or absence of traction bronchiectasis and the presence or absence of emphysema. A single observer (SLFW with 8 years’ experience) assessed the main pulmonary artery diameter (MPAD) and ascending aorta diameter (AAD) ratio in all 503 patients (appendix).

Outcome

The primary outcome was mortality. We calculated the survival period starting from the date of the baseline pulmonary function tests to the date of death, or in the case of survivors the last known point of contact. Vital status was known for all patients at the end of the study period.

Statistical analysis

Data are given as means (SD), medians (range) or as proportions stated as percentages where appropriate. We did the statistical analyses using STATA (version 12, StataCorp, College Station, Texas). We made group comparisons using the Student’s \( t \) test, Wilcoxon rank sum, \( \chi^2 \) statistics, and Fisher’s exact test where appropriate. We used the single determination standard deviation to assess interobserver agreement for continuous variables. We assessed interobserver agreement for the presence or absence of traction bronchiectasis and emphysema using the weighted kappa coefficient \( (\kappa_w) \) as follows: poor \( (\kappa_w=0.0–0.20) \), fair \( (\kappa_w=0.21–0.40) \), moderate \( (\kappa_w=0.41–0.60) \), good \( (\kappa_w=0.61–0.80) \), and excellent \( (\kappa_w=0.81–1.00) \).

The appendix shows a detailed discussion of statistical methods used to derive the staging system. In brief, we randomly split the total patient cohort into two groups—A
(test cohort) and B (validation cohort). We assessed potential predictors of mortality, including HRCT patterns and the CPI, in group A. We obtained optimum thresholds, derived against mortality, for the strongest predictors and combined them to form a simple staging system. We externally validated the staging system in group B. Finally, four test observers (two radiologists and two respiratory physicians) assessed the staging system in groups A and B combined to test the models clinical applicability.

**Role of the funding source**

The sponsors of the study did not have any role in the design, data collection, analysis and interpretation, nor in the writing of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

**Results**

We identified 660 consecutive outpatients referred to the Sarcoidosis clinic at the Royal Brompton Hospital between Jan 1, 2000, and June 30, 2010. 59 patients were excluded because the diagnosis was not confirmed at multi-disciplinary review, 89 because of no HRCT available within 90 days of baseline pulmonary function tests, and nine because of no HRCT or pulmonary function test evidence of pulmonary involvement. The remaining 503 patients made up the final study population. Of these, 302 had a biopsy confirmation of the presence of non-necrotising granulomas with no alternative causes of granulomatous inflammation (177 with transbronchial and endobronchial biopsy, 12 with surgical lung biopsy, 89 with peripheral lymph node biopsy, 20 with skin biopsy, and four with liver biopsy). All but three of the remaining 201 patients without biopsy confirmation had a clinical presentation consistent with pulmonary sarcoidosis, an HRCT, which was compatible with pulmonary sarcoidosis, and met at least one of the following criteria: lymphocytosis (>15%) on bronchoalveolar lavage (n=45), elevated serum angiotensin converting enzyme (ACE) level (n=157), demonstrable extrapulmonary features consistent with systemic sarcoidosis (n=57). In the three patients for whom none of these criteria were available, the HRCT appearances were deemed typical.

| Group A (n=251) | Group B (n=252) |
|-----------------|-----------------|
| **Age** 52.7 (11.6) | 53.0 (11.6) |
| **Sex (female)** 158 (63%) | 151 (60%) |
| **Number of deaths** 49 (20%) | 56 (22%) |
| **Treated (at 4 month follow-up)** 140 (59%) | 179 (71%) |
| **Race** |
| White 138 (55%) | 134 (53%) |
| Black, African 10 (4%) | 11 (4%) |
| Black, Caribbean 28 (11%) | 22 (9%) |
| Asian 26 (10%) | 37 (15%) |
| Mixed race 9 (4%) | 4 (2%) |
| Not stated 40 (16%) | 44 (17%) |
| **Smoking status (never, ever, current)** |
| Never 166 (66%) | 164 (66%) |
| Ever 76 (30%) | 75 (30%) |
| Current 9 (4%) | 13 (5%) |
| **Mean follow up time (months)** 50.5 (30.9) | 49.7 (30.4) |
| **Pulmonary function** |
| FVC % predicted 82.4 (24.2) | 81.3 (23.0) |
| FEV1 % predicted 72.9 (25.7) | 70.7 (24.1) |
| DLCO % predicted 58.5 (21.4) | 59.9 (20.3) |
| CPI 34.3 (18.4) | 33.9 (17.9) |
| **O2 supplementation** 19 (8%) | 12 (5%) |
| **Thin section CT** |
| Total disease extent* 41.9 (27.0) | 41.6 (26.4) |
| Extent of ground-glass opacification* 5.8 (11.9) | 5.1 (11.3) |
| Extent of fibrosis* 12.5 (16.6) | 12.2 (18.3) |
| Other* 16.6 (0.5) | 13.3 (4.2) |
| Emphysema (present)† 77 (31%) | 80 (32%) |
| Traction bronchiectasis (present)‡ 76 (30%) | 46 (18%) |
| **Hazard ratio (95% CI)** |
| Extent of fibrosis 1.03 (1.01–1.04) | 0.002 |
| CPI 1.04 (1.02–1.06) | <0.0001 |

