Sarcoidosis NEWS™
A BIONEWS™ BRAND

4 blood markers may predict outcomes in pulmonary sarcoidosis

Combined, metabolites nearly perfectly ID'd patients with disease progression

by Michela Luciano, PhD | September 2, 2025

Four blood metabolites, or intermediate or end products of the body's metabolism, could serve as noninvasive biomarkers to monitor or predict disease outcomes in people with pulmonary sarcoidosis — in which the lungs are primarily affected by this rare inflammatory disease — according to the results of a new study from researchers in China.

These molecules, namely, uric acid, testosterone sulfate, allopregnanolone sulfate, and 24,25-dihydroxyvitamin D3 (24R,25(OH)2D3), were significantly lower in the blood of patients whose disease worsened compared with those who recovered, the data showed.

Moreover, the researchers noted, when combined, the four metabolites could nearly perfectly discriminate between patients whose disease progressed and those whose did not.

"Beyond aiding in diagnosis, these metabolic markers may serve as indicators for monitoring disease progression and evaluating treatment response," the team wrote.

The study, "Serum metabolomics in pulmonary sarcoidosis: metabolic signatures across prognoses," was published in the journal *BMC Pulmonary Medicine*.

In sarcoidosis, an overly reactive immune system forms granulomas, or clusters of inflammatory immune cells, within various organs, causing symptoms. When the disease mainly affects the lungs, it is called pulmonary sarcoidosis, and is marked by persistent cough, chest pain, and shortness of breath.

"While some patients experience spontaneous resolution or respond well to treatment, others progress to chronic or [scarring] stages despite receiving [bodywide] corticosteroid therapy," the researchers wrote, noting that progression "often [results] in irreversible lung damage and significantly reduced quality of life."

A major gap in sarcoidosis care is the absence of simple, noninvasive biomarkers to predict disease progression, according to the team. Without these tools, treatment choices often depend on clinician experience instead of solid evidence, which can result in unnecessary treatments or missed opportunities for early intervention.

Seeking new biomarkers to aid diagnosis, guide treatment

Metabolomics, the study of all metabolites in an organism, cells, or bodily fluid, provides a way to identify disease-specific changes that could represent new biomarkers. Such biomarkers could then help to improve diagnosis, track progression, and guide treatment in pulmonary sarcoidosis.

Yet, the researchers wrote, "most earlier studies have been limited by narrow metabolite coverage and a lack of in-depth exploration of disease [variability] or prognostic stratification."

Now, a research team from institutions in Shanghai sought to find biomarkers linked to disease progression in pulmonary sarcoidosis. To that end, the team compared blood metabolomic profiles from 29 patients with those from 10 healthy individuals. All were enrolled at Shanghai Pulmonary Hospital between September 2021 and November 2024.

The patients had been followed for a mean of 18.45 months, or about 1.5 years. Those on corticosteroids, standard anti-inflammatory medications, in the six months prior to the study were excluded.

The patient group was mostly comprised of women (75.9%) and had a mean age of 50.41. It was then divided by outcome into a self-healing group (11 patients) and a progressive group (18 patients). The self-healing group saw their disease significantly eased or completely resolved without corticosteroid treatment over follow-up. The progressive group comprised those whose disease required corticosteroids or worsened with or without corticosteroids.

The two groups had similar levels of several blood markers commonly used to monitor disease activity, such as immune T-cells, immune signal molecules, and antibodies. In contrast, blood levels of KL-6, a protein released by damaged lung cells, were significantly higher in the progressive group.

More than 200 metabolites altered in pulmonary sarcoidosis patients

Blood metabolomic profiling showed that levels of 209 metabolites were altered in people with pulmonary sarcoidosis relative to healthy volunteers. Altogether, 10 were found at higher levels and 199 at lower levels.

Most of these metabolites were related to how the body processes amino acids, which are proteins' building blocks. Some were involved in the metabolism of fatty molecules (lipids) and in immune response pathways.

When patients were grouped by outcome, 25 metabolites, most of which were lipids, clearly differentiated self-healing cases from progressive cases. Eight were found at higher levels, and 17 were found at lower levels, in those with progressive disease.

Drawing from differences observed both between patients and healthy individuals, as well as between patients with self-healing and progressive disease, the researchers identified four key metabolites: uric acid, testosterone sulfate, allopregnanolone sulfate, and 24R,25(OH)2D3.

Uric acid is a normal waste product that results from the breakdown of DNA and RNA building blocks, and 24R,25(OH)2D3 is a vitamin D metabolite. Testosterone sulfate is the metabolite of testosterone, the main male sex hormone, while allopregnanolone sulfate is a metabolite of progesterone, a female sex hormone.

These metabolites were reduced in patients relative to healthy people, and in patients who progressed compared with those who healed without corticosteroids.

The team then assessed their potential to distinguish patients who progressed from those who did not.

The identified metabolic signatures closely reflect the prognostic differences between progressive and self-healing cases.

Tested individually, each of the four metabolites showed good discriminative ability, with an accuracy ranging between 81.8% and 89.9%. When combined, the discriminative potential increased to 97.5%.

"The identified metabolic signatures closely reflect the prognostic differences between progressive and self-healing cases," the team wrote.

Each metabolite also linked to disease activity measures

Each of these four metabolites also showed clear links to blood biomarkers of disease activity. Lower uric acid was associated with more lung injury and active inflammation, reflected by higher KL-6 and CD8 T-cells, a T-cell subtype linked to tissue damage.

Higher levels of testosterone sulfate and allopregnanolone sulfate were linked to increased IL-2, the immune signal that activates T-cells, and an antibody pattern indicating longer-lasting immune responses. Similarly, rising levels of 24R,25(OH)2D3 were associated with a prolonged antibody-based immune response.

These findings emphasize “the potential of [blood] metabolomics as a valuable tool in the clinical management of sarcoidosis,” and “offer a foundation for future research into personalized treatment and management strategies,” the researchers wrote.

About the Author

Michela Luciano, PhD Michela Luciano is a Science Writer at BioNews. Originally from the picturesque mountain town of L’Aquila, Italy, Michela holds a PhD in Molecular Biology from the University of Salzburg, where her research focused on the role of inflammation in acute myeloid leukemia. With a deep passion for scientific communication, Michela transitioned into her first role as Scientific Writer in 2022. Outside of work she enjoys street photography, mountain hikes, running, and spending as much time as possible outdoors.

UNLIZENSIERTE ÜBERSETZUNG FÜR UNSERE LESENDEN:

4 Blutmarker können den Verlauf der pulmonalen Sarkoidose vorhersagen

Kombiniert konnten die Metaboliten Patienten mit Krankheitsprogression nahezu perfekt identifizieren

von Michela Luciano, PhD | 2. September 2025

Vier Blutmetaboliten, also Zwischen- oder Endprodukte des Stoffwechsels, könnten laut den Ergebnissen einer neuen Studie von Forschern aus China als nicht-invasive Biomarker zur Überwachung oder Vorhersage des Krankheitsverlaufs bei Menschen mit pulmonaler Sarkoidose dienen – einer seltenen Entzündungskrankheit, die vor allem die Lunge befällt.

Diese Moleküle, nämlich Harnsäure, Testosteronsulfat, Allopregnanolonsulfat und 24,25-Dihydroxyvitamin D3 (24R,25(OH)2D3), waren im Blut von Patienten, deren Krankheit sich verschlimmerte, im Vergleich zu denen, die sich erholten, signifikant niedriger, wie die Daten zeigten.

Darüber hinaus stellten die Forscher fest, dass die vier Metaboliten in Kombination nahezu perfekt zwischen Patienten mit fortschreitender Erkrankung und solchen ohne Fortschreiten unterscheiden konnten.

„Über die Unterstützung bei der Diagnose hinaus können diese Stoffwechselmarker als Indikatoren für die Überwachung des Krankheitsverlaufs und die Bewertung des Ansprechens auf die Behandlung dienen“, schrieb das Team.

Die Studie „Serummetabolomik bei pulmonaler Sarkoidose: metabolische Signaturen über Prognosen hinweg“ wurde in der Fachzeitschrift BMC Pulmonary Medicine veröffentlicht.

Bei der Sarkoidose bildet ein übermäßig reaktives Immunsystem Granulome, also Ansammlungen von entzündlichen Immunzellen, in verschiedenen Organen, was zu Symptomen führt. Wenn die Erkrankung hauptsächlich die Lunge betrifft, spricht man von pulmonaler Sarkoidose, die durch anhaltenden Husten, Brustschmerzen und Atemnot gekennzeichnet ist.

„Während bei einigen Patienten eine spontane Heilung eintritt oder sie gut auf die Behandlung ansprechen, entwickeln andere trotz einer [körperweiten] Kortikosteroidtherapie ein chronisches Stadium oder [Vernarbungen]“, schrieben die Forscher und wiesen darauf hin, dass das Fortschreiten der Krankheit „oft zu irreversiblen Lungenschäden und einer erheblich verminderten Lebensqualität führt“.

Eine große Lücke in der Sarkoidose-Behandlung ist laut dem Team das Fehlen einfacher, nicht-invasiver Biomarker zur Vorhersage des Krankheitsverlaufs. Ohne diese Hilfsmittel hängen die Behandlungsentscheidungen oft von der Erfahrung des Arztes statt von soliden Beweisen ab, was zu unnötigen Behandlungen oder verpassten Chancen für eine frühzeitige Intervention führen kann.

Suche nach neuen Biomarkern zur Unterstützung der Diagnose und als Leitfaden für die Behandlung

Die Metabolomik, die Untersuchung aller Metaboliten in einem Organismus, in Zellen oder Körperflüssigkeiten, bietet eine Möglichkeit, krankheitsspezifische Veränderungen zu identifizieren, die neue Biomarker darstellen könnten. Solche Biomarker könnten dann dazu beitragen, die Diagnose zu verbessern, den Krankheitsverlauf zu verfolgen und die Behandlung der pulmonalen Sarkoidose zu steuern.

Die Forscher schrieben jedoch: „Die meisten früheren Studien waren durch eine begrenzte Abdeckung der Metaboliten und eine mangelnde eingehende Untersuchung der Krankheitsvariabilität oder der prognostischen Stratifizierung eingeschränkt."

