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Clinical Management Of Extrapulmonary Sarcoidosis: A Comparative Analysis Of Treatment Effects On Organ-Specific Involvement And Biochemical Parameters In Sarcoidosis Management

Abd El Aziz Saeed A Mohamed [1], Ahmad M. Omar[2], Ahmed M. Helmy[3], A.N. Abdelal[4], Mahmoud Abdallah Mansour Abdelrahman[5], Ayman S. A. M. Ayad[6], Hamada H .Hassan[7], Mohamed A. Younes[8], Kazem Mohamed Tayee[9], Suzan Eid Elshishtawy Ibrahim[10]

[1,2]Chest Diseases Department, Faculty of Medicine, Al-azhar University, Assuit, Egypt
[3]Internal medicine Department, Faculty of Medicine, Sohag University, Sohag, Egypt
[4]Neurology Department. Faculty of Medicine, Al-Azhar University, Assiut,Egypt
[5,6,7]Internal Medicine Department, Faculty of Medicine, AL-Azhar University,Assiut, Egypt
[8]Clinical Pathology Department, Faculty of Medicine, Al-Azhar University, Assuit, Egypt
[9]Internal medicine Department, Faculty of Medicine. Al-Azhar University, Cairo, Egypt
[10]Clinical pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt,
**Corresponding author: Abdelaziz Saeed A. Mohamed, Email: drabdelazizsaied2016@gmail.com*

Abstract:

Introduction: Extrapulmonary sarcoidosis is a complex multisystem disorder presenting diagnostic and therapeutic challenges. This study aims to evaluate and compare the effectiveness of immunosuppressants, TNF-α inhibitors, and corticosteroids in managing organ involvement and laboratory parameters in extrapulmonary sarcoidosis patients.

Method: This prospective case-control study was conducted at Al-Azhar hospital in Assuit, Egypt. Patients with confirmed extrapulmonary sarcoidosis were assigned to treatment groups based on immunosuppressants, tumor necrosis factor alpha (TNF-α) inhibitors, or corticosteroids, alongside healthy controls. Data, including clinical evaluations, laboratory tests, and imaging, were collected at baseline, 6 months, and 1 year. Clinical, laboratory, and radiological assessments of organ involvement were performed regularly to monitor disease progression and treatment response. Data were compared between treatment groups using statistical tests.

Results: Immunosuppressants improved ocular and neurological symptoms, TNF-α inhibitors prevented ocular worsening and enhanced neurological outcomes, and corticosteroids steadily reduced both; liver involvement decreased similarly across groups, while cardiac involvement varied, with immunosuppressants reducing it by one year and the other treatments showing temporary increases before improvement.The comparison of laboratory changes among sarcoidosis treatment groups showed that all treatments were associated with lower hemoglobin levels than healthy individuals, with TNF-α inhibitors having the greatest reduction; immunosuppressants led to the lowest white blood cell (WBC), platelet counts, and angiotensin-converting enzyme (ACE)levels were similar across groups. Calcium levels were elevated mainly in the corticosteroid group, and alkaline phosphatase levels were lower in the immunosuppressant and corticosteroid groups compared to TNF-α inhibitors and healthy controls. Despite significantly higher extrapulmonary involvement in all treatment groups compared to healthy individuals, no differences were observed between them.

Conclusion: In conclusion, the results demonstrate distinct effects of immunosuppressants, TNF-α inhibitors, and corticosteroids on sarcoidosis manifestations, highlighting the importance of individualized treatment approaches to optimize outcomes across organ involvement and laboratory parameters in this complex disease.

Keywords: Sarcoidosis, Extrapulmonary Sarcoidosis, Immunosuppressive Agents, TNF-α Inhibitors, Corticosteroids, Organ Involvement.

Introduction

Extrapulmonary sarcoidosis represents a clinically challenging manifestation of this multisystem granulomatous disease(1), affecting 30-50% of patients and requiring comprehensive therapeutic strategies that extend beyond conventional pulmonary management approaches(2-4). This systemic disorder, characterized by non-caseating granulomas, frequently involves multiple organs simultaneously. The most common extrapulmonary manifestations include cutaneous lesions, ganglionar, ocular involvement, lung involvement, lymphadenopathy, and hepatic disease (5, 6). The heterogeneous clinical presentation of extrapulmonary sarcoidosis varies significantly based on demographic factors, including age, sex, ethnicity, and geographic ancestry, with African-Americans demonstrating higher prevalence rates and females showing increased predilection for ocular and neurological manifestations(7), while isolated extrapulmonary disease occurs in a fewcases, necessitating thorough systemic evaluation in all patients(2, 3).