| Table 1: Demographic data and group comparisons for group A (n=251) and group B (n=252), baseline pulmonary indices, and thin section CT variable scores
| Table 2: Mortality expressed as hazard ratios on multivariate analysis for HRCT patterns and pulmonary function tests including the CPI in sarcoidosis group A (n=251)

**Figure 1:** Clinical staging algorithm for stratification of clinical risk in pulmonary sarcoidosis

CPI=composite physiological index. HRCT=high-resolution computed tomography. MPAD/AAD=main pulmonary artery diameter to ascending aorta diameter ratio.
Table 1 shows patient demographics with group comparisons for group A and group B. Frequencies of extrapulmonary manifestations of sarcoidosis, when present, are shown in the appendix. Mean follow-up time was 50.1 (SD 30.6) months (range 0.5–122.1, median 49.8, 95% CI 38.8–58.3). Patients excluded from the final study population on the basis of no HRCT being available (n=89) did not differ significantly from the study population in terms of pulmonary function, follow-up time, or survival. The appendix shows comparisons between survivors and non-survivors. Four patients were being considered for lung transplantation at the end of the follow-up period. One patient died during the study while on a transplant list and another was on a transplant list at the end of the follow-up period. No patient within the study cohort received a transplant during the study period. Interobserver agreement expressed as the single determination standard deviation (sdSD) for the HRCT pattern of total disease extent was 0.9 sdSD (0.6–1.1), for ground-glass opacification it was 1.6 sdSD (0.9–2.2), and for fibrosis 2.7 sdSD (0.14–4.4). Interobserver agreement for identifying the presence or absence of traction bronchiectasis and emphysema were good (κ=0.61 for presence and κ=0.71 for absence).

The mean size of the ascending aorta was 31.4 mm (SD 0.1) and that of the main pulmonary artery was 31.3 mm (SD 0.2), for a total of 503 patients. The mean MPAD/AAD ratio was 1.0 (SD 0.01). Interobserver agreement expressed as the single determination standard deviation (sdSD) for the HRCT pattern of total disease extent was 0.9 sdSD (0.6–1.1), for ground-glass opacification it was 1.6 sdSD (0.9–2.2), and for fibrosis 2.7 sdSD (0.14–4.4). Interobserver agreement for identifying the presence or absence of traction bronchiectasis and emphysema were good (κ=0.61 for presence and κ=0.71 for absence).

The mean size of the ascending aorta was 31.4 mm (SD 0.1) and that of the main pulmonary artery was 31.3 mm (SD 0.4), for a total of 503 patients. The mean MPAD/AAD ratio was 1.0 (SD 0.01). Correlation between the calculated MPAD/AAD category (range 0–2, appendix) and the observer’s estimate of the MPAD/AAD category was excellent (r=0.94, r²=0.88, p<0.0001).

The following variables measured at baseline were predictive of mortality on multivariate Cox proportional hazards (without interaction): CPI and extent of fibrosis on HRCT (table 2). This model was retained in 88.7% of bootstrap samples. To enhance the prognostic strength of the CPI, we generated a best-fit composite index of the FVC, FEV₁, and DLCO, derived against mortality in group A (n=251). This produced an almost identical variable, which provided parallel prognostic information (appendix). An analysis of potential clinical predictors of mortality including the CPI was also done in the 89 patients without imaging data, which were excluded from the study (appendix, expanded results). Only the CPI predicted mortality in this group.

