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Risk Indicators of Sarcoidosis Evolution-Unified Protocol (RISE-UP): protocol for a multi-centre, longitudinal, observational study to identify clinical features that are predictive of sarcoidosis progression

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ABSTRACT

Introduction Sarcoidosis is a pulmonary and systemic granulomatous disease with a wide range of potential outcomes, from spontaneous resolution to end-stage organ damage and death. Currently, clinicians have no easy-to-use risk stratification tools for important clinical outcomes in sarcoidosis, such as progressive lung disease. This study will address two clinical practice needs: (1) development of a risk calculator that provides an estimate of the likelihood of pulmonary progression in sarcoidosis patients during the follow-up period and (2) determine the optimal interval for serial clinical monitoring (eg, 6, 12, 18 months) using these risk prediction tools.

Methods and analysis The Risk Indicators of Sarcoidosis Evolution-Unified Protocol study is a National Institutes of Health-sponsored, longitudinal observational study of adults with pulmonary sarcoidosis who will be enrolled at five US tertiary care centres. Participants will be evaluated at approximately 6-month intervals for up to 60 months with collection of lung function, blood samples and clinical data. The target sample size is 557 and the primary objective is to determine which clinical features measured during a routine clinic visit carry the most prognostic information for predicting clinical progression of pulmonary sarcoidosis over the follow-up period. The primary outcome measure will be quantified by a clinically meaningful change in forced vital capacity, forced expiratory volume in 1 s or diffusing capacity of the lung for carbon monoxide. The secondary objective is to determine if blood biomarkers measured during a routine clinic visit can improve the risk assessment modelling for progression of pulmonary sarcoidosis over the follow-up period.

Ethics and dissemination The study protocol has been approved by the Institutional Review Boards at each centre and the reliance Institutional Review Board overseeing the study (WCG, Protocol #20222400). Participants will provide informed consent prior to enrolment. Results will be disseminated via publication in a relevant peer-reviewed journal.

Trial registration number NCT05567133.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ One of the largest, concerted efforts to develop a risk calculator for sarcoidosis outcomes in the USA.
⇒ Incorporation of biomarker discovery to test novel blood-based targets that could be developed for clinical practice.
⇒ Development and testing of composite clinical outcomes in sarcoidosis that mirror clinical decision-making in outpatient practice.
⇒ A potential limitation to external generalisability is the enrolment of patients through tertiary care centres.

INTRODUCTION

A major obstacle for clinicians who care for patients with sarcoidosis is the lack of reliable prognostic tools to inform clinical care decisions about which patients will have progressive disease that will require medical intervention. Because of the lack of prognostic tools, there are different approaches for managing patients. For example, some providers initiate systemic immune suppression early after diagnosis, even though the severity of inflammation may not warrant treatment. Others may wait to initiate immune suppression given the possibility of spontaneous resolution in many patients or the concern about increasing medical complications in patients with pre-existing conditions like diabetes, obesity and chronic infections. This approach of initiating treatment later in the course of disease may be reinforced given the increasing evidence that show that immunosuppressed individuals carry the highest risk for severe disease after COVID-19 infection.[1] Both of these

treatment strategies, starting early versus late, carry real negative consequences. On one hand, treating a patient who does not need treatment exposes them to potential drug toxicities with no actual benefit. On the other hand, waiting to see if treatment is necessary for someone who will need treatment could lead to organ damage that may not be fully reversible. In whom and when to initiate systemic immune suppression are only two of the major clinical practice problems that would greatly benefit from improved risk stratification tools, but there are many others as well (eg, determining the optimal interval for longitudinal testing and clinical follow-up, and improved power in clinical trials by enrolment of 'high risk' patients are two additional clinical practice problems).

The lack of prognostic tools is not due to a lack of scientific effort to discover them. On this point, there have been innumerable clinical studies focusing on the identification of risk factors and biomarkers for severe disease and mortality (reviewed in the References section[2–21]). A major barrier to translation of these discoveries to the clinics lies in the paucity of long-term follow-up studies that are designed to test the power or accuracy of these risk factors to predict future clinical outcomes. The Risk Indicators of Sarcoidosis Evolution-Unified Protocol (RISE-UP) study was designed to address the unmet need of risk assessment tools in the clinical practice of pulmonary sarcoidosis by organising five independent cohorts of sarcoidosis patients that represent geographic and racial diversity in the USA to develop and test prediction models for pulmonary outcomes. Ultimately, improved longitudinal care depends on better prognostication of the types of outcomes currently used in the outpatient clinics across our hospital systems.