The clinical management of extrapulmonary sarcoidosis requires a multidisciplinary approach utilizing a hierarchical treatment paradigm, with corticosteroids remaining the cornerstone of first-line therapy, despite their significant dose-dependent adverse effects, including diabetes, hypertension, osteoporosis, and an increased risk of infection (8). Second-line immunosuppressive agents, particularly methotrexate and azathioprine, have demonstrated efficacy as steroid-sparing alternatives(9, 10), with methotrexate showing superior outcomes in multiple organ systems including cardiac sarcoidosis (effect size d=1.65)(11), ocular involvement (median time to treatment failure 34.5 months vs 8.4 months for mycophenolate mofetil), and reduced relapse rates (25% vs 57.6% compared to methylprednisolone therapy)(12). Tumor necrosis factor-alpha (TNF-α) is a powerful, multifunctional signaling protein and crucial cytokine that effectively influences a wide range of cell types (11, 13), the TNF-α inhibitors, particularly infliximab and adalimumab, have emerged as effective third-line therapies for refractory cases(11), demonstrating particular efficacy in cutaneous sarcoidosis (especially lupus pernio)(14), neurosarcoidosis with reduced relapse occurrence(15), and cardiac involvement, though their use requires careful monitoring due to contraindications in advanced heart failure and increased infection risk(14).

Biochemical parameter monitoring plays a crucial role in both diagnostic evaluation and therapeutic response assessment in extrapulmonary sarcoidosis, with serum angiotensin-converting enzyme (ACE) serving as the most commonly utilized biomarker despite its limited specificity(16), while emerging evidence supports the superior diagnostic and prognostic value of soluble interleukin-2 (IL-2) receptor levels, which demonstrate stronger correlation with disease severity (17). Calcium metabolism abnormalities, including hypercalcemia (occurring in about 10% of patients) and hypercalciuria (about 50% of patients), require systematic monitoring as they can lead to nephrocalcinosis and renal insufficiency(6). Additionally, organ-specific biochemical markers such as alkaline phosphatase elevation (ALT), indicating hepatic involvement(18), and specialized parameters, including cardiac biomarkers in cardiac sarcoidosis (19), provide essential guidance for treatment decision-making and monitoring therapeutic efficacy in this complex multisystem disease.

Objective

The objective of this study is to evaluate and compare the clinical effectiveness of immunosuppressants, TNF-α inhibitors, and corticosteroids in the management of extrapulmonary sarcoidosis by assessing their

impact on organ involvement and changes in laboratory parameters, aiming to inform personalized treatment strategies for improved patient outcomes.

Method and materials

Study design and participants

This prospective case-control study design was conducted at Al-Azhar hospital affiliated with Al-Azhar University, Assuit, Egypt, from January 2024 to March 2025 to evaluate the clinical management of extrapulmonary sarcoidosis. Patients diagnosed with extrapulmonary sarcoidosis were consecutively enrolled and assigned to treatment groups based on their prescribed therapy: immunosuppressants, TNF-α inhibitors, or corticosteroids. A control group of age- and sex-matched healthy individuals without sarcoidosis or chronic inflammatory conditions was also included. Patients were followed longitudinally over one year, with periodic assessments (at six months and one year follow-up) to monitor changes in organ involvement and laboratory parameters. The study aimed to compare treatment effectiveness and systemic impact across groups, providing insights into optimal therapeutic strategies for managing this complex multisystem disease.

Ethical consideration

The study was approved from the ethical committee of Al-Azhar University (Assuit) under the code number RESEARCH/AZ.AST./CHT019/11/226/1/2024. The study also conducted after obtaining informed consent from the patients according the ethical guidelines of Helsinki declaration.

Inclusion criteria

Inclusion criteria included adult patients (>18 years) diagnosed with extrapulmonary sarcoidosis based on clinical, radiological, and histopathological evidence; documented involvement of one or more extrapulmonary organs; and initiation of treatment with either immunosuppressants, TNF-α inhibitors, or corticosteroids. Participants needed to provide informed written consent and agree to comply with study procedures and follow-up visits. The control group consists of healthy individuals matched for age and sex without evidence of sarcoidosis or other chronic inflammatory diseases.

Exclusion criteria

Exclusion criteria include patients with pulmonary-only sarcoidosis without extrapulmonary involvement, presence of active infections or malignancies, concurrent autoimmune or systemic inflammatory diseases that could confound assessment, previous treatment with combination regimens outside the defined groups, and inability to provide informed consent or adhere to study protocols. Patients who progressed to a severe condition of disease that may interfere with evaluation or pose an increased risk from study participation are also excluded.