Nun versuchte ein Forschungsteam aus Shanghai, Biomarker zu finden, die mit dem Krankheitsverlauf bei pulmonaler Sarkoidose in Verbindung stehen. Zu diesem Zweck verglich das Team die Blutmetabolomprofile von 29 Patienten mit denen von 10 gesunden Personen. Alle wurden zwischen September 2021 und November 2024 im Shanghai Pulmonary Hospital aufgenommen.

Die Patienten wurden durchschnittlich 18,45 Monate lang, also etwa 1,5 Jahre, beobachtet. Diejenigen, die in den sechs Monaten vor der Studie Kortikosteroide, also Standard-Entzündungshemmer, eingenommen hatten, wurden ausgeschlossen.

Die Patientengruppe bestand überwiegend aus Frauen (75,9 %) und hatte ein Durchschnittsalter von 50,41 Jahren. Sie wurde dann nach dem Ergebnis in eine Selbstheilungsgruppe (11 Patienten) und eine progressive Gruppe (18 Patienten) unterteilt. Bei der Selbstheilungsgruppe kam es während der Nachbeobachtungszeit zu einer signifikanten Linderung oder vollständigen Heilung der Erkrankung ohne Kortikosteroidbehandlung. Die progressive Gruppe umfasste diejenigen, deren Erkrankung eine Behandlung mit Kortikosteroiden erforderte oder sich mit oder ohne Kortikosteroide verschlimmerte.

Die beiden Gruppen wiesen ähnliche Werte für mehrere Blutmarker auf, die üblicherweise zur Überwachung der Krankheitsaktivität verwendet werden, wie z. B. Immun-T-Zellen, Immunsignalmoleküle und Antikörper. Im Gegensatz dazu waren die Blutwerte von KL-6, einem Protein, das von geschädigten Lungenzellen freigesetzt wird, in der progressiven Gruppe signifikant höher.

Mehr als 200 veränderte Metaboliten bei Patienten mit pulmonaler Sarkoidose

Die Blutmetabolomik-Profilierung zeigte, dass die Werte von 209 Metaboliten bei Menschen mit pulmonaler Sarkoidose im Vergleich zu gesunden Probanden verändert waren. Insgesamt wurden 10 Metaboliten mit höheren Werten und 199 mit niedrigeren Werten gefunden.

Die meisten dieser Metaboliten standen im Zusammenhang mit der Verarbeitung von Aminosäuren, den Bausteinen von Proteinen, durch den Körper. Einige waren am Stoffwechsel von Fettmolekülen (Lipiden) und an Immunreaktionswegen beteiligt.

Als die Patienten nach ihrem Krankheitsverlauf in Gruppen eingeteilt wurden, unterschieden 25 Metaboliten, von denen die meisten Lipide waren, eindeutig zwischen selbstheilenden und progressiven Fällen. Bei den Patienten mit progressiver Erkrankung wurden acht Metaboliten in höheren Konzentrationen und 17 in niedrigeren Konzentrationen gefunden.

Ausgehend von den Unterschieden, die sowohl zwischen Patienten und gesunden Personen als auch zwischen Patienten mit Selbstheilung und fortschreitender Erkrankung beobachtet wurden, identifizierten die Forscher vier wichtige Metaboliten: Harnsäure, Testosteronsulfat, Allopregnanolonsulfat und 24R,25(OH)2D3.

Harnsäure ist ein normales Abfallprodukt, das beim Abbau von DNA- und RNA-Bausteinen entsteht, und 24R,25(OH)2D3 ist ein Vitamin-D-Metabolit. Testosteronsulfat ist der Metabolit von Testosteron, dem wichtigsten männlichen Sexualhormon, während Allopregnanolonsulfat ein Metabolit von Progesteron, einem weiblichen Sexualhormon, ist.

Diese Metaboliten waren bei Patienten im Vergleich zu gesunden Menschen und bei Patienten, deren Erkrankung fortschritt, im Vergleich zu denen, die ohne Kortikosteroide geheilt waren, reduziert.

Das Team bewertete dann ihr Potenzial, Patienten, deren Erkrankung fortschritt, von denen zu unterscheiden, bei denen dies nicht der Fall war.

Die identifizierten metabolischen Signaturen spiegeln die prognostischen Unterschiede zwischen fortschreitenden und selbstheilenden Fällen genau wider.

Bei individueller Untersuchung zeigte jeder der vier Metaboliten eine gute Unterscheidungsfähigkeit mit einer Genauigkeit zwischen 81,8 % und 89,9 %. In Kombination stieg das Unterscheidungspotenzial auf 97,5 %.

„Die identifizierten metabolischen Signaturen spiegeln die prognostischen Unterschiede zwischen progressiven und selbstheilenden Fällen genau wider“, schrieb das Team.

Jeder Metabolit stand auch in Zusammenhang mit Messungen der Krankheitsaktivität

Jeder dieser vier Metaboliten zeigte auch einen klaren Zusammenhang mit Blutbiomarkern für die Krankheitsaktivität. Ein niedrigerer Harnsäurespiegel war mit einer stärkeren Schädigung der Lunge und einer aktiven Entzündung verbunden, was sich in höheren KL-6- und CD8-T-Zellen widerspiegelte, einem T-Zell-Subtyp, der mit Gewebeschäden in Verbindung steht.

Höhere Spiegel von Testosteronsulfat und Allopregnanolonsulfat standen im Zusammenhang mit einem Anstieg von IL-2, dem Immunsignal, das T-Zellen aktiviert, und einem Antikörpermuster, das auf länger anhaltende Immunreaktionen hindeutet. In ähnlicher Weise war ein Anstieg der 24R,25(OH)2D3-Spiegel mit einer verlängerten antikörperbasierten Immunantwort verbunden.

Diese Ergebnisse unterstreichen „das Potenzial der [Blut-]Metabolomik als wertvolles Instrument für die klinische Behandlung von Sarkoidose“ und „bieten eine Grundlage für zukünftige Forschungen zu personalisierten Behandlungs- und Managementstrategien“, schrieben die Forscher.

Der Originalartikel: https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-025-03863-y

BMC Pulmonary Medicine

RESEARCH

Open Access

Serum metabolomics in pulmonary sarcoidosis: metabolic signatures across prognoses

Dafu Zhu[1†], Jianglong Chen[2†], Li Zhang[1†], Hongxu Li[2], Jingyi Wang[3], Jiacui Song[1], Dong Weng[1,4], Pengcheng Zhang[2], Qiuhong Li[1*], Yuan Zhang[1*] and Mengmeng Zhao[1*]

Abstract

Background Sarcoidosis is a systemic inflammatory disease, primarily affecting the lungs, with a prognosis that varies widely among patients. While some patients recover spontaneously after diagnosis, others experience disease progression. Currently, the metabolomic profile associated with pulmonary sarcoidosis and its different clinical outcomes remains poorly understood.

Methods Serum samples from 29 pulmonary sarcoidosis patients and 10 healthy controls were analyzed using untargeted UPLC-MS/MS metabolomics. Univariate and multivariate analyses identified differentially expressed metabolites, followed by pathway enrichment to evaluate their biological relevance. Patients were further stratified into self-healing ($n=11$) and progressive ($n=18$) subgroups based on prognosis. Differential metabolites between subgroups were compared, potential biomarkers were selected, and their diagnostic performance assessed. Correlations with clinical parameters were also analyzed to explore associations with disease progression.

Results Sarcoidosis patients showed distinct serum metabolic profiles compared to healthy controls, with 10 upregulated and 199 downregulated metabolites. Pathway analysis indicated enrichment in amino acid, lipid, and immune-related pathways. Between prognostic subgroups, 25 differential metabolites were identified. Uric acid, testosterone sulfate, allopregnanolone sulfate, and 24,25-dihydroxyvitamin D_3 emerged as key metabolites with prognostic value and moderate correlations with clinical parameters.

Conclusions This study highlights distinct serum metabolic profiles associated with sarcoidosis prognosis, suggesting that specific metabolic alterations may aid in monitoring and predicting disease outcomes. These findings offer a foundation for future research into personalized treatment and management strategies.

†Dafu Zhu, Jianglong Chen and Li Zhang contributed equally to this work.

*Correspondence:
Qiuhong Li
qiuhongl@126.com
Yuan Zhang
zhs0905@126.com
Mengmeng Zhao
mmzhao_tongji@163.com

Full list of author information is available at the end of the article

Keywords Sarcoidosis, Metabolomics, Prognosis, UPLC-MS/MS, Serum

Background

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, primarily affecting the lungs and lymphatic system, with an annual incidence of 1 to 15 cases per 100,000 people [1]. Pulmonary sarcoidosis is diagnosed through a combination of chest imaging that reveals infiltrates or lymphadenopathy, bronchoscopy with biopsies confirming non-necrotizing granulomas, and excluding infections or other interstitial lung diseases [2]. The pathogenesis of sarcoidosis remains unclear, and its clinical course is highly heterogeneous. While some patients experience spontaneous resolution or respond well to treatment [3], others progress to chronic or fibrotic stages despite receiving systemic corticosteroid therapy, often resulting in irreversible lung damage and significantly reduced quality of life.

A major clinical challenge in managing sarcoidosis lies in the absence of reliable, non-invasive prognostic biomarkers to accurately predict disease progression. Consequently, therapeutic decisions—particularly regarding the initiation and intensity of corticosteroid treatment—are often guided by clinical experience and empirical judgment, which may result in overtreatment or delayed intervention. Given the minimally invasive nature of serum collection, considerable efforts have been directed toward identifying serum-based biomarkers to support diagnosis, prognosis, and treatment stratification in sarcoidosis [4–6]. Considering the disease's complexity and heterogeneity, omics-based and systems biology approaches offer powerful tools for uncovering the underlying biological mechanisms across different phenotypes [7]. However, most previous studies have focused on differentiating various types of interstitial lung diseases [8] or distinguishing sarcoidosis patients from healthy controls [9], rather than addressing prognosis. This underscores the translational value of identifying novel biomarkers for personalized management of sarcoidosis.

