



Original Research

Renal disease in sarcoidosis patients in a German multicentric retrospective cohort study



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ARTICLE INFO

ABSTRACT

Keywords:

Sarcoidosis

Interstitial nephritis

Chronic kidney failure

Biomarkers

Introduction: Sarcoidosis is a systemic granulomatous disease potentially affecting every organ system. Renal involvement is reportedly rare, and the evidence consists of case reports and cohort studies. Systematic investigations are scarce and show a varying prevalence ranging from <1% to 30–50%.

Methods: We retrospectively analyzed data from patients with a recent diagnosis of sarcoidosis from five tertiary care centers focusing on renal sarcoidosis.

Results: We analyzed data from 327 patients with sarcoidosis between 2001 and 2021. Of 327 patients, 109 (33.3%) had probable or definite renal sarcoidosis. 90 (27.5%) had histopathologic confirmation. 57 (64%) had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m². The most prominent associated finding was an elevated soluble interleukin-2 receptor. Patients with renal sarcoidosis more frequently received glucocorticoids than other non-renal sarcoidosis patients (92% vs. 78%, *p* < 0.01). Also, azathioprine (38% vs. 16%, *p* < 0.001) and mycophenolate mofetil (5% vs. 1%, *p* < 0.05) were more frequently used in renal sarcoidosis compared to non-renal sarcoidosis, whereas methotrexate was used less frequently (7% vs. 17%, *p* < 0.05).

Conclusions: Our data of the largest cohort with biopsy-confirmed renal sarcoidosis demonstrate a higher prevalence (27.5% of all patients) than previously published with a relevant disease burden. The urinary findings in most cases were only mildly abnormal, and some patients did not have renal biopsy despite abnormal urinary results. A renal workup should be performed in all patients with a new diagnosis of sarcoidosis.

1. Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology affecting potentially every organ system [1]. It is the most common granulomatous disease in Northern Europe and North America, with incidences ranging from 10 to 30/100.000 people [2–7]. Pulmonary sarcoidosis is the most frequent organ manifestation in approximately 90–95% of all cases. Other frequently affected organs include the lymph nodes, skin, eyes, liver, heart, parotid glands, and the musculoskeletal system [1,8]. Renal manifestations of sarcoidosis are well-described, but their prevalence is considered rare, with a reported prevalence of less than 5% of patients [9–11]. In some recent reviews, renal manifestations

are not mentioned at all [1]. Available data are reported in case reports and relatively small cohort studies. Thus, the true prevalence of renal disease in sarcoidosis is unknown [12–15]. Systematic investigations and larger cohorts are scarce and show a substantial variability ranging from <1% [9,11] to 30–50% [15–17] of all sarcoidosis patients. In rare cases, isolated renal sarcoidosis may also occur [18]. Significant shortcomings of the available data are differences in case definitions and study designs, especially the lack of available kidney biopsy data and its correlation with other organ manifestations and laboratory findings.

The most common histological form of renal sarcoidosis is, according to previous data, granulomatous interstitial nephritis (GIN), but granulomas can be absent (interstitial nephritis, IN) [12–14]. Other

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manifestations are secondary forms of glomerulonephritis (sGN), nephrocalcinosis (NC), or nephrolithiasis [14,19–27]. Here, we aimed to investigate the prevalence of renal sarcoidosis in a sizeable German registry from five regionally dispersed tertiary care centers and identify clinical, laboratory, and histopathological parameters associated with renal sarcoidosis.

2. Methods

2.1. Patient population and setting

We retrospectively analyzed cross-sectional patient data with a diagnosis of sarcoidosis made during their hospital stay in five tertiary care centers from different areas in Germany (Darmstadt, Göttingen, Ludwigshafen, Offenbach, Trier). Hospitalized patients were identified through the hospital databases according to the international classification of diseases (ICD) codes for sarcoidosis and not through specialty clinics. We excluded acute presentations of sarcoidosis, i.e., Löfgren's syndrome or Heerfordt's syndrome. A diagnosis of sarcoidosis was obtained by histological evidence of non-caseating epithelioid granulomas in at least one organ and exclusion of other granulomatous diseases in all patients, in line with the latest recommendations on the diagnosis of sarcoidosis [28]. Inclusion criteria were: (1) patients with a diagnosis of sarcoidosis based on the American Thoracic Society (ATS) recommendations [28], and (2) at least one of three urine abnormalities: diminished estimated glomerular filtration rate (eGFR), proteinuria, or abnormal urinary sediment.