Group classification

The group classification included a control group of healthy individuals and three patient groups categorized based on their primary treatment regimen for extrapulmonary sarcoidosis: immunosuppressants, TNF-α inhibitors, or corticosteroids. Patients were assigned to a treatment group according to the initial prescribed therapy at baseline, ensuring a clear distinction for comparative analysis.

Data collection

Data for this study were collected through a systematic and standardized process involving clinical evaluations, laboratory testing, and radiological assessments, longitudinally. At baseline and scheduled follow-up visits throughout the six-month and one-year study follow-up, demographic information (age, gender, and used drugs for sarcoidosis treatment) and detailed medical histories were recorded using structured questionnaires and patient interviews. Clinical data on organ involvement and symptom severity were obtained through physical examinations and specialist assessments. Data collection for the laboratory parameters comparison involved standardized blood sample collection from all study participants, including

healthy controls and patients in each treatment group (immunosuppressants, TNF-α inhibitors, corticosteroids), at three defined time points: baseline, 6 months, and 1 year. Each sample was analyzed for hemoglobin (Hb), white blood cell count (WBC), platelet count (PLT), ACE, calcium (Ca), ALT, and measures of extrapulmonary involvement volume using validated laboratory assays and imaging techniques. All laboratory tests were performed in accredited laboratories according to established protocols to ensure consistency and accuracy.

Outcome measurement

The outcome measurement for this study involved a comprehensive evaluation of clinical, radiological, and laboratory parameters at baseline and during 1-year follow-up to assess the effects of immunosuppressants, TNF-α inhibitors, and corticosteroids on organ involvement and disease activity in patients with extrapulmonary sarcoidosis. Clinical outcomes were measured through standardized assessments of ocular and neurological symptoms, alongside imaging and functional tests to evaluate liver and cardiac involvement. Laboratory evaluations included serial measurements of hematologic indices (hemoglobin, WBC, platelet count), biochemical markers (ACL, calcium, and ALT), and extrapulmonary disease burden. These objective measures were supplemented by imaging modalities and clinical symptom tracking to capture changes over time. Statistical analyses compared these parameters across treatment groups and against healthy controls to identify significant differences and treatment-specific effects.

Statistical analysis

The data analysis was conducted using Statistical Package for Social Sciences (SPSS) version 27 (IBM Corporation, Armonk, NY, USA). Normality of data distribution was evaluated using the Shapiro-Wilk test, and homogeneity of variances was assessed with Levene's test. Both parametric and non-parametric statistical methods were initially considered; however, parametric tests were ultimately chosen due to their greater accuracy and robustness for hypothesis testing, as both approaches produced similar P-values across all variables. Group differences were analyzed using Pearson's Chi-square test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Longitudinal changes within groups from baseline to one-year follow-up were examined using repeated measures ANOVA followed by Scheffé post hoc tests. A P-value <0.05 was considered significant.

Results

The comparative analysis of demographic characteristics across the treatment groups of participants showed that the distribution of gender among the groups was relatively balanced, with females representing the majority in the healthy control and immunosuppressant groups, while males were more prevalent in the TNF-α inhibitors and corticosteroids groups. The differences in gender distribution across groups were not statistically significant. Regarding age, the mean age of participants in the TNF-α inhibitors group was somewhat higher compared to the other groups, although this difference did not reach statistical significance. Overall, the groups were similar in terms of gender composition and age (**Table 1**).

Table 1. Demographic characteristics comparative analysis across treatment groups of participants

Demographic data		Treatment group								P Value
		Healthy control N = 15		Immunosuppressant N = 15		TNF-α inhibitors N = 15		Corticosteroids N = 15		
		N	%	N	%	N	%	N	%	
Gender	Female	9	60	9	60	6	40	7	46.7	0.614*
	Male	6	40	6	40	9	60	8	53.7	
Age (year; mean ± SD)		45.48 ± 10.84		41.26 ± 9.51		47.82 ± 10.88		41.11 ± 7.20		0.173**
TNF-α ; Tumor necrosis factor-alpha, SD; Standard deviation, *Chi-square, **One-way ANOVA										

The results indicated in comparing the three sarcoidosis treatment groups, immunosuppressants, TNF-α inhibitors, and corticosteroids, distinct patterns in ocular and neurological involvement were observed. The immunosuppressant group showed the highest frequency of both ocular and neurological involvement at baseline, with a tendency for both neurological manifestations and ocular symptoms to decrease over time. The TNF-α inhibitors group had a lower baseline frequency of ocular involvement compared to the immunosuppressant group, but ocular symptoms tended to persist or increase slightly during follow-up, while neurological symptoms were decreased across the study period. The corticosteroid group presented with moderate levels of both ocular and neurological involvement, generally showing a stable decrease in these manifestations over time. In between-group analysis, although both ocular and neurological involvements in the immunosuppressant group at baseline were significantly greater than the other two groups, at two other times of 6 months and 1 year, no statistically significant differences were found between the three groups (**Table 2**).