Metabolomics can delineate the metabolic changes in the process of immune response, discover the key pathways and potential biomarkers related to immune activation, inhibition or dysregulation, and provide an important basis for early diagnosis, therapeutic monitoring and targeted therapy of immune diseases. Previous NMR-based metabolomics studies have shown that the metabolic disturbances observed in sarcoidosis patients can be interpreted as a holistic fingerprint of their physiological or pathological state, potentially influenced by environmental exposures and sample-related factors [10–12]. Interestingly, the metabolomic profiles of sarcoidosis patients display overlapping characteristics with both uveitis [13] and tuberculosis [14], indicating that serum metabolomic analysis could serve as a non-invasive alternative for sarcoidosis diagnosis and management. Despite these advances, most earlier studies have been limited by narrow metabolite coverage and a lack of in-depth exploration of disease heterogeneity or prognostic stratification [15, 16]. A recent NMR-based metabolomics study revealed distinct serum profiles between sarcoidosis resolvers and progressors, with elevated trimethylamine N-oxide and taurine, and reduced glycolate, alanine, and proline in progressors [17]. These findings highlight the potential of metabolomics for monitoring disease trajectory. Nonetheless, comprehensive LC-MS-based profiling linked to clinical outcomes remains insufficiently explored.

In this study, an untargeted metabolomics approach based on ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) was employed to analyze the serum metabolic profiles of pulmonary sarcoidosis patients. Additionally, metabolic differences among patients with varying prognoses were explored to gain further insights into disease progression.

Methods

Study design and participants

The study was approved by the Institutional Review Board of Shanghai Pulmonary Hospital (K21-074Z). Participants were recruited at Shanghai Pulmonary Hospital between September 2021 and November 2024. Patients with pathologically confirmed sarcoidosis who had been followed for more than one year and had a clearly defined prognosis were included. To minimize potential confounding effects on metabolite analysis, individuals who had received corticosteroid treatment within the preceding six months were excluded. Peripheral serum samples were collected during the patients' initial clinical visits. Written informed consent was obtained from all participants prior to enrollment.

The diagnostic criteria for sarcoidosis followed the 2020 guideline of the American thoracic society [18]. Pathological tissue biopsies were obtained from all patients, revealing non-necrotizing granulomas. Other granulomatous diseases, including tuberculosis, fungal infections, parasitic infections, tumors, and vasculitis, were excluded. Tuberculosis was specifically ruled out in patients with negative sputum smears using TB-PCR [19], GeneXpert MTB/RIF Assay, and a multi-parameter scoring system for distinguishing sarcoidosis from sputum negative tuberculosis (variables in the scoring systems include the results of the tuberculin skin test, the presence of tachypnea, extrathoracic presentation,

symmetrical lymphadenopathy, cavity or calcification and lesion location in radiography) [20]. We evaluated patients' clinical manifestations, serological markers (e.g., 1,3-β-d-Glucan Testing, galactomannan test, cryptococcal antigen latex agglutination test, QuantiFERON-TB Gold detection and autoantibody profiles), radiological features (including chest CT and PET/CT), as well as pathological features. All patients included in the study showed pathological evidence of non-necrotizing granulomas. Special stains (acid-fast, PAS, iron, and hexamine silver) were performed to further exclude tumors and granulomas caused by environmental factors or fungal infections. All patients were followed up for more than one year. The entry date was defined as the date when bilateral mediastinal lymph node enlargement or lung opacities suggestive of sarcoidosis were identified on chest CT scans. Follow-up evaluations, including telephone interviews or outpatient visits, were performed every three months. The mean follow-up time was 18.45 ± 4.99 months.

The healthy control (HC) group consisted of 10 individuals. Based on clinical diagnosis, 29 patients were categorized into two subgroups: (1) the self-healing group (SG, $n = 11$), defined as those who, over multiple follow-up visits, exhibited significant reduction or complete resolution of pulmonary lesions on chest CT without corticosteroid treatment, accompanied by marked symptom alleviation or resolution; and (2) the progressive group (PG, $n = 11$), which included patients who, despite not receiving corticosteroid therapy, showed an increase in pulmonary lesions and/or worsening symptoms over multiple follow-ups, those who were clinically determined to require steroid treatment after comprehensive evaluation, or those who experienced significant disease progression or relapse despite undergoing corticosteroid therapy.

Sample collection and preparation

Before UPLC-MS/MS analysis, serum samples were thawed in an ice-water bath. Each sample was transferred to a 1.5 mL centrifuge tube and mixed with three volumes of pre-chilled methanol/acetonitrile (1:1, v/v) for protein precipitation. After thorough vortexing, the mixture was centrifuged at 4 °C. The resulting supernatant was divided into two aliquots, lyophilized, and stored at − 80 °C until further use.

One aliquot was reconstituted in 50% methanol/water for reverse-phase chromatography, while the other was reconstituted in 80% methanol/water for hydrophilic interaction liquid chromatography (HILIC). Both were centrifuged prior to injection. Additionally, equal volumes from individual samples were pooled to prepare quality control (QC) samples.

Liquid chromatography

Chromatographic separation was performed using a Waters ACQUITY UPLC HSS T3 column (1.8 μm, 2.1 × 100 mm), maintained at 40 °C on a Waters Acquity UPLC I-Class system. The mobile phase comprised water containing 0.1% formic acid (A) and acetonitrile containing 0.1% formic acid (B), delivered at a flow rate of 0.4 mL/min. The gradient began with 0.5% B for 1 min, followed by a linear increase to 95% B over 20 min. Afterward, the column was flushed with 95% B for 5 min and re-equilibrated for 5 min before subsequent injections.

For HILIC, separation was achieved using a Waters ACQUITY UPLC BEH HILIC column (1.7 μm, 2.1 × 100 mm), maintained at 45 °C. The mobile phases included A (10 mM ammonium acetate in 95% acetonitrile/5% water) and B (10 mM ammonium acetate in 50% water/50% acetonitrile), with a flow rate of 0.4 mL/min. The gradient program was as follows: 0–1.0 min, 2% B; 1.0–12.0 min, 2–45% B; 12.0–14.0 min, 45–90% B; 14.0–16.5 min, 90% B; and 16.5–20.0 min, 2% A. All samples were injected with a fixed volume of 3 μL.

Mass spectrometry

The Q-Exactive mass spectrometer (Thermo Fisher Scientific, MA, USA) equipped with an electrospray ionization source was operated in both positive and negative ion modes, with spray voltages of 3.8 kV and 3.2 kV, respectively. The capillary temperature was set at 320 °C, with sheath and auxiliary gas flow rates at 40 and 10 arbitrary units. The S-lens RF level was 50, and the auxiliary gas heater temperature was 450 °C. Data acquisition covered an m/z range of 70–1,050 at a resolution of 70,000. The eight most intense ions were selected for data-dependent MS2 analysis at a resolution of 17,500. System calibration and QC were rigorously maintained. Three blank samples and six QC samples were initially run to stabilize the system. QC samples were injected every 8–10 runs during the UPLC analysis to monitor data quality and assess variability.

Data analysis

The UPLC-MS/MS raw data were processed using Compound Discoverer 3.3 software, which utilized an untargeted metabolomics workflow for peak alignment, feature filtering, gap filling and metabolite annotation. The retention time (RT) tolerance was set to 0.2 min, and the mass tolerance was set to 5 ppm. The signal-to-noise (S/N) ratio threshold was 1.5, and a peak intensity threshold of 10,000 was applied. To ensure reliable features, a peak rating threshold of 5 was implemented, and only those peaks detected in at least five samples were retained. This approach aimed to minimize poorly reproducible features and ensure accurate and comprehensive matrix data generation.

Metabolites were annotated using online and in-house databases, including the human metabolome database (HMDB), Massbank, mzCloud, ChemSpider, and mzVault, by matching detected MS/MS spectra or exact masses with reference data. In the positive ion mode, $[M+H]^+$ was the primary ion selected, along with $[M+Na]^+$, $[M+K]^+$, and $[M+NH_4]^+$, while in the negative ion mode, $[M-H]^-$ was used as the primary ion. Potential peaks originating from mobile phase contaminants such as acetonitrile, formic acid, or dehydration byproducts were also taken into account. Pathway enrichment analysis was performed via the Metaboanalyst 6.0 (www.metaboanalyst.ca) [21], and the related pathways of differential metabolites were analyzed by using the KEGG online database.

Table 1 Demographic data of sarcoidosis patients and healthy control group

	Sarcoidosis (*n*=29)		Control (*n*=10)	*p*-value
	SG (n=11)	PG (n=18)		
Age (years)	51.18 ± 12.06	49.94 ± 10.90	40.30 ± 6.62	0.27
Gender (male/female)	4/14	3/8	5/5	N/A
BMI (kg/m^2)*	25.39 (21.76, 27.31)	22.15 (20.98, 24.90)	24.53 (21.83, 26.81)	0.30
Race	Asian	Asian	Asian	/
Smoking status				
No	10	17	9	/
Former or current smoker	1	1	1	0.90
Follow-up time (months)	17.82 ± 3.09	18.83 ± 5.91	/	0.55
Organ involvement				
Lung	11	18	/	
Peripheral lymph node	6	6	/	0.26
Spleen	1	0	/	0.19
Skin	1	3	/	0.57
Eye	0	2	/	0.25
Organ involvement				
1	5	8	/	0.96
2	4	9	/	0.47
≥3	2	1	/	0.28
Scadding stage				
0	0	0	/	/
I	1	3	/	0.57
II	7	10	/	0.67
III	3	5	/	0.98
IV	0	0	/	/
Comorbidities				
Hypertension	2	3	1	0.86
Diabetes mellitus	2	1	0	0.27
Coronary artery disease	0	1	0	0.55
Autoimmune diseases	0	0	0	/

BMI Body Mass Index

*Data are presented as median (25th, 75th percentile)

Statistical analysis

All statistical analyses were performed using GraphPad Prism 8 and R (version 4.4.2). Data normality was assessed using the Shapiro–Wilk test. For normally distributed data, values are expressed as mean ± standard deviation (SD), and comparisons between groups were performed using Student's t-test or one-way ANOVA. For non-normally distributed data, results are presented as median (interquartile range), with group comparisons analyzed using the Mann-Whitney U test or Kruskal-Wallis test. Statistical significance was defined as $p<0.05$ for all analyses. Categorical data were compared using the chi-square test.