We selected the CPI for threshold analysis on the basis of three observations—first, it was the strongest independent predictor of mortality in group A; second, a best fit composite of lung function derived against mortality offered no advantage in predicting outcome over the CPI (appendix); and third, the prognostic strength of the CPI was robust in subgroup analyses, including treated patients, untreated patients, smokers, non-smokers, patients with and without HRCT evidence of emphysema, and patients with and without histological confirmation of diagnosis (appendix). We only did a threshold analysis after all continuous variables had been fully explored. We identified an optimum CPI threshold of 40 units in group A (HR 4.24, p<0.0001, 95% CI 2.84–6.33, c-statistic=0.72, bootstrap corrected 95% CI 0.69–0.82; appendix).

We then did a multivariate analysis of HRCT patterns in these two subgroups (ie, CPI≤40 and CPI>40) to see whether HRCT data could be used to improve the prognostic separation provided by the CPI≤40. Again, we used a bootstrap procedure to internally validate model selection (ie, drawing 1000 random samples with replacement and selecting the model most frequently obtained among the 1000 samples). First, in patients with CPI higher than 40, no HRCT variable was predictive of mortality. Therefore, a CPI>40
was taken as indicative of a poor prognosis for staging purposes (figure 1). Second, in patients with CPI equal or lower than 40, the MPAD/AAD category and extent of fibrosis were strongly predictive of mortality on univariate analysis (HR 2.27, 95% CI 1.57–8.96, p<0.0001 for the MPAD/AAD category; HR 1.05, 1.02–1.08, p<0.0001 for extent of fibrosis). These variables were retained in 78.9% of the samples. We identified an optimum threshold of 20% for extent of fibrosis in this group using the same methods of identification and discrimination used in the primary threshold analysis (HR 3.43, 1.94–6.06, p<0.0001, c-index 0.63, bootstrap corrected 95% CI 0.57–0.72). In this patient group, an adverse prognosis was assigned on the basis of MPAD/AAD category of 1 or higher (ie, MPAD>AAD), or extent of fibrosis on HRCT higher than 20% (figure 1).

The final staging model provided a clear prognostic separation in group A (HR 5.71, 95% CI 3.20–13.32, p<0.0001, c-index 0.74, bootstrap corrected 95% CI 0.70–0.82). We confirmed goodness of fit by comparing predicted survival with the empirical Kaplan-Meier estimates (figure 2).

Both the extent of fibrosis on HRCT (HR 1.02, 95% CI 1.01–1.03, p<0.0001) and CPI (HR 1.04, 1.03–1.06, p<0.0001) were independently predictive of mortality in group B. The CPI threshold was confirmed as the optimum threshold (HR 4.24, 2.84–6.33, p<0.0001, c-index 0.70, bootstrap corrected 95% CI 0.66–0.78). Again, the sarcoid staging system provided the strongest prognostic separation of group B (HR 5.89, 2.68–10.08, p<0.0001, c-index 0.72, bootstrap corrected 95% CI 0.68–0.78). Goodness of fit was confirmed by comparing predicted survival with the empirical Kaplan-Meier estimates (figure 3).

To assess the applicability of the system in clinical practice, four observers (two radiologists and two respiratory physicians) classified all 503 patients (group A and B combined) as having a good or poor prognosis on the basis of the sarcoid staging system shown in figure 1. Interobserver agreement between radiologists and physicians was excellent (κ=0.70). The sarcoid staging system was strongly predictive for all observers with (HR 4.91–5.45; table 3).

The sarcoid staging system provided sharp prognostic discrimination in the following subgroups: treated patients, untreated patients, smokers, non-smokers, patients with and without HRCT evidence of emphysema, and patients with and without histological confirmation of diagnosis, selected from group A and group B combined (n=503, table 4).

Discussion

We describe an easily applicable staging system for patients with pulmonary sarcoidosis, integrating the CPI and two HRCT variables, which provides rapid identification of patients at high clinical risk. The staging system was derived and rigorously tested in a large cohort of patients with confirmed pulmonary sarcoidosis before being externally validated in a new patient population. Additionally, two radiologists and two respiratory physicians subsequently verified the clinical applicability of the staging system by applying it to the combined cohorts. Further, we have shown that the staging system retained its prognostic strength in patient subgroups including: treated and untreated patients, smokers and non-smokers, patients with and without HRCT evidence of emphysema, and patients with and without histological confirmation of the diagnosis of sarcoidosis (panel).