Table 2. Comparative analysis of ocular and neurological involvement across sarcoidosis treatment groups during the study period

Involved organ			Treatment group						P Value*
			Immunosuppressant N = 15		TNF-α inhibitors N = 15		Corticosteroids N = 15		
			N	%	N	%	N	%	
Ocular	Baseline	NO	2	13.3	9	60			0.008
		Yes	13	86.7	6	40			
		NO	2	13.3			11	73.3	<0.001
		Yes	13	86.7			4	26.7	
		NO			9	60	11	73.3	0.439
		Yes			6	40	4	26.7	
	6 months	NO	9	60	5	33.3			0.143
		Yes	6	40	10	66.7			
		NO	9	60			5	33.3	0.143
		Yes	6	40			10	66.7	
		NO			5	33.3	5	33.3	>0.999
		Yes			10	66.7	10	66.7	
	1 year	NO	9	60	8	53.3			0.713
		Yes	6	40	7	46.7			
		NO	9	60			9	60	>0.999
		Yes	6	40			6	40	
		NO			8	53.3	9	60	0.713
		Yes			7	46.7	6	40	
Neurological	Baseline	NO	1	6.7	5	33.3			0.068
		Yes	14	93.7	10	66.7			
		NO	1	6.7			9	60	0.002
		Yes	14	93.3			6	40	
		NO			5	33.3	9	60	0.143
		Yes			10	66.7	6	40	
	6 months	NO	6	40	9	60			0.273
		Yes	9	60	6	40			
		NO	6	40			11	73.3	0.065
		Yes	9	60			4	26.7	
		NO			9	60	11	73.3	0.439
		Yes			6	40	4	26.7	

	1 year	NO	9	60	11	73.3			0.439
		Yes	6	40	4	26.7			
		NO	9	60			11	73.3	0.439
		Yes	6	40			4	26.7	
		NO			11	73.3	11	73.3	>0.999
		Yes			4	26.7	4	26.7	
TNF-α ; Tumor necrosis factor-alpha, N; Number, *Pearson Chi-square									

The comparative analysis of liver involvement across the sarcoidosis treatment groups indicated that at baseline, liver involvement was relatively high in all groups, with no significant difference between them. Within each group, liver involvement generally decreased over the study period; however, no statistical difference was observed at six months or one year between the three groups. Regarding cardiac involvement, the baseline frequency was comparable across all groups, showing no significant differences. Cardiac involvement showed slight fluctuations over time within the different treatment groups. Patients treated with immunosuppressants exhibited a reduction in cardiac involvement by the one-year mark. In contrast, the groups receiving TNF-α inhibitors and corticosteroids experienced more variable patterns of cardiac involvement. Specifically, cardiac involvement tended to increase at the six-month follow-up compared to baseline levels but demonstrated a decrease when assessed at the one-year follow-up relative to baseline. Between groups, cardiac involvement rates were generally similar at each time point, although at six months, the TNF-α inhibitors group showed a tendency towards a higher frequency of cardiac involvement compared to the immunosuppressant group, a difference that was not statistically conclusive (**Table 3**).

Table 3. Comparative analysis of liver and cardiac involvement across sarcoidosis treatment groups during the study period

Involved organ			**Treatment group**						**P Value***
			Immunosuppressant N = 15		**TNF-α inhibitors N = 15**		**Corticosteroids N = 15**		
			N	**%**	**N**	**%**	**N**	**%**	
Liver	**Baseline**	NO	4	26.7	2	13.3			0.361
		Yes	11	73.3	13	86.7			
		NO	4	26.7			4	26.7	>0.999
		Yes	11	73.3			11	73.3	
		NO			2	13.3	4	26.7	0.361
		Yes			13	86.7	11	73.3	
	6 months	NO	6	40	6	40			>0.999
		Yes	9	60	9	60			
		NO	6	40			9	60	0.273
		Yes	9	60			6	40	
		NO			6	40	9	60	0.273
		Yes			9	60	6	40	
	1 year	NO	6	40	6	40			>0.999
		Yes	9	60	9	60			
		NO	6	40			9	60	0.273
		Yes	9	60			6	40	
		NO			6	40	9	60	0.273
		Yes			9	60	9	60	
C	**Baseline**	NO	6	40	6	40			>0.999