2.2. Data collection

We collected routine epidemiologic and clinical data, including age, sex, and organ manifestations of sarcoidosis. Renal data included estimated glomerular filtration rate (eGFR), urine sediment, proteinuria, and, if available, renal histopathology. In addition, laboratory data, such as markers of inflammation, including complete blood count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), were recorded. Furthermore, the potentially valuable markers of disease activity, angiotensin-converting enzyme (ACE), and soluble interleukin-2 receptor (sIL-2R) were analyzed. Finally, serum calcium, and vitamin D3 (25-OH and 1,25-OH), were collected, if available. Missing data were also recorded. Data were collected during the evaluation (usually the entire hospital stay) and reflected the worst pathological value for all captured parameters.

The eGFR (in ml/min/1.73 m²) was calculated according to the CKD-EPI formula [29]. Proteinuria was documented in a 24-h urine collection in mg/24 h or milligram per gram creatinine (mg/g crea) in spot urine samples. Parameters of the urinary sediment searched for included erythrocytes, leukocytes, and casts (erythrocyte, leukocyte, or granular casts). Findings of ≥ 5 erythrocytes per high power field (HPF) and ≥ 5 leucocytes per HPF without evidence of bacteriuria were interpreted as pathologic. Any detection of a cast was also judged as a pathologic finding.

2.3. Classification of diagnostic certainty

If applicable, organ manifestations were classified according to the WASOG organ assessment instrument as previously published [30]. In addition, the diagnostic assessment of an organ manifestation was stratified as either 'not investigated', 'investigated but unremarkable', 'clinical suspicion', 'suspicion based on laboratory/imaging', or 'histopathologic confirmation'. The indication for a kidney biopsy was based on the treating physicians' decision (abnormal eGFR, proteinuria, pathologic urine sediment).

There is no widely accepted definition for renal sarcoidosis, and the WASOG organ assessment instrument offers no consensus definition of what constitutes a "highly probable" renal sarcoidosis [30]. Thus, renal

findings were stratified into five groups: (1) 'not investigated'; (2) 'not suspicious for renal sarcoidosis' or classified as 'unremarkable'; (3) 'suspicious results for renal sarcoidosis', but without histologic evidence (i.e., tubular proteinuria, abnormal urinary sediment, or diminished eGFR in a sarcoidosis patient without an alternative explanation, such as diabetes or arterial hypertension); (4) available kidney biopsy with 'compatible histopathology' (GIN, interstitial nephritis [IN], NC, nephrolithiasis [NL], and sGN); (5) kidney biopsy with a 'histopathology result other than sarcoidosis' (e.g., diabetic nephropathy, hypertensive nephropathy, other). Renal sarcoidosis was defined as "probable" or "definite" when there were laboratory and urine findings consistent with sarcoidosis after the exclusion of other causes in the absence of biopsy results (probable) or consistent findings with an available kidney biopsy showing one of the above findings (definite).

For group comparisons between renal and non-renal sarcoidosis, patients were classified as having either probable or definite renal sarcoidosis (groups 3 and 4, as mentioned above) or non-renal sarcoidosis.

2.4. Statistical analysis

Demographic data of the study population were analyzed by descriptive statistics. Non-parametric between-group comparisons were performed, depending on the data, using Pearson's Chi-Square, Fisher's exact, Mann-Whitney, and Kruskal Wallis tests. Post-hoc analysis for multiple comparisons was performed with Dunn's test. Univariate logistic regression was performed to identify variables associated with an increased risk of renal sarcoidosis. Venn diagrams were plotted to compare diagnostic properties of laboratory and renal parameters suggestive of renal sarcoidosis. Sensitivity, specificity, negative and positive predictive values of simple, two-outcome rules and using a recursive partition tree [31] with exact 95% confidence intervals [32].

Two-sided p-values <0.05 were considered statistically significant. Data analyses were performed with GraphPad Prism (version 9.3.1 for macOS, GraphPad Software, San Diego, California, USA) and R (version 4.1.3).

2.5 Ethics approval

Each participating center obtained approval from the respective ethics committee as per local requirements, or ethics approval was waived due to the retrospective nature of routine data analysis.

3. Results

We analyzed data from 327 patients recruited from five centers with a diagnosis of sarcoidosis between 2001 and 2021. Of 327 patients, 109 (33.3%) had a probable or definite diagnosis of renal sarcoidosis (groups 3 and 4 as per the definition above), 197 (60.2%) patients were classified as non-renal sarcoidosis, and 21 (6.4%) were unclassifiable because renal sarcoidosis had not been assessed.