METHODS AND ANALYSIS
Study design
The study is an observational longitudinal study that will enrol and monitor adults with pulmonary sarcoidosis at five academic universities with established clinical centres in sarcoidosis care and research: UT Southwestern Medical Center in Dallas, Texas, Vanderbilt University Medical Center in Nashville, Tennessee, Wayne State University in Detroit, Michigan, University of Maryland in Baltimore, Maryland and University of California, San Francisco (UCSF) in San Francisco, California. The total target sample size is 557 with enrolment across all sites

Table 1 Proposed sample size, stratified by clinical centre

Clinical centre	Target sample size
University of California, San Francisco	136
UT Southwestern	100
Vanderbilt	100
Wayne State	121
University of Maryland	100

(table 1). The study proposal was reviewed by the Center for Scientific Review at the National Institutes of Health in October of 2021 and was funded in April 2022. Longitudinal follow-up visits are anticipated to be completed by January 2026. Some cohorts had completed prospective enrolment at the time of federal funding and so the National Clinical Trial registry information specifies the remaining study population to be enrolled.

Eligibility criteria
Adults diagnosed with pulmonary sarcoidosis according to criteria endorsed by the American Thoracic Society (ATS) are eligible for this study.[22] Because the goal of this study is to develop prediction tools that can be translated to clinical care, the eligibility criteria were intentionally broad to mimic the population of patients evaluated in the US clinics. For example, concurrent use of immunosuppressive therapy is allowed given the prevalence of treatment in this patient population. Additional eligibility criteria for enrolment are presented in box 1.

Study procedures and data collection
The Standard Operating Procedures (SOP) manual for the RISE-UP study details the protocols for performing the clinical procedures and data collection methods. A list of procedures to be performed at study visits are presented in box 2. Deidentified clinical data will be entered and stored in a UCSF-hosted REDCap database (https://www. project-redcap.org) that was created for the RISE-UP study. Data instruments include demographic information, organ involvement using a modified organ assessment tool,[23] medical history, social history, medications, questionnaire responses, pulmonary function measurements, complete blood counts and details related to the blood biospecimen collection. Each centre will follow recommended ATS/European Respiratory Society guidelines for test performance for spirometry[24] and diffusing capacity of lung for carbon monoxide (DLCO).[25] Blood samples will be processed for serum using methods and collection tubes detailed in the SOP. The clinical data will be included as predictor variables in the statistical modelling.

Sample assays
Sera will be used to measure clinically and non-clinically available protein markers. For clinically available protein markers, we will include markers that have been associated with disease chronicity, ^{18}F-fluorodeoxyglucose-avidity on positron emission tomography scan, organ number and severity of sarcoidosis chest X-ray stage and lung function values (eg, lymphocyte count, soluble interleukin 2 (IL-2) receptor, lysozyme, vitamin D isoforms, C reactive protein (CRP).[26–38] For non-clinically available protein markers, we will include interferon-inducible chemokines that have been associated with a shorter time-to-decline in lung function in patients with pulmonary sarcoidosis (eg, CXCL10, CXCL11) or a greater number of organ involvement in patients with systemic

Box 1   Inclusion and exclusion criteria

Inclusion criteria

A histopathological diagnosis of sarcoidosis according to the American Thoracic Society/European Respiratory Society sarcoidosis statement with the exception of Lofgren's syndrome which are exempt from a pathological diagnosis.

Any chest X-ray scadding stage (chest X-ray stage 0 would require lung or thoracic lymph node biopsy confirming granulomatous inflammation to confirm thoracic involvement of inflammation).

Exclusion criteria

Inability to tolerate study procedures as determined by the PI.

Pregnant or breast feeding.

Concurrent medical diagnoses that would influence the expression of biomarkers will be considered an exclusion criterion. This includes diseases such as common variable immunodeficiency, present or history of malignancy, HIV infection or autoimmune diseases.

Concurrent interstitial lung diseases such as hypersensitivity pneumonitis or idiopathic pulmonary fibrosis.

Haematocrit (packed cell volume) <25%.

sarcoidosis (CXCL9).[39 40] The blood marker measurements will be included as predictor variables in the statistical modelling.