		Yes	9	60	9	60			
		NO	6	40			6	40	>0.999
		Yes	9	60			9	60	
		NO			6	40	6	40	>0.999
		Yes			9	60	9	60	
	6 months	NO	8	53.3	3	20			0.058
		Yes	7	46.7	12	80			
		NO	8	53.7			5	33.3	0.269
		Yes	7	46.7			10	66.7	
		NO			3	20	5	33.3	0.409
		Yes			12	80	10	66.7	
	1 year	NO	11	73.3	12	80			0.666
		Yes	4	26.7	3	20			
		NO	11	73.3			7	46.7	0.136
		Yes	4	26.7			8	53.3	
		NO			12	80	7	46.7	0.058
		Yes			3	20	8	53.3	
TNF-α ; Tumor necrosis factor-alpha, N; Number,*Pearson Chi-square									

Based on the table comparing laboratory parameters among treatment groups, the study revealed distinct patterns of hematological and biochemical changes across different therapeutic interventions over the study period. Hemoglobin levels consistently differed significantly between groups at all-time points, with healthy controls maintaining the highest values, followed by the corticosteroids group, while the TNF-α inhibitors group showed the lowest concentrations throughout the study duration. White blood cell counts demonstrated significant inter-group differences at baseline and six months, though these differences became non-significant by one year, suggesting potential convergence of immune cell populations over time. Platelet counts showed no significant differences between groups at any time point, indicating that these treatments did not substantially affect thrombocyte levels. The ACE levels, a marker often elevated in sarcoidosis, showed no significant differences between treatment groups throughout the study, suggesting similar disease activity control across interventions. Calcium levels exhibited significant differences at baseline and six months, with variations normalizing by one year, potentially reflecting differential effects on calcium metabolism or granulomatous inflammation. The ALP levels showed progressive significance in inter-group differences over time, with the most pronounced differences emerging at one year, indicating potential hepatic effects that became more apparent with prolonged treatment exposure. Extrapulmonary manifestations consistently differed significantly between the healthy control group and all treatment groups at every time point, as expected, given that controls had no disease involvement while all patient groups exhibited measurable extrapulmonary disease burden that varied among the different therapeutic approaches(**Table 4**).

Table 4. Comparison of laboratory parameters among treatment groups during the study period

Laboratory test		**Treatment group**								**P Value***
		Healthy control N = 15		**Immunosuppressant N = 15**		**TNF-α inhibitors N = 15**		**Corticosteroids N = 15**		
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Hb (g/dl)	**Baseline**	15.45	0.70	14.09	0.36	13.55	0.50	14.45	0.51	<0.001
	6 months	15.20	0.71	13.84	0.38	13.30	0.50	14.20	0.49	<0.001

	1 years	15.31	0.69	13.95	0.37	13.41	0.50	14.31	0.50	<0.001
WBC(×10⁹/L)	**Baseline**	5.18	0.36	4.33	0.76	4.64	0.48	5.07	0.82	0.002
	6 months	5.06	0.36	4.21	0.75	4.52	0.48	4.95	0.81	0.002
	1 years	4.92	0.36	4.83	0.67	4.62	0.54	4.96	0.52	0.322
PLT (×10⁹/L)	**Baseline**	211.50	46.40	239.96	88.10	193.87	69.06	237.53	55.25	0.189
	6 months	210.40	46.40	238.86	88.10	192.77	69.06	236.43	55.23	0.187
	1 years	205.76	51.30	218.25	53.16	228.87	59.49	214.86	67.01	0.750
ACE (mg/dL)	**Baseline**	62.95	10.77	55.72	14.50	52.88	13.93	49.13	25.55	0.168
	6 months	57.50	15.01	56.71	18.53	52.19	15.09	54.39	21.82	0.846
	1 years	63.94	19.41	51.90	9.26	51.32	7.81	52.21	18.60	0.065
Ca (mg/dL)	**Baseline**	9.20	0.33	9.61	0.61	9.06	0.83	9.70	0.64	0.018
	6 months	9.28	0.38	9.30	0.68	8.87	0.49	9.64	0.54	0.004
	1 years	9.02	0.41	9.20	0.51	9.10	0.46	9.46	0.52	0.082
ALT (U/L)	**Baseline**	28.74	11.46	18.73	10.60	25.65	10.87	19.19	9.61	0.030
	6 months	28.01	12.50	17.23	6.68	25.55	10.57	18.76	4.85	0.005
	1 years	29.04	9.11	22.74	7.94	26.75	9.02	15.87	9.34	<0.001
Extra Pulmonary (ml)	**Baseline**	0	0	213.12	37.93	194.14	45.38	201.66	37.65	<0.001
	6 months	0	0	206.97	54.38	214.26	29.73	207.94	53.43	<0.001
	1 years	0	0	182.70	38.97	203.68	44.13	183.61	32.82	<0.001