In addition, renal data were available for almost all 109 patients: eGFR was available for 108/109 (99.1%) patients, data from urine sediments for 104/109 (95.4%), and data on proteinuria for 103/109 patients (94.5%). The patient disposition is depicted in Fig. 1.

3.1. Characteristics of the study cohort: renal vs. non-renal sarcoidosis patients

The median age of the total cohort was 52 years (range 18–86 years), and the sex was balanced with 49% female patients. The baseline characteristics, including organ manifestations, laboratory data, and treatments, are shown in Table 1, stratified according to the presence or absence of renal sarcoidosis. Twenty-one unclassifiable patients were excluded from further analyses.

Patients with probable or definite renal sarcoidosis were

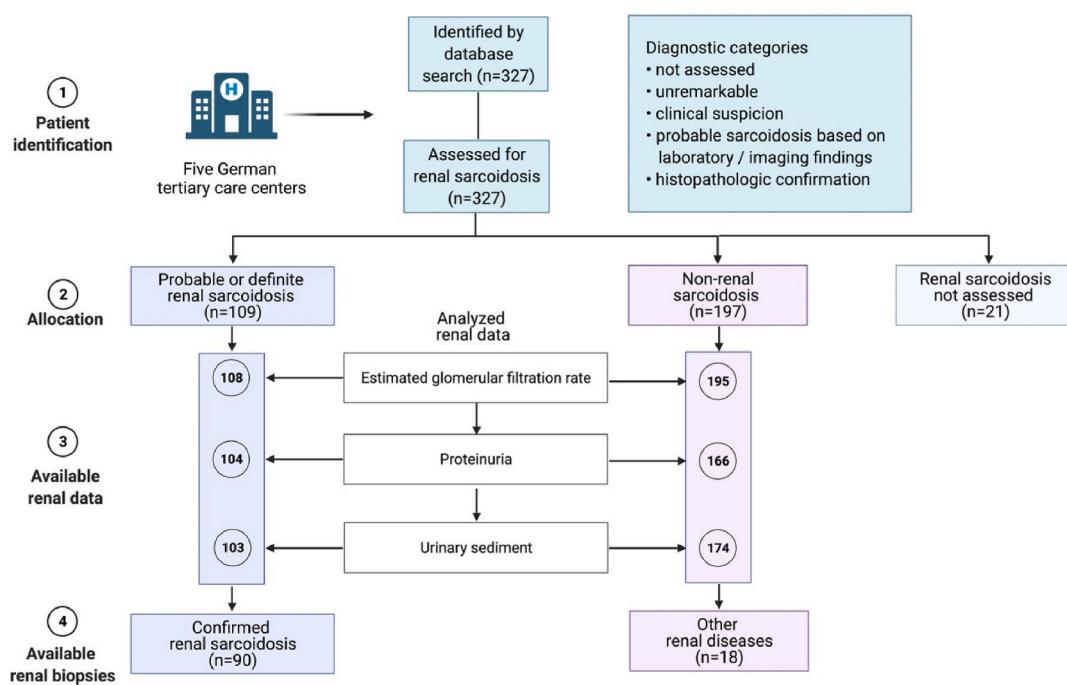


Fig. 1. STROBE flowchart of the study population. Patients were stratified according to renal vs. non-renal sarcoidosis. The availability of renal data for both groups is shown. Twenty-one patients were excluded because they had not been assessed for renal sarcoidosis. Created with [biorender.com](#).

significantly older (58 [18–86] vs. 51 [19–85] years, $p < 0.01$), and significantly fewer females were affected (45 [41%] vs. 114 [58%], $p < 0.01$) compared to patients without renal sarcoidosis. In addition, patients with renal sarcoidosis had significantly more extrapulmonary lymph node abnormalities (44 [40%] vs. 52 [26%], $p < 0.05$).

The groups did not differ in non-specific markers of inflammation (leukocytes, ESR, and CRP). ACE and sIL-2R levels as potential markers of disease activity were available in 265/327 and 266/327 patients, respectively. ACE (65 [8–1100] vs. 39 IU/L [2–215]) and sIL-2R (2325 [304–12000] vs. 936 IU/mL [18–7050]) levels were significantly higher in patients with renal sarcoidosis ($p < 0.001$, respectively). Calcium metabolism also differed between groups: Serum calcium was slightly higher in renal sarcoidosis (2.43 [2.02–3.99] vs. 2.37 [1.92–3.59] mmol/L, $p < 0.01$), whereas vitamin D levels (neither 25-OH-vitamin D3 nor 1,25-OH-vitamin D3) did not differ.