Outcomes

The primary outcome will use a binary classification for a clinically meaningful decline in lung function defined by a ≥10% fall in absolute forced vital capacity (FVC) or forced expiratory volume in 1 s (FEV1) or a ≥15% fall in absolute DLCO between two consecutive study visits occurring between enrolment and the last follow-up visit for each participant. We used lung function decline thresholds that have precedent in the interstitial lung disease literature.[41–43] This lung function outcome was chosen because it is an objective measurement used in pulmonary clinics as a non-invasive way of monitoring progressive pulmonary disease.[22] Significant declines in lung function can be one of the clinical triggers to initiate long-term immunosuppression therapy.

Box 2   List of visit procedures and forms

Study procedures and forms

Informed consent/assent.

Collection of demographic information.

Collection of medical and social history.

Symptom questionnaires.

Review of medical history by study physician.

Blood draw.

Height and weight.

Spirometry.

Diffusing capacity.

Completion of clinical and organ assessment by study physician.

Collection of results from any chest imaging performed as part of clinical care.

Clinical and laboratory predictors

We propose to examine the following clinical predictors in the models: age, sex, race, smoking history (pack-years), CXR stage 0–4, lung function (FVC%, FEV1%, DLCO%), sarcoidosis severity scores, number and type of organ involvement, months since biopsy (duration of sarcoid), use of immune-suppressant medications, comorbid illnesses (such as asthma, Chronic Obstructive Pulmonary Disease, pulmonary hypertension, heart failure or diabetes), education level and access to medical insurance. Many of these variables have been associated with disease severity or chronicity and therefore, could be risk factors for progressive lung disease. We propose to also examine the following laboratory measures as predictors in the models: soluble IL-2 receptor, lysozyme, vitamin D isoforms (25-OH vitamin D and 1,25-DOH vitamin D), CRP, and WBC and per cent of lymphocytes, serum CXCL10 and CXCL11, and RNA transcripts CXCL9, and CD28, ITK and LEF1. These measures may reflect sarcoidal inflammation and may contribute additional prognostic information to the models.

Data management

The data analyst will perform data validation in accordance with the study-wide SOP specifications. Quarterly data check programmes will be run to identify discrepancies in entered data. Study sites will be notified about data discrepancies and subsequent query resolution will be performed. Discrepancies to be flagged will include inconsistent data, missing data, range checks and deviations from the protocol. There will be a final data validation check of the study-wide dataset and the database will be locked after approval from all investigators.

Statistical analysis plan

The primary objective is to build a model consisting of the most prognostic *clinical* predictors. To accomplish this objective, we will implement Least Absolute Shrinkage and Selection Operator (LASSO)-penalised Cox proportional hazards regression analysis on the set of all clinical predictors listed above. We will optimise the LASSO tuning parameter, λ, using 10-fold cross-validation to choose the tuning parameter with the smallest cross-validation error. The resulting covariates with non-zero coefficient estimates represent the covariates to be included in the *clinical* prediction model. Next, we will add the set of *laboratory* predictors listed above to the already identified clinical model by use of double-LASSO methods.[44] Our modelling approach will mimic the use of the prediction model in the clinic setting which would get updated with new clinical data each time there was a clinic visit. Specifically, we will include data from multiple visits for each subject in the Cox analysis and use robust standard errors to account for the intra-subject correlation. We will perform model checking by assessing whether proportional hazards assumptions hold using the Schoenfeld residuals method and if not, stratify on covariates as appropriate.[45] Internal model validation will

be accomplished by bootstrapping as recommended by Steyerberg.[46] We will perform a temporal validation using the data collected at the end of study period and refit all data to the final models. For both internal and temporal validation, we will examine metrics appropriate to survival models for discrimination (eg, Harrell's c-statistic, time-varying area under the Receiver Operating Characteristic curve (AUC)[47]) and calibration (eg, graphical calibration plots and the integrated calibration index[48]).

Power analysis and sample size

For sample size considerations, we follow the recent recommendations of the TRIPOD author group,[49] which for a target AUC, number of model predictors and outcome prevalence, computes a minimum sample size needed to achieve (1) acceptably low overfitting of model coefficients, (2) acceptably low optimism in model discrimination indices and (3) high precision in predicted risk levels. With an anticipated c-statistic of 0.8 and an outcome prevalence of ~30% our sample size is more than adequate to fit prognostic models with at least 15 predictors. We will gain additional power through inclusion of multiple events per subject as described above.