Multivariate statistical analyses were performed using MetaboAnalyst 6.0 or Metware Cloud (https://cloud.metware.cn). Normalized data were subjected to principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA), and orthogonal partial least squares discriminant analysis (OPLS-DA). To assess the risk of model overfitting in OPLS-DA, permutation tests were conducted 200 times. Differential metabolites were identified based on the OPLS-DA S-plot, Variable Importance in Projection (VIP) score (>1.0), and independent-samples *t*-test ($p<0.05$). Key metabolic alterations were further evaluated for their diagnostic potential using receiver operating characteristic (ROC) curve analysis. Spearman's correlation coefficient was calculated for correlation analysis.

Results

Clinical characteristics of participants

This study included 29 patients with sarcoidosis and 10 healthy controls, with no significant differences in age or BMI between the groups (Table 1). The patient cohort comprised 22 females and 7 males, with a mean age of 50.41 ± 11.16 years and a mean BMI of 24.06 ± 3.33. Based on prognosis, patients were further stratified into a progressive group (PG) and a self-healing group (SG). No statistically significant differences were observed between these two subgroups in terms of blood lipid levels, T-cell subsets, immune-related cytokines, or immunoglobulin levels (Table 2). However, KL-6 levels were significantly higher in the PG group compared to the SG group (Fig. S1).

Statistical analysis of Serum metabolic profiles in sarcoidosis patients

Serum samples from each group were analyzed using UPLC-Q Exactive Orbitrap MS to obtain metabolic profiles. PCA was performed to assess the initial group classifications. As shown in Fig. 1A, QC samples clustered tightly, indicating system stability and minimal operational variability. A noticeable trend toward differentiation between the Case and HC groups was observed,

Table 2 Clinical characteristics of sarcoidosis patients stratified into progressive and self-healing groups

Characteristics	SG ($n=11$)	PG ($n=18$)	*p*-value
Stage (active/stable)	0/11	5/18	N/A
SACE (IU/L)	35.90 ± 10.25	49.14 ± 29.82	0.1687
ESR (mm/h)*	14.00 (4.00, 16.00)	16.5 (10.00, 22.50)	0.3218
24-h urinary calcium*	4.97 (3.77, 6.01) ($n=9$)	6.32 (4.75, 9.73) ($n=16$)	0.2022
TG (mmol/L)*	1.38 (0.76, 3.23) ($n=5$)	1.26 (1.14, 2.31) ($n=9$)	0.8981
TC (mmol/L)	1.870 ± 1.676 ($n=5$)	1.640 ± 0.8586 ($n=9$)	0.7360
HDL-C (mmol/L)	0.9800 ± 0.1564 ($n=5$)	1.068 ± 0.2282 ($n=9$)	0.4619
LDL-C (mmol/L)	2.826 ± 0.6677 ($n=5$)	2.838 ± 0.7976 ($n=9$)	0.9782
ApoA-I (g/L)	1.506 ± 0.3232 ($n=5$)	1.424 ± 0.2667 ($n=9$)	0.6194
ApoB (g/L)	0.7680 ± 0.1143 ($n=5$)	0.8889 ± 0.2141 ($n=9$)	0.2686
Lp(a) (mg/L)	147.1 ± 118.9 ($n=5$)	81.86 ± 41.67 ($n=10$)	0.1339
Hcy (IU/L)	9.291 ± 3.501 ($n=11$)	11.06 ± 1.290 ($n=14$)	0.0933
IL-1β (pg/mL)	1.323 ± 1.064 ($n=6$)	1.904 ± 1.905 ($n=9$)	0.5115
IL-2 (pg/mL)	1.487 ± 0.6791 ($n=6$)	0.9144 ± 0.6692 ($n=9$)	0.1307
IL-4 (pg/mL)	1.818 ± 1.262 ($n=6$)	1.796 ± 0.8431 ($n=9$)	0.9670
IL-5 (pg/mL)	0.9933 ± 0.8801 ($n=6$)	0.8933 ± 0.8572 ($n=9$)	0.8300
IL-6 (pg/mL)*	4.26 (3.02, 6.69) ($n=6$)	3.04 (2.50, 7.46) ($n=9$)	0.3884
IL-8 (pg/mL)*	5.18 (3.05, 21.65) ($n=6$)	8.76 (8.41, 12.64) ($n=9$)	0.0663
IL-10 (pg/mL)*	2.51 (1.88, 3.87) ($n=6$)	4.41 (2.64, 6.26) ($n=9$)	0.0937
IL-12 p70 (pg/mL)	1.013 ± 0.9578 ($n=6$)	1.354 ± 0.9092 ($n=9$)	0.4979
IL-17 A (pg/mL)*	1.87 (0.06, 5.64) ($n=6$)	0.87 (0.12, 1.84) ($n=9$)	0.5273
TNF-α (pg/mL)	1.963 ± 0.9074 ($n=6$)	0.8756 ± 1.023 ($n=9$)	0.0553
IFN-α (pg/mL)	1.515 ± 0.6934 ($n=6$)	1.893 ± 1.522 ($n=9$)	0.5813
IFN-γ (pg/mL)	1.602 ± 0.8940 ($n=6$)	2.577 ± 1.882 ($n=9$)	0.2618
KL-6 (U/mL)*	142.5 (125.00, 161.25) ($n=8$)	173.00 (165.53, 298.00) ($n=11$)	0.0112
CD3 (%)	63.53 ± 5.707 ($n=7$)	67.37 ± 10.19 ($n=9$)	0.3882
CD4 (%)	44.46 ± 3.506 ($n=7$)	39.81 ± 8.003 ($n=9$)	0.1751
CD8 (%)	16.49 ± 5.455 ($n=7$)	23.24 ± 9.139 ($n=9$)	0.1070
CD4/CD8	3.043 ± 1.241 ($n=7$)	2.142 ± 1.382 ($n=9$)	0.1984
IgG (g/L)	12.02 ± 2.098 ($n=11$)	13.78 ± 3.005 ($n=13$)	0.1166
IgA (g/L)*	1.03 (0.91, 1.39) ($n=11$)	1.14 (0.84, 1.35) ($n=13$)	0.9547
IgM (g/L)*	2.29 (1.59, 2.71) ($n=11$)	2.34 (1.48, 3.68) ($n=13$)	0.7646
IgE (IU/mL)*	29.5 (18.45, 75.75) ($n=9$)	19.40 (16.70, 22.30) ($n=13$)	0.0986

SACE serum angiotensin converting enzyme, *ESR* erythrocyte sedimentation rate, *TG* Triglyceride, *TC* Total cholesterol, *HDL-C* High-Density Lipoprotein Cholesterol, *LDL-C* Low-Density Lipoprotein Cholesterol, *Lp(a)* Lipoprotein(a), *Hcy* homocysteine, *KL-6* Krebs von den Lungen-6

*Data are presented as median (25th, 75th percentile)

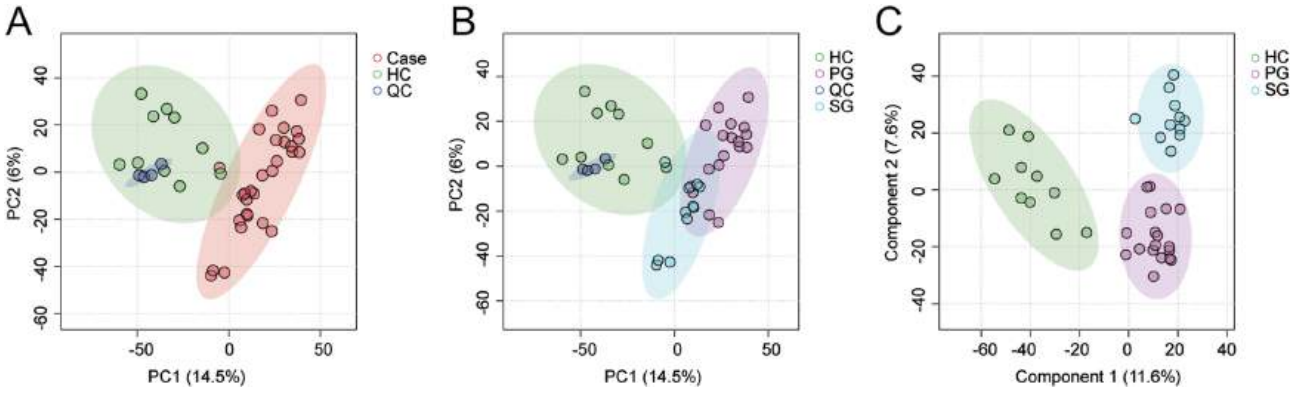

Fig. 1 Statistical analysis of serum metabolic profiles. **A**, **B** PCA score plots illustrating the distribution of different groups with and without prognostic information. **C** PLS-DA score plots for various groups. HC: Healthy control; SG: Self-healing group; PG: Progressive group; QC: Quality control

suggesting metabolic disruptions in sarcoidosis patients. When considering prognostic differences, a trend toward distinct metabolic profiles was seen between self-healing patients and those with disease progression (Fig. 1B). To further investigate the metabolic differences across groups, supervised PLS-DA was conducted. The PLS-DA model demonstrated robust and reliable performance, supported by strong statistical indicators (R^2 = 0.998, Q^2 = 0.552) (Fig. 1C).

Characterizing metabolic alterations in patients compared to healthy controls

To better capture intergroup differences, OPLS-DA was applied to maximize metabolic separation and identify significantly altered metabolites between the sarcoidosis and control groups (Fig. 2A). The model's validity was confirmed by permutation testing, with all permuted R^2 and Q^2 values falling below the original values and the Q^2 (cum) intercept at −0.257 (Fig. 2B). These results demonstrate that the OPLS-DA model was both reliable and effective in distinguishing sarcoidosis patients from healthy controls.