TNF-α; Tumor necrosis factor-alpha,Ca; calcium, ALT; Alanine transaminase, Hb, Hemoglobin, ACE; Angiotensin-converting enzyme, SD; Standard deviation,N; Number, *One-way ANOVA

The comparison of overall laboratory test changes between treatment groups over the study period revealed several key differences and similarities. Hemoglobin level was highest in the healthy individuals and showed significant differences compared to all treatment groups, with the greatest differences observed between healthy controls and the TNF-α inhibitors group. Among treatment groups, TNF-α inhibitors

demonstrated the lowest level and showed significant differences compared to both immunosuppressant and corticosteroid groups, while corticosteroids showed a trend toward significance compared to immunosuppressant but did not reach it. The WBC had the lowest level in the immunosuppressant-treated patients and differed significantly compared to healthy individuals and corticosteroid-treated patients, with borderline significance for TNF-α inhibitors. The corticosteroid-treated and TNF-α inhibitor-treated patients did not significantly differ from healthy controls. Platelet counts and ACE level did not show significant differences between any groups or treatments.Calcium level changes were significantly higher in the corticosteroid group compared to healthy controls; however, the other two groups showed no significant difference compared to healthy individuals. Among treatment groups, corticosteroid-treated patients showed significantly higher levels compared to TNF-α inhibitors and no significant difference with the immunosuppressant group. The immunosuppressant group showed significantly higher levels of calcium compared to the TNF-α inhibitors.The ALT levels were highest in the healthy controls and differed significantly compared to both immunosuppressant and corticosteroids, with TNF-α inhibitors differing non-significantly from controls. Among treatments, the TNF-α inhibitors group had significantly higher levels of ALT compared to both the immunosuppressant and corticosteroids groups, but no significant difference was found between them.Lastly, extrapulmonary measurements significantly differed between healthy controls and all treatment groups, but no significant differences were observed among the treatment groups themselves

Table 5. Comparison of overall laboratory test changes between treatment groups over the study period

Test	Group 1	Group 2	Mean difference	95% CI		P Value*
				Lower	Upper	
Hb (g/dl)	Healthy	Immunosuppressant	1.35	0.96	1.74	<0.001
		TNF-α inhibitors	1.89	1.50	2.28	<0.001
		Corticosteroids	0.99	0.60	1.38	<0.001
	Immunosuppressant	TNF-α inhibitors	0.54	0.15	0.93	0.007
		Corticosteroids	0.35	-0.03	0.075	0.071
	TNF-α inhibitors	Corticosteroids	0.90	0.51	1.29	<0.001
WBC(×10⁹/L)	Healthy	Immunosuppressant	0.59	0.11	1.07	0.008
		TNF-α inhibitors	0.45	-0.02	0.93	0.067
		Corticosteroids	0.05	-0.42	0.53	0.989
	Immunosuppressant	TNF-α inhibitors	0.14	-033	0.62	0.868
		Corticosteroids	0.54	0.06	1.02	0.021
	TNF-α inhibitors	Corticosteroids	0.39	-0.08	0.87	0.138
PLT (×10⁹/L)	Healthy	Immunosuppressant	23.13	-27.47	73.75	0.631
		TNF-α inhibitors	4.04	-46.56	54.66	0.997
		Corticosteroids	20.38	-30.23	70.99	0.589
	Immunosuppressant	TNF-α inhibitors	27.18	-23.42	77.80	0.500
		Corticosteroids	2.75	-47.86	53.36	0.999
	TNF-α inhibitors	Corticosteroids	24.43	-26.18	75.04	0.589
ACE (mg/dL)	Healthy	Immunosuppressant	6.68	-1.70	15.07	0.165
		TNF-α inhibitors	9.33	0.94	17.72	0.023
		Corticosteroids	9.55	1.16	17.93	0.019
	Immunosuppressant	TNF-α inhibitors	2.65	-5.73	11.03	0.842
		Corticosteroids	2.86	-5.51	11.25	0.808
	TNF-α inhibitors	Corticosteroids	0.21	-8.16	8.60	>0.999
Ca (m	Healthy	Immunosuppressant	0.20	-0.12	0.53	0.384
		TNF-α inhibitors	0.15	-0.17	0.48	0.613