Patient and public involvement

The study design was motivated by clinical experience and expert opinion reports that emphasise the need for better prognostication tools. Patients and the public have not been involved in the study design.

ETHICS AND DISSEMINATION

This multi-centre study is being conducted in accordance with globally accepted standards of good practice, in agreement with the Declaration of Helsinki and with local regulations. The study protocol has been approved by the Institutional Review Boards at each centre and by the single reliance Institutional Review Board overseeing the study (WCG, Protocol #20222400). Eligible participants will provide informed consent prior to enrolment. The study's findings will be published in a relevant peer-reviewed journal. Additional dissemination of results will occur at national and international conferences, newsletters to research participants, patient advocacy organisations and through the study website.

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REFERENCES

1 Agrawal U, Bedston S, McCowan C, *et al*. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in england, northern ireland, scotland, and wales. *Lancet* 2022;400:1305–20.
2 Baughman RP, Wells A. Advanced sarcoidosis. *Curr Opin Pulm Med* 2019;25:497–504.
3 Kraaijvanger R, Janssen Bonás M, Vorselaars ADM, *et al*. Biomarkers in the diagnosis and prognosis of sarcoidosis: current use and future prospects. *Front Immunol* 2020;11:1443.
4 Chopra A, Kalkanis A, Judson MA. Biomarkers in sarcoidosis. *Expert Rev Clin Immunol* 2016;12:1191–208.
5 Bonham CA. Biomarkers in sarcoidosis: can microRNAs fill the gap? *Am J Respir Cell Mol Biol* 2018;58:1–2.
6 Umei M, Akazawa H. MicroRNAs as biomarkers for cardiac sarcoidosis: no matter how small. *J Cardiol* 2018;72:449–51.
7 Ramos-Casals M, Retamozo S, Sisó-Almirall A, *et al*. Clinically-useful serum biomarkers for diagnosis and prognosis of sarcoidosis. *Expert Rev Clin Immunol* 2019;15:391–405.
8 Bagnato F, Stern BJ. Neurosarcoidosis: diagnosis, therapy and biomarkers. *Expert Rev Neurother* 2015;15:533–48.
9 Carleo A, Bennett D, Rottoli P. Biomarkers in sarcoidosis: the contribution of system biology. *Curr Opin Pulm Med* 2016;22:509–14.
10 Casanova N, Zhou T, Knox KS, *et al*. Identifying novel biomarkers in sarcoidosis using genome-based approaches. *Clin Chest Med* 2015;36:621–30.
11 Arger NK, O'Connor B, Koth LL. Molecular profiling in sarcoidosis. *Curr Opin Pulm Med* 2020;26:562–7.
12 Tarasidis A, Arce S. Immune response biomarkers as indicators of sarcoidosis presence, prognosis, and possible treatment: an immunopathogenic perspective. *Autoimmun Rev* 2020;19:102462.
13 Terrington DL, Hayton C, Peel A, *et al*. The role of measuring exhaled breath biomarkers in sarcoidosis: a systematic review. *J Breath Res* 2019;13:036015.
14 Taibi L, Boursier C, Clodic G, *et al*. Search for biomarkers of neurosarcoidosis by proteomic analysis of cerebrospinal fluid. *Ann Biol Clin (Paris)* 2017;75:393–402.
15 Patel DC, Valeyre D. Advanced pulmonary sarcoidosis. *Curr Opin Pulm Med* 2020;26:574–81.
16 Nagai S, Handa T, Ito Y, *et al*. Outcome of sarcoidosis. *Clin Chest Med* 2008;29:565–74,
17 Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. *Chest* 2003;124:922–8.

18 Spagnolo P, Rossi G, Trisolini R, *et al*. Pulmonary sarcoidosis. *Lancet Respir Med* 2018;6:389–402.

19 Trivieri MG, Spagnolo P, Birnie D, *et al*. Challenges in cardiac and pulmonary sarcoidosis: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;76:1878–901.

20 Gerke AK. Morbidity and mortality in sarcoidosis. *Curr Opin Pulm Med* 2014;20:472–8.

21 Kouranos V, Jacob J, Wells AU. Severe sarcoidosis. *Clin Chest Med* 2015;36:715–26.

22 Hunninghake GW, Costabel U, Ando M, *et al*. ATS/ERS/WASOG statement on sarcoidosis. American thoracic society/european respiratory society/world association of sarcoidosis and other granulomatous disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;16:149–73.