Our sarcoidosis clinic is a regional and national referral centre for patients with pulmonary sarcoidosis. A unifying feature of our population is that patients referred to our centre are not straightforward—either the referrer perceives a difficulty managing the disease, or the patient has had a significant loss of quality of life despite standard therapies. Additionally, because of increased patient involvement in management decisions, in some cases, the referral is driven by the patient. For this reason it is difficult to standardise and document the referral criteria. Recent prognostic assessment in pulmonary sarcoidosis has been largely confined to transplantation populations, which are inherently biased towards endstage disease.19 In unselected patients with sarcoidosis, mortality is arguably too low for survival analyses to be powered. By contrast, the higher mortality expected in referral centre populations,19 allows the derivation and testing of a prognostic algorithm that is anchored to survival, as in the present study. Our findings apply to the important

### Table 3: Mortality expressed as hazard ratios on univariate analysis for the entire cohort (n=503), in relation to the sarcoidosis staging model, categorised by radiologists (n=2) and physicians (n=2)

| Number | Hazard ratio | p value |
|--------|--------------|---------|
| Radiologist 1 | 5.45 (3.31–8.99) | <0.0001 |
| Radiologist 2 | 5.28 (3.26–8.53) | <0.0001 |
| Physician 1 | 5.36 (3.21–8.93) | <0.0001 |
| Physician 2 | 4.91 (3.18–8.23) | <0.0001 |

### Table 4: Mortality expressed as hazard ratios on univariate analysis for the sarcoidosis staging model in various patient subgroups within the entire cohort (group A and group B, n=503)

| Number | Hazard ratio | p value |
|--------|--------------|---------|
| Treated (intention to treat) | 328 | 6.20 (3.13–12.27) | 0.001 |
| Not treated (intention to observe) | 175 | 6.19 (2.44–16.64) | <0.0001 |
| Smoker | 122 | 3.62 (1.68–7.79) | 0.001 |
| Non smoker | 321 | 3.70 (1.55–8.80) | <0.0001 |
| Emphysema | 149 | 2.85 (1.35–8.60) | 0.006 |
| No emphysema | 354 | 10.61 (4.80–20.41) | <0.0001 |
| Biopsy | 302 | 3.89 (2.99–11.57) | <0.0001 |
| No biopsy | 201 | 7.74 (2.98–16.07) | <0.0001 |
Panel: Research in context

Systematic review

We did a PubMed search on Oct 1, 2013, using the search terms “pulmonary sarcoidosis and prognosis” for the period between Jan 1, 1990, and Oct 1, 2013. Our search was restricted to publications that were written in English. We identified 12 key publications that were pertinent to our study. All of these studies investigated different methods for predicting prognosis in pulmonary sarcoidosis and their efficacy. Additionally, several reports on the prevalence and prognostic significance of pulmonary arterial hypertension in the setting of pulmonary sarcoidosis. We could not find any study that reported on staging of patients with pulmonary sarcoidosis with integrated clinical and radiological data. Interpretation

Attempts to devise a reliable prognostic method for sarcoidosis, until now, have been largely unsuccessful and this has represented a substantial obstacle to the development of consensus management and treatment recommendations for this disease. Our study describes an easily applied and powerful staging system that identifies patients with pulmonary sarcoidosis who are at high clinical risk. This staging system was constructed with the composite physiological index and two HRCT variables in a large cohort of patients with pulmonary sarcoidosis. Two radiologists and two respiratory physicians found the system easy to use. Although this staging system was derived in a tertiary referral centre population of patients with pulmonary sarcoidosis, it was constructed with tests that are routinely done in most patients and can therefore, in principle, be applied to patients with pulmonary sarcoidosis in less selected populations. Ideally, this staging system should undergo further assessment in patients with less severe disease or at other less specialised centres.

However, as pulmonary hypertension in patients with sarcoidosis is, in most cases, a precapillary phenomenon, engorgement of the pulmonary microvasculature does not usually occur, making elevations of the DLCO unlikely. As an example, it is known that in patients with systemic sclerosis related pulmonary hypertension (which is also a precapillary phenomenon), pulmonary capillary blood volume does not increase and consequently no increase in DLCO is noted. As the CPI incorporates pulmonary function indices that capture the physiological effect of vasculopathy (DLCO) as well as those that reflect restrictive interstitial physiology (FEV1 and FVC), we formed an a priori hypothesis that the CPI would be a strong predictor of outcome in these patients. This hypothesis was tested and validated by two findings. First, a composite of lung function derived against mortality and the CPI were collinear and, second, the CPI remained a strong predictor of mortality in various patient subgroups.