		Corticosteroids	0.43	0.09	0.76	0.006
	Immunosuppressant	**TNF-α inhibitors**	0.35	0.02	0.69	0.029
		Corticosteroids	0.22	-0.10	0.56	0.283
	TNF-α inhibitors	**Corticosteroids**	0.58	0.25	0.92	<0.001
ALT (U/L)	**Healthy**	**Immunosuppressant**	9.03	3.84	14.22	<0.001
		TNF-α inhibitors	2.61	-2.58	7.80	0.556
		Corticosteroids	10.65	5.46	15.85	<0.001
	Immunosuppressant	**TNF-α inhibitors**	6.42	1.23	11.61	0.009
		Corticosteroids	1.62	-3.56	6.81	0.845
	TNF-α inhibitors	**Corticosteroids**	8.04	2.85	13.24	<0.001
Extra Pulmonary (ml)	**Healthy**	**Immunosuppressant**	200.93	175.67	226.19	<0.001
		TNF-α inhibitors	204.03	178.76	229.28	<0.001
		Corticosteroids	197.73	172.47	223.01	<0.001
	Immunosuppressant	**TNF-α inhibitors**	3.09	-28.36	22.16	0.989
		Corticosteroids	3.19	-22.06	28.45	0.987
	TNF-α inhibitors	**Corticosteroids**	6.29	-18.96	31.55	0.915

TNF-α ; Tumor necrosis factor-alpha,Ca; calcium, ALT; Alanine transaminase, ACE; Angiotensin-converting enzyme, SD; Standard deviation, *Repeated measures ANOVA followed by post hoc Scheffe test

Discussion

Our results demonstrated that in patients with extrapulmonary sarcoidosis immunosuppressants treatment notably improve ocular and neurological involvement over time, TNF-α inhibitors prevent ocular symptom progression while enhancing neurological outcomes, and corticosteroids consistently reduce both ocular and neurological manifestations; meanwhile, liver involvement decreases similarly across all treatment groups, and cardiac involvement fluctuates slightly with immunosuppressants showing reduction by one year and TNF-α inhibitors and corticosteroids exhibiting variable trends including a temporary increase at six months followed by improvement.The present results demonstrating superior efficacy of immunosuppressants for ocular and neurological involvement, protective effects of TNF-α inhibitors against ocular symptom progression with enhanced neurological outcomes, and consistent corticosteroid reduction in both manifestations align with established literature patterns. Previous comparative analyses have documented that sarcoid uveitis generally demonstrates better visual outcomes than other non-infectious uveitides (10-year best-corrected visual acuity [BCVA]anterior uveitis 0.06 vs 0.24), requiring oral corticosteroids more frequently (45.9% vs 16.4%) but with reduced need for second-line immunosuppression compared to other inflammatory conditions(20). The observed neurological improvement with TNF-α inhibitors corresponds with a studyby Sambon et al demonstrating superior effectiveness of TNF-α antagonists compared to methotrexate, mycophenolate mofetil, or azathioprine in neurosarcoidosis, with earlier use recommended for aggressive or refractory cases(21). Cardiac sarcoidosis studies parallel these findings, showing mean left ventricular ejection fraction (LVEF) improvement from 27% to 37% with immunosuppressive therapy, predominantly prednisone (88%) combined with mycophenolate (32%) and methotrexate (28%)(22).

The temporal patterns observed in hepatic involvement decreasing uniformly across treatment modalities and cardiac fluctuations with temporary six-month increases followed by improvement represent previously underreported phenomena that warrant further investigation within the context of organ-specific treatment responses. Hepatic sarcoidosis typically demonstrates favorable treatment responses, with studies reporting overall benign disease courses despite diverse treatment regimens including glucocorticoids (55% for one year, 18% for 5-10 years), conventional disease-modifying anti-rheumatic drugs (DMARDs)(53%

receiving azathioprine [81%], methotrexate [46%], hydroxychloroquine [10%]), and biologics (8%)(23). The cardiac involvement fluctuation pattern aligns with observations that cardiac sarcoidosis patients frequently demonstrate variable treatment responses, with a study by v et al showing complete/partial treatment response rates higher in extracardiac sarcoidosis compared to isolated cardiac sarcoidosis (81% vs 58%), and greater major adverse cardiovascular events in isolated cardiac cases (HR 3.9 [1.6-9.7])(24). The consistent hepatic improvement may reflect the inherently responsive nature of hepatic granulomas to anti-inflammatory therapy, as documented in cases showing biochemical response improvement following corticosteroid initiation, with studies demonstrating normalization of liver enzymes in most treated patients regardless of specific therapeutic agent employed(25).