To investigate the differences in metabolites between the case and HC groups, metabolites with $p < 0.05$, $|\log_2 FC| > 1$, and VIP > 1.0 were considered as differential metabolites (Fig. 2C). A total of 209 metabolites were annotated (Fig. 2D, Table S1), with 10 metabolites showing a significant increase in the case group, including 1-stearoylglycerophosphoserine, 5-hydroxyuracil, and LysoPC(14:0/0:0). In contrast, 199 metabolites exhibited a notable decrease, such as histidine, 25-hydroxycholesterol, and uric acid (UA).

To explore the aberrant metabolic pathways in sarcoidosis patients, candidate metabolites were imported into MetaboAnalyst 6.0 for pathway enrichment analysis, with the goal of identifying relevant metabolic pathways and potential biological functions (Fig. S2). The results revealed that the differentially expressed metabolites were mainly associated with amino acid metabolism, particularly histidine and β-alanine pathways. Dysregulation

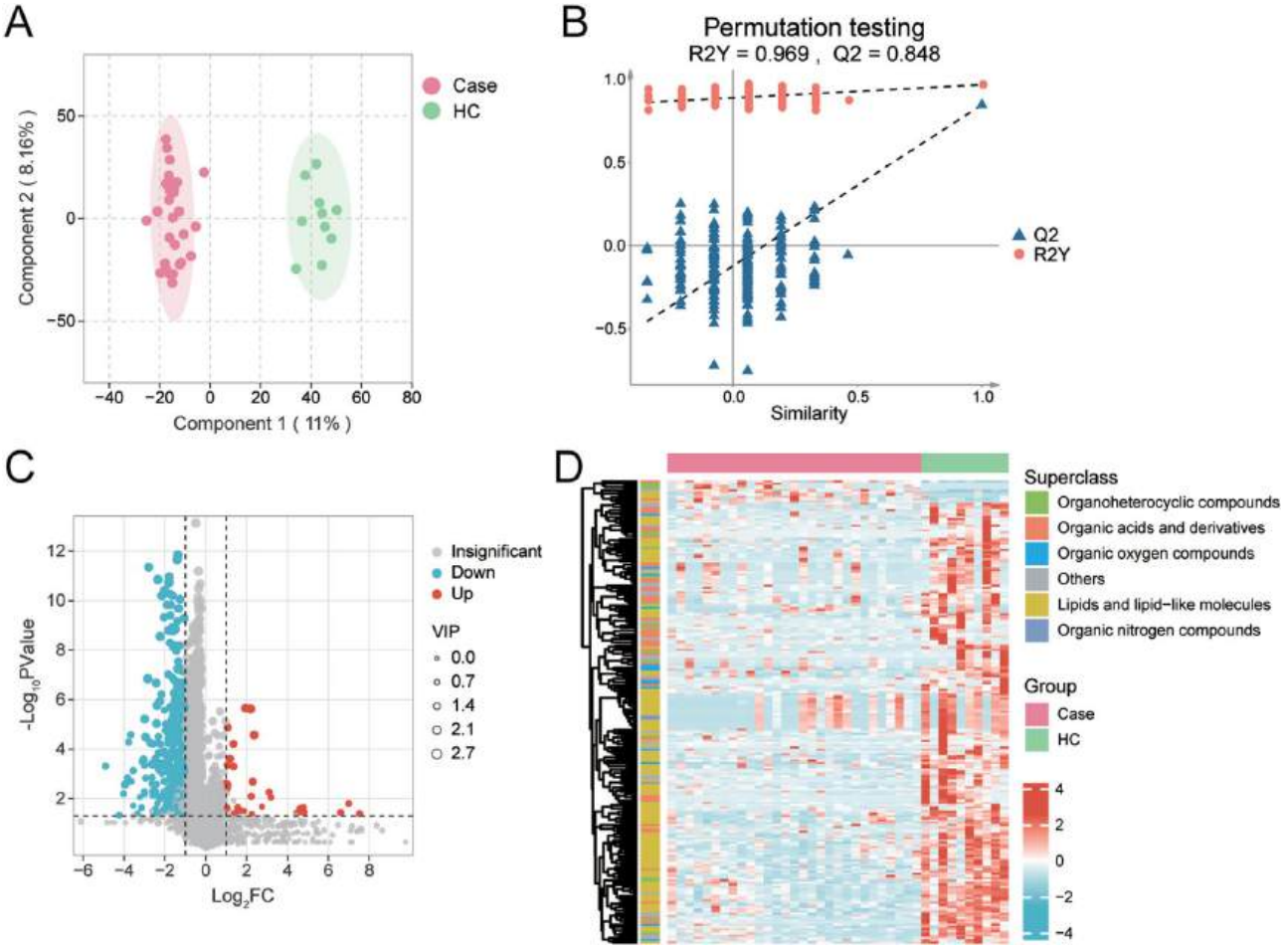

Fig. 2 Serum metabolomic analysis of sarcoidosis patients and healthy controls. **A** OPLS-DA score plot comparing sarcoidosis patients and healthy controls. **B** Permutation test for model validation. **C** Volcano plot of differential metabolites. **D** Heatmap of differential metabolites

in lipid metabolism was also observed, including alterations in bile acid and sphingolipid metabolism. Additionally, several pathways linked to immune responses—such as purine, pyrimidine, and arachidonic acid metabolism—were implicated. These metabolic disturbances underscore a complex interplay between energy homeostasis, immune signaling, and chronic inflammation in sarcoidosis.

Comparative analysis of metabolic profiles in progressive and self-healing sarcoidosis patients

To explore the serum metabolic characteristics of sarcoidosis patients with different prognoses, we performed OPLS-DA on metabolomics data from the PG and SG groups. The robustness and predictive performance of the OPLS-DA model were evaluated through 200 permutation tests, which confirmed strong predictive capability with R^2Y and Q^2 values of 0.975 and 0.65, respectively (Fig. 3A and B). Significant differential metabolites between the PG and SG groups were identified ($p < 0.05, |\log_2 FC| > 1$, and VIP > 1.0), revealing 8 upregulated and 17 downregulated metabolites (Fig. 3C and D, Table S2). Notably, most of these metabolites were lipids, suggesting that different lipid species may play distinct biological roles in sarcoidosis.

Key metabolites for differentiating sarcoidosis and its prognoses

Based on the differential metabolites identified between sarcoidosis patients and healthy controls, as well as between the progressive and self-healing groups, we identified four key metabolites: uric acid (UA), testosterone sulfate (TS), allopregnanolone sulfate (AS), and 24,25-dihydroxyvitamin D_3 ($24R,25(OH)_2D_3$) (Fig. 4A and B). To assess their predictive value for disease progression, we performed ROC curve analysis and compared their respective area under the curve (AUC) values, which were 0.848, 0.899, 0.818, and 0.879, respectively—comparable to that of KL-6 (Fig. 4C and S3). Furthermore, logistic regression analysis was conducted, with sarcoidosis set as the dependent variable and the four identified metabolites as independent variables

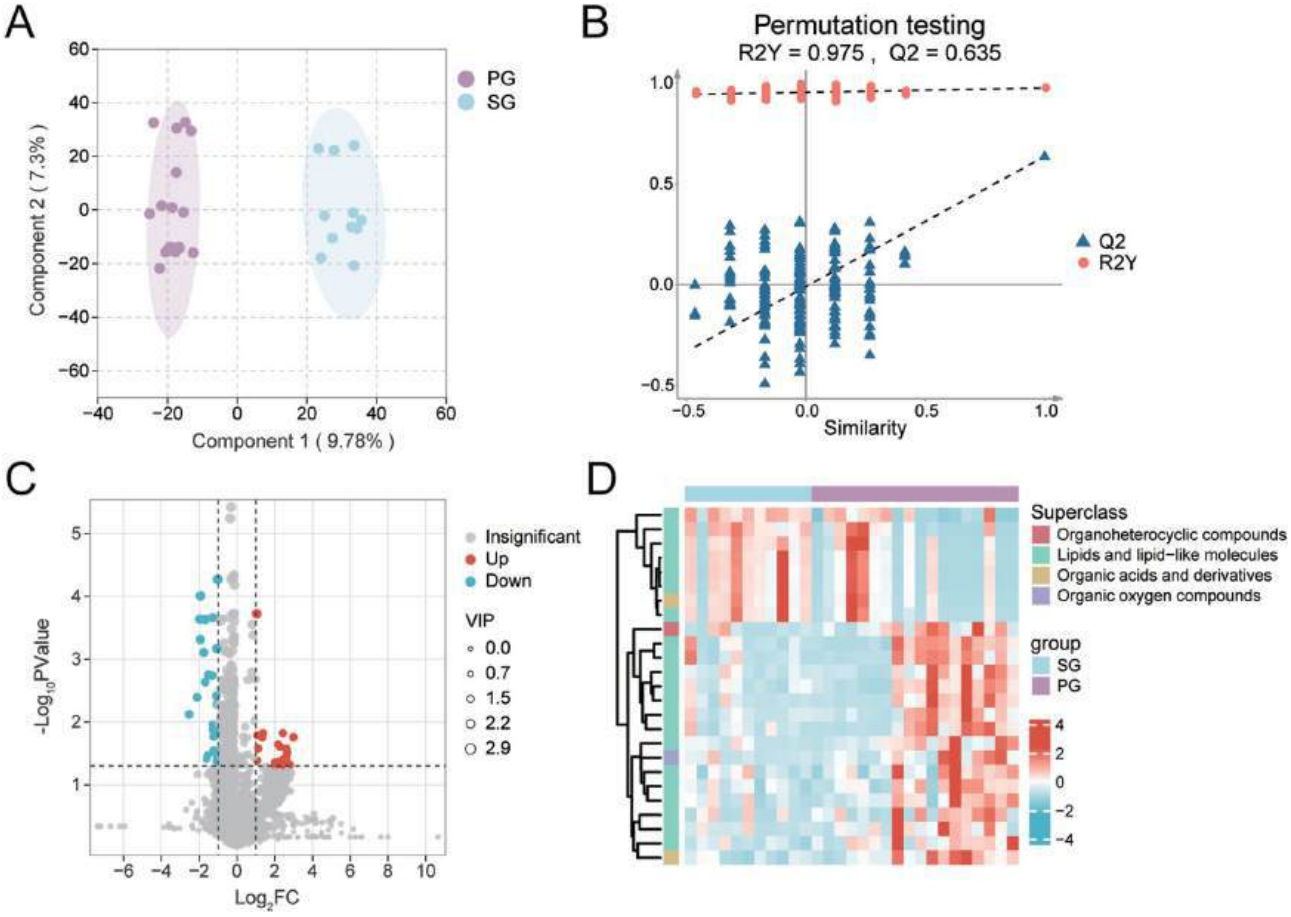

Fig. 3 Serum metabolomics analysis of the progressive group and self-healing group in sarcoidosis. OPLS-DA score plot (**A**), permutation test (**B**), and volcano plot (**C**) comparing the progressive and self-healing groups. **D** Heatmap of differential metabolites