In view of the importance of pulmonary arterial hypertension in determining mortality in sarcoidosis, the vascular measurement used in our study warrants examination. CT signs of pulmonary arterial hypertension have been investigated extensively in the setting of various diffuse lung diseases including idiopathic pulmonary fibrosis, but less is known about the accuracy of these signs in pulmonary sarcoidosis. The ratio of MPAD/AAD has been shown to predict pulmonary arterial hypertension in patients with interstitial lung disease more reliably than the MPAD alone. This finding has been extended to include patients with fibrotic lung disease. In our study, the MPAD/AAD category was predictive of mortality independently of all other HRCT patterns, suggesting that in sarcoidosis, the MPAD/AAD ratio might capture the prognostic effect of an underlying vasculopathy. Furthermore, visual estimates of the MPAD/AAD ratio correlate closely with electronic calliper measurements enhancing the clinical use of this finding. Although it might be, that other investigations could be included in the staging system, such as echocardiography or right heart catheterisation, a central aim of this model was to provide clinicians with a prognostic method that can be applied easily to most patients; only a few patients with pulmonary sarcoidosis undergo right heart catheterisation.

Management decisions in diffuse lung disease are often dichotomous, such as the decision to treat when disease is likely to be responsive versus the decision not to treat in inexorably progressive disease. Clinicoradiological and physiological scores and multivariate systems previously described in other diffuse lung diseases are usually continuous and for this reason might not be easily applied to these decisions. This provides the rationale for staging patients by classifying them into one of two prognostically distinct groups and is an approach already used in the setting of systemic sclerosis related interstitial lung disease. By integrating the CPI with CT data, we have devised a staging system, which captured the most deaths

subset of patients in whom pulmonary disease is more severe and often difficult to manage; in these patients, assessment of prognosis is especially valuable. The development of a staging system against mortality in a more general population with sarcoidosis with prolonged follow-up, although ideal in principle, is likely to be an unrealistic goal, requiring the recruitment of a huge population of patients with sarcoidosis outside of referral centres. Importantly, our prognostic algorithm was constructed from tests that are appropriate in the investigation of pulmonary involvement in general and can, thus, be readily applied to patients with overt pulmonary sarcoidosis in less selected populations. Outcome in pulmonary sarcoidosis is largely influenced by two separate pathological processes—interstitial fibrosis and pulmonary arterial hypertension. The latter is increasingly being recognised as relatively frequent in sarcoidosis. In unselected cohorts about 5–6% of patients with pulmonary sarcoidosis have pulmonary arterial hypertension at rest and as many as 43% of patients with normal resting pulmonary artery pressures develop pulmonary arterial hypertension during exercise. Moreover, pulmonary arterial hypertension is found in up to 47% of patients with sarcoidosis with dyspnoea out of proportion to their pulmonary function deficit. Importantly, pulmonary arterial hypertension is not confined to those with advanced fibrotic disease—about half of patients with pulmonary arterial hypertension have no radiographic evidence of fibrosis. In some cases of pulmonary hypertension, increases in the capillary blood pool might result in a normal or elevated DLCO.
when tested prospectively in a large cohort of patients with pulmonary sarcoidosis. To our knowledge, no other prognostic index in pulmonary sarcoidosis provides such a sharp separation of patients into groups with a low and high risk of mortality respectively.

The effectiveness of HRCT lies in its ability to capture patients initially classified as having a good prognosis using the CPI₄₀ threshold, and reclassifying them based on either a large main pulmonary artery (vascular disease), or presence of fibrosis (interstitial disease). It is conceivable that the CPI might be a less sensitive predictor of mortality in patients with a low DLCO (due to pulmonary arterial hypertension) but quite preserved spirometry, which explains why some patients with a poor prognosis have a low CPI. This notion highlights the important complimentary role of HRCT in the assessment of patients with pulmonary sarcoidosis.