Finally, patients with renal sarcoidosis received glucocorticosteroid (GC) (98 [92%] vs. 148 [78%], $p < 0.01$), azathioprine (AZA, 38 [38%] vs. 25 [16%], $p < 0.001$), and mycophenolate mofetil (5 [5%] vs. 1 [1%], $p < 0.05$) significantly more frequently, but received methotrexate (MTX) less frequently (7 [7%] vs. 25 [17%], $p < 0.05$).

3.2. Urine abnormalities in the study cohort

Table 2 shows the urinary findings of the study cohort. Again, we distinguished patients with biopsy-proven renal sarcoidosis from those without renal and other biopsy-confirmed renal diseases.

The median eGFR was significantly lower in patients with renal sarcoidosis (41.5 [range 4–129] ml/min/1.73 m²) compared to both other groups of patients (93 [range 11–146] for non-renal sarcoidosis, and 84 [11 to 110] for other renal diseases, $p < 0.001$).

In addition, proteinuria was significantly higher in patients with any renal disease (sarcoidosis or other) compared to patients without renal sarcoidosis (median 328 [0 to 3425] mg/g crea in renal sarcoidosis and 262 [0 to 6869] mg/g crea in other renal diseases, respectively, vs. 60 [0–495] mg/g crea in non-renal sarcoidosis, $p < 0.001$).

Lastly, patients with renal sarcoidosis had more pathologic findings in the urine sediment compared to the other groups (53 [52%] vs. 46

[39.3%] and 5 [27.8%], $p < 0.001$), mostly explained by leukocyturia.

3.3. Histopathologic findings

Renal biopsies were performed in 108/327 (33%) patients based on a clinical indication by the respective treating physicians. Of these, 90 had one or more sarcoidosis-associated histopathologic findings. The most frequent finding was IN (n = 38, 35.2% of all patients with a biopsy), followed by gIN (n = 35, 32.4%), NC (n = 24, 22.2%), sGN (n = 11, 10.2%), and nephrolithiasis (n = 1, 0.9%). There were 127 findings in 90 patients with biopsy-proven renal sarcoidosis (Fig. 2, blue dots). Other renal findings were nephroangiosclerosis/hypertensive nephropathy (n = 11, 10.2%), diabetic nephropathy (DN, n = 3, 2.8%), and tubular damage (n = 1, 0.9%). Three performed biopsies (2.8%) were unremarkable (Fig. 2, red dots).

3.4. Frequency of decreased renal function and associated parameters in renal sarcoidosis

Of all patients with a biopsy-confirmed renal disease and available data (89/90 [99%] for sarcoidosis; 18/18 [100%] for other renal diseases), the frequency of each eGFR range was determined (Fig. 3A). Findings were dichotomized into eGFR <60 or ≥60 ml/min/1.73 m² because the former are at higher risk for progressing to end-stage renal disease and cardiovascular morbidity and mortality. Here, 57 (64%) patients with renal sarcoidosis had an eGFR <60 ml/min/1.73 m². Of 18 patients with other renal diseases, only 4 (22%) showed this degree of decreased eGFR. The difference was statistically significant ($p < 0.01$).

Next, we performed a logistic regression to identify variables associated with a worse eGFR (<60 ml/min/1.73 m² or worse). Of all analyzed parameters, including the presence of other organ manifestations and laboratory values, only sIL-2R levels correlated with the probability of decreased renal function (Fig. 3B). The median of sIL-2R in patients with an eGFR <60 ml/min/1.73 m² was 2453 IU/mL (range 0–11970) compared to 1031 IU/mL (range 0–12000) in patients with an eGFR ≥60 ml/min/1.73 m². A value of ~6000 IU/mL corresponded to a 75% probability of having an eGFR <60 ml/min/1.73 m².

Table 1
Baseline epidemiologic and disease-related characteristics of the study population.