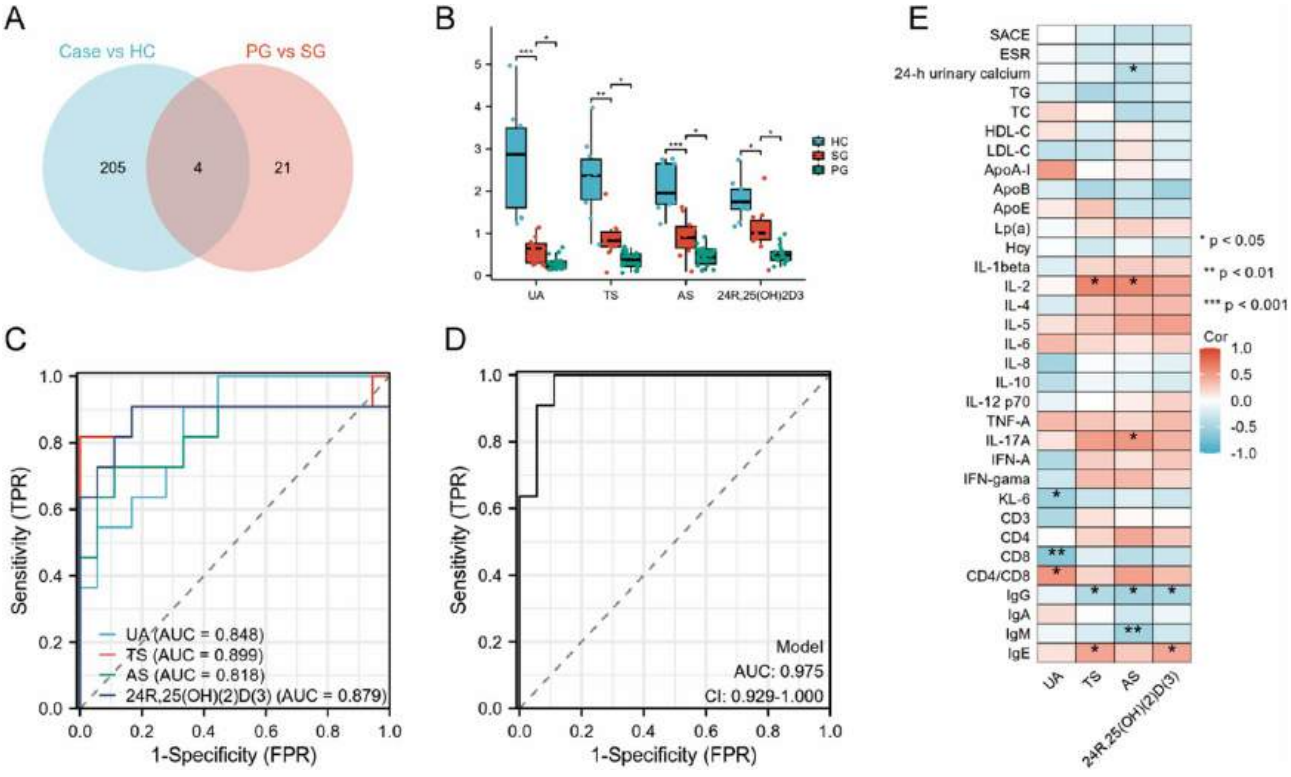

Fig. 4 Analysis of key metabolites in sarcoidosis patients. **A** Venn diagram showing the identification of key metabolites. **B** Expression levels of key metabolites across different groups. **C** ROC analysis of four key metabolites or a panel of metabolites (**D**) for distinguishing SG and PG groups. **E** Correlation analysis between metabolites and clinical parameters. UA: Uric acid; TS: Testosterone sulfate; AS: Allopregnanolone sulfate; 24R,25(OH)$_2$D$_3$: 24,25-Dihydroxyvitamin D$_3$, TPR, true positive rate; FPR, false positive rate. * $P < 0.05$. *** $P < 0.001$

(Fig. 4D). The ROC curve analysis of the resulting model demonstrated a robust predictive performance, achieving an AUC of 0.975, highlighting their potential as valuable diagnostic and prognostic biomarkers.

To explore the relationship between serum metabolites and clinical parameters, correlation analyses were conducted on key metabolites that showed significant changes in sarcoidosis patients. Several clinical parameters exhibited notable correlations with these metabolites (Fig. 4E). For instance, KL-6 and CD8$^+$were negatively correlated with UA, while IL-2 showed positive correlations with both TS and AS. Additionally, IgG and IgM were positively and negatively correlated with TS, AS, and 24R,25(OH)$_2$D$_3$, respectively. These findings suggest potential associations between serum metabolites and clinical parameters in sarcoidosis patients.

Discussion

Serum is widely used in clinical metabolomics because it reflects systemic metabolic changes. Although research on sarcoidosis-related metabolic alterations remains limited, emerging evidence points to distinct disruptions, particularly in lipid metabolism. For example, Lim et al. reported enrichment of cholesterol metabolism pathways in monocytes and macrophages from chronic sarcoidosis patients [22]. Other studies have linked sarcoidosis with an increased risk of atherosclerosis [23], and alterations in polyunsaturated fatty acid profiles have been proposed as potential predictors of disease involvement [24]. Consistent with these findings, our study analyzed serum samples from sarcoidosis patients at initial diagnosis and identified significant dysregulation in amino acid, lipid, and immune-related metabolic pathways. Notably, we observed reduced bile acid metabolism, which is essential for cholesterol elimination and lipid homeostasis [25]. This disruption may contribute to lipid accumulation and heightened atherosclerotic risk, potentially exacerbated by systemic inflammation and immune dysregulation—hallmarks of sarcoidosis [26]. To minimize the confounding effects of glucocorticoids, which are known to affect lipid metabolism, we only included patients who had never received steroids or had discontinued them at least six months prior to sampling. Thus, the lipid abnormalities observed are more likely attributable to intrinsic disease mechanisms.

Recent studies further support the link between lipid metabolism and immune activation in sarcoidosis. For instance, extracellular heat shock protein 90α (eHSP90α), secreted by macrophages, has been shown to drive inflammation and fibrosis in interstitial lung diseases,

including sarcoidosis, through interference with LRP1, STAT-3, and PI3K/AKT pathways [27]. In line with this, our study found reduced levels of 25-hydroxycholesterol (25HC), an oxysterol produced by activated macrophages. While 25HC can promote pro-inflammatory cytokines like IL-1 and IL-8 [28], it also has anti-inflammatory functions by suppressing NLRP3 inflammasome activation [29]. Its reduction may thus reflect impaired anti-inflammatory regulation and contribute to chronic inflammation in sarcoidosis. Additionally, we detected elevated LysoPC(14:0/0:0), a subtype of lysophosphatidylcholine (LPC), which is known to activate oxidative stress and inflammatory pathways, stimulate IFN-γ secretion, and promote B cell activity [30, 31]. Interestingly, LPC can also enhance regulatory T cell function via G2A receptor signaling, promoting Foxp3 expression and immunosuppressive activity [32]. This dual role underscores the immunometabolic complexity of sarcoidosis, where lipid mediators may simultaneously drive immune activation and regulation.

Pulmonary sarcoidosis exhibits a highly variable clinical course, ranging from asymptomatic cases and spontaneous remission to chronic progressive disease involving multiple organs and requiring systemic therapy. Given that many patients remit spontaneously, treatment benefits may sometimes reflect the natural disease trajectory, while exposing patients to corticosteroid-related side effects [33]. Currently, no reliable tools exist to predict prognosis, and the mechanisms underlying this variability remain unclear. The preferred clinical strategy is to closely monitor newly diagnosed patients and initiate treatment only upon signs of progression. In our study, serum metabolomics effectively distinguished between remitting and progressive sarcoidosis. Notably, four metabolites—UA, TS, AS, and 24R,25$(OH)_2D_3$—emerged as potentially relevant prognostic markers.

Uric acid, the end product of purine metabolism, is primarily excreted by the kidneys, and up to one-third of sarcoidosis patients may present with renal involvement [34]. In this study, a significant decrease in serum UA levels was observed, aligning with previous findings [35]. Emerging evidence suggests a potential bidirectional regulatory relationship between UA metabolism and vitamin D metabolism [36–38]. We observed decreased serum levels of 24R,25$(OH)_2D_3$—a metabolite generated in the kidney from 25-hydroxyvitamin D_3 via 24-hydroxylation—indicating disrupted vitamin D metabolism. Previous studies indicate that sarcoidosis patients often have elevated levels of 1,25-dihydroxyvitamin D, primarily due to the excessive activation of 1α-hydroxylase in granuloma macrophages, this is also one of the reasons for hypercalcemia in patients with sarcoidosis [39, 40], and 25-hydroxyvitamin D, as a precursor form, is deficient or normal in most patients with sarcoidosis [41]. The reduction in 24R,25$(OH)_2D_3$, particularly in progressive cases, may result from negative feedback by elevated 1,25-dihydroxyvitamin D or impaired synthesis due to renal tubular injury. Given the shared metabolic link between cholesterol and vitamin D synthesis, further studies are warranted to explore the interplay between vitamin D dysregulation, lipid metabolism, and renal function in sarcoidosis.