Our study used a relatively simple approach to HRCT pattern evaluation. The choice of patterns was based on three criteria: (1) the pattern had to be frequently present and extensive enough to identify with confidence, (2) the pattern had to be readily recognisable for both non-experts and experts, and (3) the pattern had to be a plausible prognostic determinant. The prognostic effect of so-called difficult to assess patterns, is unlikely to be useful in clinical practice. For these reasons, the readily recognised patterns of ground glass opacification and fibrosis, as well as traction bronchiectasis were selected. The relatively high levels of interobserver agreement seen in the current study for these patterns vindicated these choices. It should be pointed out, that a characteristic feature of pulmonary sarcoidosis is that its HRCT presentation is very variable making it difficult to standardise its quantification on HRCT.

Patient treatment was documented at baseline and at 4 months’ follow-up and therapeutic status was analysed according to whether or not treatment was deemed warranted at presentation. This coarse distinction was necessary as the choice, timing, and duration of treatment varied widely during follow-up, and could not realistically be accounted for in the analysis. We therefore provided separate statements for two patient subgroups: intention to treat (when treatment was introduced or continued at presentation) and intention to observe, an approach, also used in the development of prognostic staging systems in the setting of systemic sclerosis. In this analysis, the staging system provided equal prognostic information regardless of whether patients were treated or observed (table 4).

Not all cases included in the study had confirmation of diagnosis by biopsy. When patients are involved in decisions on whether to biopsy, or where pulmonary impairment is too severe, the number of cases with a histological confirmation of diagnosis will necessarily be less. Furthermore, it has been argued that there is no diagnostic gold standard in sarcoidosis. The diagnosis is often made after assimilation of all data available and possible alternatives have been excluded. A strength of our study is the rigorous approach taken to patient selection when confirmation by biopsy was not available. At the outset, cases with or without a confirmed diagnosis by biopsy presented with clinical and HRCT features compatible with pulmonary sarcoidosis. Those without confirmation by biopsy were required to meet at least one more diagnostic criterion. Additionally, steps were taken to eliminate possible contamination of the population with cases of chronic hypersensitivity pneumonitis by ensuring that those with a lymphocytosis on bronchoalveolar lavage also met one of the other diagnostic criteria. We noted no survival difference between patients with confirmation by biopsy of their diagnosis and those for whom the diagnosis was based on the diagnostic criteria described above.

We used an all-cause mortality endpoint rather than attempting to analyse only patients who died directly as a result of their primary pulmonary disease. Just as intention to treat is considered the gold standard study design in treatment trials, we used the intention to prognosticate approach in the present study to maintain clinical applicability. When a staging system is applied in clinical practice, it is never known whether an individual patient might eventually die from an unrelated cause. Thus, the utility of a prognostic system in separating survivors from non-survivors must be tested against all-cause mortality. This approach has also been recommended in the setting of idiopathic pulmonary fibrosis for which all-cause mortality is regarded the most easily interpreted mortality-related endpoint in phase 3 clinical trials. Furthermore, there are inherent difficulties separating respiratory and non-respiratory deaths. A cardiac event for example, might ultimately result in death, but might be triggered by hypoxia caused by pulmonary disease. Lastly, our study was retrospective in design and drew its study population from one centre. Although we used a split sample method to validate the system, ideally it should be tested in a separate large cohort of patients with pulmonary sarcoidosis, garnered from another centre.

In conclusion, by integrating the CPI with HRCT measures of the pulmonary vasculature and interstitial disease, we propose an easily applied staging system that identifies patients at high clinical risk. This system has been rigorously assessed using internal and external validation and subsequent testing for clinical applicability by two radiologists and two physicians. In principle, this model might be used by the clinician as a simple but powerful prognostic method for risk stratification of patients in routine clinical practice and the enrolment of patients in clinical trials.

Contributors
SLFW contributed to the study design, data collection and review, and statistical analysis, and was responsible for writing, editing, and revising the report. AUW contributed to the study design, statistical analysis, and editing and revision of the report. NS scored the HRCT images. LC contributed to data collection. GJK, KMA, SJMc, and AD were responsible for testing the staging systems clinical applicability. TMM and ER were...
responsible for supplying patient data for the study and editing the report. AGN was responsible for histopathological analysis and participated in editing the report. DMH was the coordinator of the study, contributed to study design, scored the HRCT images and contributed to the editing and revision of the report.

Conflicts of interest
We declare that we have no conflicts of interest.

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