23 Judson MA, Costabel U, Drent M, *et al*. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;31:19–27.

24 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.

25 Graham BL, Brusasco V, Burgos F, *et al*. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J* 2017;49:00016–2016.

26 Kiani A, Abedini A, Adcock IM, *et al*. Association between vitamin D deficiencies in sarcoidosis with disease activity, course of disease and stages of lung involvements. *J Med Biochem* 2018;37:103–9.

27 Selroos O, Koivunen E. Prognostic significance of lymphopenia in sarcoidosis. *Acta Med Scand* 1979;206:259–62.

28 Vagts C, Ascoli C, Fraidenburg DR, *et al*. Unsupervised clustering reveals sarcoidosis phenotypes marked by a reduction in lymphocytes relate to increased inflammatory activity on 18FDG-PET/CT. *Front Med (Lausanne)* 2021;8:595077.

29 Zhou Y, Zhang Y, Zhao M, *et al*. SIL-2R levels predict the spontaneous remission in sarcoidosis. *Respir Med* 2020;171:106115.

30 Grutters JC, Fellrath J-M, Mulder L, *et al*. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. *Chest* 2003;124:186–95.

31 Uysal P, Durmus S, Sozer V, *et al*. Ykl-40, soluble IL-2 receptor, angiotensin converting enzyme and C-reactive protein: comparison of markers of sarcoidosis activity. *Biomolecules* 2018;8:84.

32 Miyoshi S, Hamada H, Kadowaki T, *et al*. Comparative evaluation of serum markers in pulmonary sarcoidosis. *Chest* 2010;137:1391–7.

33 Ogata-Suetsugu S, Hamada N, Takayama K, *et al*. The clinical value of serum soluble interleukin-2 receptor in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2017;34:41–7.

34 Bargagli E, Bianchi N, Margollicci M, *et al*. Chitotriosidase and soluble IL-2 receptor: comparison of two markers of sarcoidosis severity. *Scand J Clin Lab Invest* 2008;68:479–83.

35 Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PGH, *et al*. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003;49:1510–7.

36 Tomita H, Sato S, Matsuda R, *et al*. Serum lysozyme levels and clinical features of sarcoidosis. *Lung* 1999;177:161–7.

37 Kavathia D, Buckley JD, Rao D, *et al*. Elevated 1, 25-dihydroxyvitamin D levels are associated with protracted treatment in sarcoidosis. *Respir Med* 2010;104:564–70.

38 McDonnell MJ, Saleem MI, Wall D, *et al*. Predictive value of C-reactive protein and clinically relevant baseline variables in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2016;33:331–40.

39 Arger NK, Ho M, Woodruff PG, *et al*. Serum CXCL11 correlates with pulmonary outcomes and disease burden in sarcoidosis. *Respir Med* 2019;152:89–96.

40 Arger NK, Ho ME, Allen IE, *et al*. CXCL9 and CXCL10 are differentially associated with systemic organ involvement and pulmonary disease severity in sarcoidosis. *Respir Med* 2020;161:105822.

41 Collard HR, King TE, Bartelson BB, *et al*. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:538–42.

42 Khanna D, Mittoo S, Aggarwal R, *et al*. Connective tissue disease-associated interstitial lung diseases (CTD-ILD)-report from OMERACT CTD-ILD Working group. *J Rheumatol* 2015;42:2168–71.

43 Judson MA, Baughman RP, Thompson BW, *et al*. Two year prognosis of sarcoidosis: the ACCESS experience. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:204–11.

44 Belloni A, Chernozhukov V, Hansen C. Inference on treatment effects after selection among high-dimensional controls. *The Review of Economic Studies* 2014;81:608–50.

45 Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika* 1982;69:239–41.

46 EW S. *Clinical prediction models A practical approach to development, validation, and updating*. 2019.

47 Blanche P, Latouche A, Viallon V. Time-dependent AUC with right-censored data:a survey. In: *Risk Assessment and Evaluation of Predictions*. 2013.

48 Austin PC, Harrell FE Jr, van Klaveren D. Graphical calibration curves and the integrated calibration index (ICI) for survival models. *Stat Med* 2020;39:2714–42.

49 Riley RD, Ensor J, Snell KIE, *et al*. Calculating the sample size required for developing a clinical prediction model. *BMJ* 2020;368:m441.