TS and AS are steroid hormones that serve as precursors or metabolites of adrenal corticosteroids. Previous studies have shown that serum testosterone levels are significantly decreased in patients with chronic lung disease [42, 43], and a notable proportion of male outpatients with sarcoidosis (46.7%) exhibit low circulating testosterone concentrations [44]. Sarcoidosis, a disease characterized by immune system dysregulation, may impair specific hormone synthesis pathways due to persistent immune activation. This ongoing immune response can negatively impact adrenal function, leading to decreased synthesis and secretion of these hormones. Furthermore, sarcoidosis patients often face challenges such as inadequate nutrient intake or increased metabolic demands, which can result in insufficient levels of precursor substances essential for hormone synthesis, such as vitamin D and zinc. This, in turn, further disrupts the synthesis of adrenal corticosteroids.

KL-6 is a mucin-like glycoprotein widely used as a biomarker for sarcoidosis and other interstitial lung diseases, with elevated levels linked to poorer prognosis and higher mortality risk [45–49]. In our study, KL-6 levels were significantly higher in the progressive group than in the self-healing group ($p = 0.0278$), likely reflecting greater and sustained alveolar epithelial injury. Notably, KL-6 levels showed a negative correlation with UA, suggesting interplay between immune activation and metabolic disturbance. Given UA's antioxidant and immunomodulatory roles, its reduction may be influenced by chronic inflammation or altered renal handling. To rule out confounding by renal function, we conducted multivariate logistic regression adjusting for age, gender, BMI, and eGFR. Serum UA remained significantly associated with disease progression (OR = 0.99996, $p = 0.030$; Table S3), indicating that UA reduction likely reflects disease-related metabolic and inflammatory alterations rather than impaired kidney function alone.

Our previous research found that IL-2R can serve as a serum biomarker for assessing multi-organ involvement and prognosis in sarcoidosis [50]. IL-2 is an important cytokine primarily produced by activated T cells, and it plays a crucial role in maintaining immune homeostasis. IL-2R can bind to IL-2, thus regulating its activity. In this study, we found that IL-2 was positively correlated with two decreased steroid hormones, which may reflect the complex interplay between immune system

activation and steroid hormone synthesis. This correlation might also suggest a potential link between immune dysregulation and hormonal imbalance in sarcoidosis patients. Additionally, the negative correlation between $CD8^+$ T cells and UA levels indicates a potential enhancement of peripheral $CD8^+$ cytolytic T cell responses in these patients [51]. The observed correlations between multiple key metabolites and IgG and IgE in sarcoidosis patients could be attributed to various factors, including chronic inflammatory responses, immune system activation, shifts in Th1/Th2 balance, and changes in the cytokine environment. However, a more comprehensive understanding of the disease course requires considering other clinical and laboratory parameters.

A major strength of this study lies in its comprehensive approach, employing UPLC-MS/MS to profile serum metabolites not only between sarcoidosis patients and healthy controls but also across prognostic subgroups defined through long-term clinical follow-up. Our findings suggest that metabolomic subtyping at diagnosis may help predict disease progression. Supporting this, a recent preprint by Dr. Drake's group using NMR-based metabolomics similarly identified distinct serum metabolic profiles between regressing and progressive sarcoidosis [17]. While their study reported elevated trimethylamine N-oxide and taurine and reduced glycerate, alanine, and proline in progressors, our cohort showed a similar increase in taurine but no significant changes in alanine or proline (Fig. S4)—possibly reflecting population differences. Despite methodological differences, both studies converge on the presence of distinct metabolic phenotypes, highlighting the promise of metabolomics in sarcoidosis prognosis.

This study has several limitations. First, the relatively small sample size and absence of a disease control group limit the interpretation of disease-specific metabolic alterations. Second, as a retrospective study, some clinical data extracted from medical records may be incomplete, potentially affecting the accuracy of correlation analyses. Third, although we excluded patients with recent corticosteroid use to reduce medication-related confounding, other factors such as dietary habits were not systematically assessed due to a lack of standardized data—this represents a methodological limitation, as diet can influence metabolomic profiles. Finally, this study focused on a single omics layer. Future research should incorporate multi-omics approaches and prospectively control for variables such as medications, comorbidities, and diet to better elucidate the metabolic landscape of sarcoidosis. Despite these limitations, our findings provide meaningful insights into disease-related metabolic heterogeneity and lay the groundwork for further prognostic studies.

Conclusions

This study expands our understanding of serum metabolomic alterations in patients with sarcoidosis. The identified metabolic signatures closely reflect the prognostic differences between progressive and self-healing cases. Several metabolites showed associations with key clinical parameters, underscoring the potential of serum metabolomics as a valuable tool in the clinical management of sarcoidosis. Beyond aiding in diagnosis, these metabolic markers may serve as indicators for monitoring disease progression and evaluating treatment response.

Abbreviations

$24R,25(OH)_2D_3$	24,25-Dihydroxyvitamin D_3
25HC	25-hydroxycholesterol
AS	Allopregnanolone Sulfate
AUC	Area Under Curve
FC	Fold Change
HC	Healthy Control
HILIC	Hydrophilic Interaction Liquid Chromatography
KEGG	Kyoto Encyclopedia Gene and Genome database
KL-6	Krebs von den Lungen 6
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
OPLS-DA	Orthogonal Partial Least Squares Discriminant Analysis
PCA	Principal Component Analysis
PG	Progressive Group
PLS-DA	Partial Least Squares Discriminant Analysis
QC	Quality Control
ROC	Receiver Operating Characteristic
SG	Self-healing Group
TS	Testosterone Sulfate
UA	Uric Acid
UPLC-MS/MS	Ultra-Performance Liquid Chromatography - Tandem Mass Spectrometry
VIP	Variable Importance in Projection

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03863-y.

Supplementary Material 1: Appendix A. Supplementary data. Supplemental figures and tables.

Acknowledgements

We sincerely appreciate all the patients whose generosity and commitment to regular visits made this study possible. This work was supported by the HPC Platform of ShanghaiTech University.

Authors' contributions

Dafu Zhu: Investigation, Writing– original draft. Jianglong Chen: Investigation. Li Zhang: Data curation, Resources. Hongxu Li: Investigation. Jingyi Wang: Investigation. Jiacui Song: Investigation. Dong Weng: Funding acquisition. Pengcheng Zhang: Supervision. Qiuhong Li: Data curation, Funding acquisition. Yuan Zhang: Conceptualization, Funding acquisition, Project administration, Writing– review and editing. Mengmeng Zhao: Conceptualization, Funding acquisition, Writing– review and editing.

Funding

This study has been supported by National Natural Science Foundation of China (82100073, 82270064, 82000068), Clinical Research Youth Project of Shanghai Health Commission (20234Y0275), Shanghai Pulmonary Hospital Project Newcomer Program (Fkxr2304), Tongji University Medicine-X Interdisciplinary Research Initiative (2025-0554-YB-03, 2025-0554-YB-04), Natural Science Foundation of Shanghai (22ZR1452300, 20ZR1446800),

and the National Key Research and Development Program of China (2024YFA1108900).

Data availability
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study has been approved by the institutional review board of Shanghai Pulmonary Hospital (No. K21-074Z). Written informed consent was obtained from all participants. All procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pulmonary and Critical Care Medicine, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200433, China
[2]School of Biomedical Engineering, ShanghaiTech University, Shanghai 201210, China
[3]School of Medicine, Tongji University, Shanghai 200092, China
[4]Institute of Respiratory Medicine, School of Medicine, Tongji University, Shanghai 200433, China

Received: 28 April 2025 / Accepted: 16 July 2025
Published online: 02 August 2025