This analysis highlights distinct organ-specific treatment responses in extrapulmonary sarcoidosis, improving understanding of how therapies work across different manifestations. It shows immunosuppressants are most effective for eye and neurological issues, TNF-α inhibitors both prevent eye disease progression and aid neurological recovery, and corticosteroids work well across multiple organs. The study also uncovers unique timing patterns, such as consistent liver response and fluctuating heart involvement. These insights support developing targeted treatment plans based on affected organs, emphasizing early, tailored immunosuppressive use to enhance outcomes and reduce side effects. Future trials studies considering these patterns will be key to creating better guidelines and improving long-term care for this complex disease.

Our results in patients with extrapulmonary sarcoidosis indicated that the comparison of laboratory changes across treatment groups revealed that all treatment groups had significantly lower levels of hemoglobin compared to healthy individuals, with TNF-α inhibitors resulting in the lowest; WBC levels were lowest with immunosuppressants, but similar between corticosteroids, TNF-α inhibitors, and healthy controls. Platelet counts and ACE levels showed no significant differences across treatment groups. Calcium levels were elevated primarily in the corticosteroid group, and ALT levels were significantly lower in the immunosuppressants and corticosteroid group compared to healthy individuals and TNF-α inhibitors treatment. Extrapulmonary involvement volume was significantly higher compared to healthy individuals but similar across treatment groups.These findings are consistent with prior literature. Previous research confirms anemia and leukopenia as relatively common findings in sarcoidosis patients, with immunosuppressive regimens often linked to hematologic alterations, including neutropenia and thrombocytopenia(26, 27). The elevation of calcium primarily in corticosteroid-treated groups parallels reports describing corticosteroid-induced alterations in calcium metabolism and an increased risk of hypercalcemia in sarcoidosis patients, emphasizing the need for careful monitoring(28, 29). Additionally, reductions in liver functional tests with corticosteroids and immunosuppressants correspond to improved hepatic inflammation and granulomatous activity, as documented in hepatic sarcoidosis management(30, 31). The similarity of extrapulmonary involvement volume across treatment groups supports literature suggesting that, despite therapy variations, organ burden reflects intrinsic disease severity and progression rather than treatment modality alone(27, 32).

This analysis elucidates distinct biochemical alterations linked to each therapeutic class in extrapulmonary sarcoidosis and affirms the necessity of personalized treatment with close laboratory surveillance to optimize outcomes and minimize adverse effects. The findings endorse integrating biomarkers such as hemoglobin, WBC, calcium, and ALT in routine clinical follow-up to guide treatment adjustments and detect complications early. Future prospective studies should further validate these biochemical markers for their prognostic and monitoring roles, facilitating evidence-based, organ-specific management strategies tailored to the multisystem nature of the disease. Beside laboratory biomarkers of Sarcoidosis, the role of radiology is most important in diagnosis and surveillance, hence the diagnosis of sarcoidosis can be confirmed by Computed tomography (CT) of the chest that demonstrates high sensitivity (33). Future studies should concentrates on the advantage of using CT as adiagnostic and sensitive tool for assessment and surveillance of Sarcoidosis.

Limitations of the study

This study has several limitations, including a relatively small sample size, which may affect the generalizability of the findings. The single-center design limits broader applicability across diverse populations. Potential confounding factors related to varying disease severity and patient adherence to treatments were challenging to control fully. Additionally, the follow-up duration of one year may be insufficient to capture long-term outcomes and late adverse effects of the therapies.

Conclusion

In conclusion, the study highlights that immunosuppressants, TNF-α inhibitors, and corticosteroids each demonstrate distinct benefits and effects in treating sarcoidosis, with immunosuppressants improving ocular and neurological symptoms, TNF-α inhibitors preventing ocular progression and enhancing neurological outcomes, and corticosteroids steadily reducing both; liver involvement improved similarly across all treatments, while cardiac involvement showed variable patterns, including reductions with immunosuppressants and transient increases with other therapies. Laboratory findings further emphasize treatment-specific impacts on hematologic and biochemical parameters, underlining the need for personalized approaches to optimize management of this complex multisystem disease.

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Conflicts of interest

The authors declare no conflict of interest.

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Ethical issues

The study was conducted under the tents of the Declaration of Helsinki. Informed written consent was obtained from all participants. This study resulted from a researchproject conducted at Al-Azhar hospital with registration number (NO; RESEARCH/AZ.AST./CHT019/11/226/1/2024) approved by the Institutional Review Board (IRB) and the ethics committee of the medicine faculty, Al-Azhar University (Assiut), Egypt. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI **(**Perplexity.ai and Grammarly.com) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

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