	Total cohort (n=327 (n=21 not assessed for renal sarcoidosis)				Renal sarcoidosis n=109		Non-renal sarcoidosis n=197		p-value (renal vs. non-renal)
Epidemiologic characteristics									
Age, years; median (range)	18	52	86	18	58	86	19	51	<0.01
Female sex, n (%)		161	(49)		45	(41)		114	(58)
Organ manifestation*, n (%)									
Pulmonary	323	274	(85)	88	(81)	167	(87)	0.42	
Extrapulmonary lymph nodes	267	103	(39)	44	(40)	52	(26)	<0.05	
Liver	310	63	(20)	27	(25)	31	(16)	0.07	
Musculoskeletal	279	41	(15)	15	(14)	26	(13)	>0.99	
Skin	301	37	(12)	15	(14)	22	(11)	0.58	
Cardiac	278	34	(11)	14	(13)	18	(9)	0.33	
Ophthalmologic	247	27	(11)	14	(13)	13	(7)	0.09	
Joint	275	26	(9)	10	(9)	16	(8)	0.83	
HEENT	208	21	(10)	4	(4)	17	(9)	0.15	
Neurosarcoidosis	246	18	(7)	8	(7)	9	(5)	0.31	
Bone	164	10	(6)	4	(4)	6	(3)	0.75	
Muscle	176	7	(4)	2	(2)	5	(3)	>0.99	
Laboratory parameters; median (range) [normal range]									
<i>Markers of inflammation</i>									
Leukocytes ($10^3/\mu\text{L}$)	[4-10]	321	6.9	7.4	19.8	3.3	7.3	19.8	0.58
ESR (mm/h)	[m <15; f <25]	200	0	22	135	0	30	122	0.05
C-reactive protein (mg/dL)	[<0.5]	318	0	1	33	0	1	24	0.16
<i>Disease activity markers</i>									
ACE (IU/L)	[20-70]	265	2	46	1 100	8	65	1 100	<0.001
elevated (n, %)							38	(39)	<0.001
Soluble IL-2 receptor (IU/mL)	[223-710]	266	18	1155	12 000	304	2325	12 000	<0.001
elevated (n, %)							81	(92)	<0.001
<i>Calcium and Vitamin D levels</i>									
Calcium (mmol/L)	[2.2-2.55]	305	1.9	2.38	3.99	2.02	2.43	3.99	<0.01
elevated (n, %)							39	(37)	<0.001
25-OH-Vitamin D3 (µg/L)	[20-100]	121	4	15	90	4	15	49	0.95
1,25-OH-Vitamin D3 (ng/L)	[19.9-79.3]	64	2	48	350	2	41	108	0.05
Immunosuppressive therapies, n (%)									
Glucocorticoids		316		260	(82)		98	(92)	
<i>Disease-modifying anti-sarcoidosis drugs</i>									
Azathioprine		271		66	(24)		38	(38)	<0.001
Methotrexate		272		36	(13)		7	(7)	<0.05
Myophenolate mofetil		271		7	(3)		5	(5)	<0.05
(Hydroxy)chloroquine		270		7	(3)		1	(1)	0.41
Cyclosporine A		271		4	(2)		1	(1)	>0.99
Leflunomide		271		2	(1)		0	(0)	0.52
Cyclophosphamide		270		1	(0)		1	(1)	0.39
<i>Biologics</i>									
Infliximab		268		6	(2)		2	(2)	>0.99
Adalimumab		268		3	(1)		1	(1)	>0.99
Tocilizumab		268		1	(0)		0	(0)	>0.99

*Defined as compatible laboratory/imaging findings or histopathologic confirmation. n available: number of patients with available data. ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; f, female; HEENT, head eyes ears nose throat; IL, interleukin; m, male; n, number.

Table 2
Renal findings in the study cohort.

	n available	Renal sarcoidosis n=109			Non-renal sarcoidosis n=197 (n=21 excluded)			p-value
		Non-renal sarcoidosis n=179		Other renal disease n=18				
Excretory function								
eGFR (ml/min/1.73m ²), median (range)	4	41.5	120	11	93	146	11	84 110 <0.001*
≥ 90, n (%)		15	(13.9)		101	(57.1)		8 (44.4)
60-89, n (%)		21	(19.4)		70	(39.5)		6 (33.3)
45-59, n (%)		15	(13.9)		4	(2.3)		0 (0)
30-44, n (%)		14	(13)		1	(0.6)		3 (16.7)
15-29, n (%)		25	(23.1)		1	(0.6)		0 (0)
<15, n (%)		18	(16.7)		0	(0)		1 (5.6)
Protein excretion	n available	104/109			146/179			18/18
Proteinuria (mg/g crea or /24 h), median (range)	0	328	3425	0	60	465	0	262 6860 <0.001#
<300, n (%)		47	(45.2)		144	(98.6)		11 (61.1)
300-999, n (%)		48	(46.2)		1	(0.7)		4 (22.2)
≥ 1000, n (%)		9	(8.7)		1	(0.7)		3 (16.7)
Urinary sediment findings; n (%)	n available	102/109			157/179			18/18
Pathologic sediment		53	(52)		46	(29.3)		5 (27.8) <0.001*
Leukocyturia		37	(36.3)		41	(26.1)		2 (11.1)
Erythrocyturia		35	(34.3)		22	(14)		3 (16.7)
Casts		7	(6.9)		2	(1.3)		0 (0)

Crea, creatinine; eGFR, estimated glomerular filtration rate; n, number; n available, n of patients with available data.