References

1. Rossides M, Darlington P, Kullberg S, Arkema EV. Sarcoidosis: epidemiology and clinical insights. J Intern Med. 2023;293:668–80.
2. Belperio JA, Shaikh F, Abtin FG, Fishbein MC, Weigt SS, Saggar R, Lynch JP. Diagnosis and treatment of pulmonary sarcoidosis: a review. JAMA. 2022;327:856–67.
3. Valeyre D, Prasse A, Nunes H, Uzunhan Y, Brillet PY, Muller-Quernheim J. Sarcoidosis. Lancet. 2014;383:1155–67.
4. Ramos-Casals M, Retamozo S, Siso-Almirall A, Perez-Alvarez R, Pallares L, Brito-Zeron P. Clinically-useful serum biomarkers for diagnosis and prognosis of sarcoidosis. Expert Rev Clin Immunol. 2019;15:391–405.
5. Kraaijvanger R, Janssen Bonas M, Vorselaars ADM, Veltkamp M. Biomarkers in the diagnosis and prognosis of sarcoidosis: current use and future prospects. Front Immunol. 2020;11: 1443.
6. Della Zoppa M, Bertuccio FR, Campo I, Tousa F, Crescenzi M, Lettieri S, Mariani F, Corsico AG, Piloni D, Stella GM. Phenotypes and serum biomarkers in sarcoidosis. Diagnostics. 2024. https://doi.org/10.3390/diagnostics14070709.
7. Carleo A, Bennett D, Rottoli P. Biomarkers in sarcoidosis: the contribution of system biology. Curr Opin Pulm Med. 2016;22:509–14.
8. Bergantini L, d'Alessandro M, Vietri L, Rana GD, Cameli P, Acerra S, Sestini P, Bargagli E. Utility of serological biomarker' panels for diagnostic accuracy of interstitial lung diseases. Immunol Res. 2020;68:414–21.
9. Kim J, Lee S, Moodley Y, Yagnik L, Birnie D, Dwivedi G. The role of the host-microbiome and metabolomics in sarcoidosis. Am J Physiol Cell Physiol. 2023;325:C1336-53.
10. Geamanu A, Gupta SV, Bauerfeld C, Samavati L. Metabolomics connects aberrant bioenergetic, transmethylation, and gut microbiota in sarcoidosis. Metabolomics. 2016. https://doi.org/10.1007/s11306-015-0932-2.
11. Banoei MM, Iupe I, Bazaz RD, Campos M, Vogel HJ, Winston BW, Mirsaeidi M. Metabolomic and metallomic profile differences between veterans and civilians with pulmonary sarcoidosis. Sci Rep. 2019;9:19584.
12. Duchemann B, Triba MN, Guez D, Rzeznik M, Savarin P, Nunes H, Valeyre D, Bernaudin JF, Le Moyec L. Nuclear magnetic resonance spectroscopic analysis of salivary metabolome in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33:10–6.
13. Shimizu H, Usui Y, Asakage M, Nezu N, Wakita R, Tsubota K, Sugimoto M, Goto H. Serum metabolomic profiling of patients with Non-Infectious uveitis. J Clin Med 2020;9:3955. https://www.mdpi.com/2077-0383/9/12/3955.
14. Rai MK, Yadav S, Jain A, Singh K, Kumar A, Raj R, Dubey D, Singh H, Guleria A, Chaturvedi S, et al. Clinical metabolomics by NMR revealed serum metabolic signatures for differentiating sarcoidosis from tuberculosis. Metabolomics. 2023;19: 92.
15. Ji HL, Xi NMS, Mohan C, Yan X, Jain KG, Zang QS, Gahtan V, Zhao R. Biomarkers and molecular endotypes of sarcoidosis: lessons from omics and non-omics studies. Front Immunol. 2023;14: 1342429.
16. Tang DQ, Zou L, Yin XX, Ong CN. HILIC-MS for metabolomics: an attractive and complementary approach to RPLC-MS. Mass Spectrom Rev. 2016;35:574–600.
17. Ma B, Samavati L, Drake WP. Sarcoidosis resolvers and progressors demonstrate distinct systemic metabolomic profiles. bioRxiv. 2025.
18. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, Abston E, Bernstein RC, Blankstein R, Chen ES, et al. Diagnosis and detection of sarcoidosis. An official American thoracic society clinical practice guideline. Am J Respir Crit Care Med. 2020;201:e26–51.
19. Zhou Y, Li HP, Li QH, Zheng H, Zhang RX, Chen G, Baughman RP. Differentiation of sarcoidosis from tuberculosis using real-time PCR assay for the detection and quantification of *Mycobacterium tuberculosis*. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25:93–9.
20. Li QH, Li HP, Shen YP, Zhao L, Shen L, Zhang Y, Jiang DH, Baughman RP. A novel multi-parameter scoring system for distinguishing sarcoidosis from sputum negative tuberculosis. Sarcoidosis Vasc Diffuse Lung Dis. 2012;29:11–8.
21. Pang Z, Lu Y, Zhou G, Hui F, Xu L, Viau C, Spigelman AF, MacDonald PE, Wishart DS, Li S, Xia J. Metaboanalyst 6.0: towards a unified platform for metabolomics data processing, analysis and interpretation. Nucleic Acids Res. 2024;52:W398-406.
22. Lim CX, Redl A, Kleissl L, Pandey RV, Mayerhofer C, El Jammal T, Mazic M, Gonzales K, Sukhbaatar N, Krausgruber T, et al. Aberrant lipid metabolism in macrophages is associated with granuloma formation in sarcoidosis. Am J Respir Crit Care Med. 2024;209:1152–64.
23. Bargagli E, Rosi E, Pistolesi M, Lavorini F, Voltolini L, Rottoli P. Increased risk of atherosclerosis in patients with sarcoidosis. Pathobiology. 2017;84:258–63.
24. Suzuki T, Karayama M, Inoue Y, Hozumi H, Suzuki Y, Furuhashi K, Fujisawa T, Enomoto N, Nakamura Y, Inui N, Suda T. Associations of serum long-chain fatty acids with multiple organ involvement in patients with sarcoidosis. BMC Pulm Med. 2022;22: 290.
25. Chiang JY. Bile acid metabolism and signaling. Compr Physiol. 2013;3:1191–212.
26. Hoss S, Grinberg T, Eisen A. The interrelationship between sarcoidosis and Atherosclerosis-Complex yet rational. J Clin Med. 2022;11:433. https://www.mdpi.com/2077-0383/11/2/433.
27. Isshiki T, Sunakawa M, Vierhout M, Ayoub A, Ali P, Naiel S, Miyoshi S, Naqvi A, Hambly N, Kishi K, et al. Upregulation of HSP90alpha in the lungs and circulation in sarcoidosis. Front Med (Lausanne). 2025;12:1532437.
28. Serquina AKP, Tagawa T, Oh D, Mahesh G, Ziegelbauer JM. 25-Hydroxycholesterol inhibits Kaposi's sarcoma herpesvirus and Epstein-Barr virus infections and activates inflammatory cytokine responses. mBio. 2021;12: e0290721.
29. Reboldi A, Dang EV, McDonald JG, Liang G, Russell DW, Cyster JG. Inflammation. 25-Hydroxycholesterol suppresses interleukin-1-driven inflammation downstream of type I interferon. Science. 2014;345:679–84.
30. Huang YH, Schafer-Elinder L, Wu R, Claesson HE, Frostegard J. Lysophosphatidylcholine (LPC) induces proinflammatory cytokines by a platelet-activating factor (PAF) receptor-dependent mechanism. Clin Exp Immunol. 1999;116:326–31.
31. Yang LV, Radu CG, Wang L, Riedinger M, Witte ON. Gi-independent macrophage chemotaxis to lysophosphatidylcholine via the immunoregulatory GPCR G2A. Blood. 2005;105:1127–34.
32. Hasegawa H, Lei J, Matsumoto T, Onishi S, Suemori K, Yasukawa M. Lysophosphatidylcholine enhances the suppressive function of human naturally occurring regulatory T cells through TGF-beta production. Biochem Biophys Res Commun. 2011;415:526–31.
33. Arcana RI, Crisan-Dabija R, Cernomaz AT, Buculei I, Burlacu A, Zabara ML, Trofor AC. The risk of sarcoidosis misdiagnosis and the harmful effect of corticosteroids when the disease picture is incomplete. Biomedicines. 2023;11:175. https://www.mdpi.com/2227-9059/11/1/175.
34. Bonella F, Dm Vorselaars A, Wilde B. Kidney manifestations of sarcoidosis. J Autoimmun. 2024;149:103207.

35. Boots AW, Drent M, Swennen EL, Moonen HJ, Bast A, Haenen GR. Antioxidant status associated with inflammation in sarcoidosis: a potential role for antioxidants. Respir Med. 2009;103:364–72.
36. Copur S, Demiray A, Kanbay M. Uric acid in metabolic syndrome: does uric acid have a definitive role? Eur J Intern Med. 2022;103:4–12.
37. Isnuwardana R, Bijukchhe S, Thadanipon K, Ingsathit A, Thakkinstian A. Association between vitamin D and uric acid in adults: a systematic review and meta-analysis. Horm Metab Res. 2020;52:732–41.
38. Chen Y, Cheng J, Chen Y, Wang N, Xia F, Chen C, Han B, Lu Y. Association between serum vitamin D and uric acid in the Eastern Chinese population: a population-based cross-sectional study. BMC Endocr Disord. 2020;20: 79.
39. Tebben PJ, Singh RJ, Kumar R. Vitamin D-mediated hypercalcemia: mechanisms, diagnosis, and treatment. Endocr Rev. 2016;37:521–47.
40. Toriu N, Sumida K, Oguro M, Oshima Y, Mizuno H, Hasegawa E, Suwabe T, Kawada M, Ueno T, Hayami N, et al. Increase of 1,25 dihydroxyvitamin D in sarcoidosis patients with renal dysfunction. Clin Exp Nephrol. 2019;23:1202–10.
41. Bucova M, Suchankova M, Tibenska E, Tedlova E, Demian J, Majer I, Novosadova H, Tedla M. TREM-2 Receptor Expression Increases with 25(OH)D Vitamin Serum Levels in Patients with Pulmonary Sarcoidosis. Mediators Inflamm. 2015;2015:181986.
42. Atlantis E, Fahey P, Cochrane B, Wittert G, Smith S. Endogenous testosterone level and testosterone supplementation therapy in chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. BMJ Open. 2013. https://doi.org/10.1136/bmjopen-2013-003127.
43. Bercea RM, Mihaescu T, Cojocaru C, Bjorvatn B. Fatigue and serum testosterone in obstructive sleep apnea patients. Clin Respir J. 2015;9:342–9.
44. Spruit MA, Thomeer MJ, Gosselink R, Wuyts WA, Van Herck E, Bouillon R, Demedts MG, Decramer M. Hypogonadism in male outpatients with sarcoidosis. Respir Med. 2007;101:2502–10.
45. Shigemura M, Nasuhara Y, Konno S, Shimizu C, Matsuno K, Yamguchi E, Nishimura M. Effects of molecular structural variants on serum Krebs von den Lungen-6 levels in sarcoidosis. J Transl Med. 2012;10:111.
46. Miyoshi S, Hamada H, Kadowaki T, Hamaguchi N, Ito R, Irifune K, Higaki J. Comparative evaluation of serum markers in pulmonary sarcoidosis. Chest. 2010;137:1391–7.
47. Kobayashi J, Kitamura S. Serum KL-6 for the evaluation of active pneumonitis in pulmonary sarcoidosis. Chest. 1996;109:1276–82.
48. Janssen R, Sato H, Grutters JC, Bernard A, van Velzen-Blad H, du Bois RM, van den Bosch JM. Study of Clara cell 16, KL-6, and surfactant protein-D in serum as disease markers in pulmonary sarcoidosis. Chest. 2003;124:2119–25.
49. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. J Intern Med. 2006;260:429–34.
50. Zhou Y, Chen X, Zhao M, Lower EE, Baughman RP. SACE and IL-2R as serum biomarkers for evaluation of multi-organ involvement and prognosis of sarcoidosis. Respir Res. 2023;24: 219.
51. Parasa VR, Forsslund H, Enger T, Lorenz D, Kullberg S, Eklund A, Skold M, Wahlstrom J, Grunewald J, Brighenti S. Enhanced CD8(+) cytolytic T cell responses in the peripheral circulation of patients with sarcoidosis and non-Lofgren's disease. Respir Med. 2018;138S:S38–44.

Publisher's Note