*renal vs. non-renal sarcoidosis and other renal disease

#renal sarcoidosis and other renal disease vs. non-renal sarcoidosis

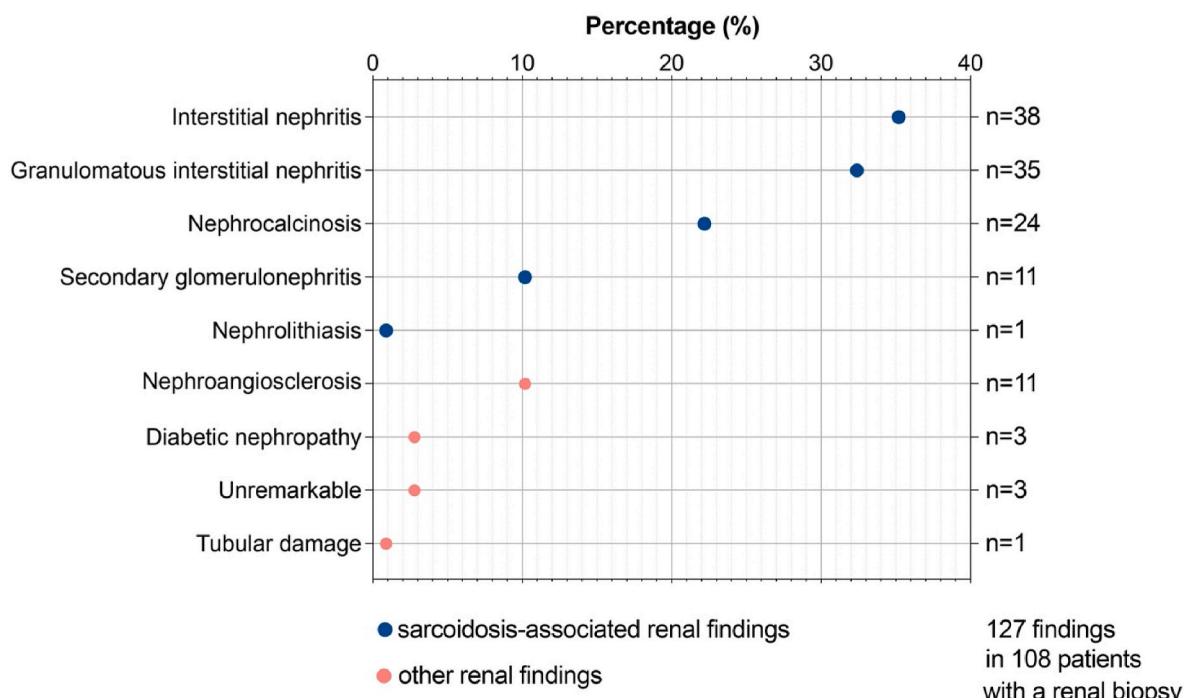


Fig. 2. Histopathologic findings in patients with available biopsy. Sarcoidosis-associated findings (blue dots) were more frequently identified than other renal diseases (red dots). The most frequent finding was interstitial nephritis with or without granulomas, present in about two-thirds of the patients. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 4 shows the age-related eGFR in the study cohort for females (Fig. 4A) and males (Fig. 4B). Of all patients, 21 were not assessed for renal sarcoidosis. Two (9.5%) of these had an eGFR below the normal range. In 19 patients with suspected renal sarcoidosis, seven (36.8%) had eGFR values below their age-related normal ranges.

3.4.1. Combining sIL-2 receptor and urine findings for the assessment of renal sarcoidosis

To assess the diagnostic properties of sIL-2R and abnormal urine findings (eGFR <60 ml/min/1.73 m², proteinuria >300 mg/g creatinine, or a pathologic urine sediment) for the presence or absence of renal sarcoidosis, we constructed Venn diagrams with these four parameters (Fig. 5).

Data are based on patients in which all four parameters were

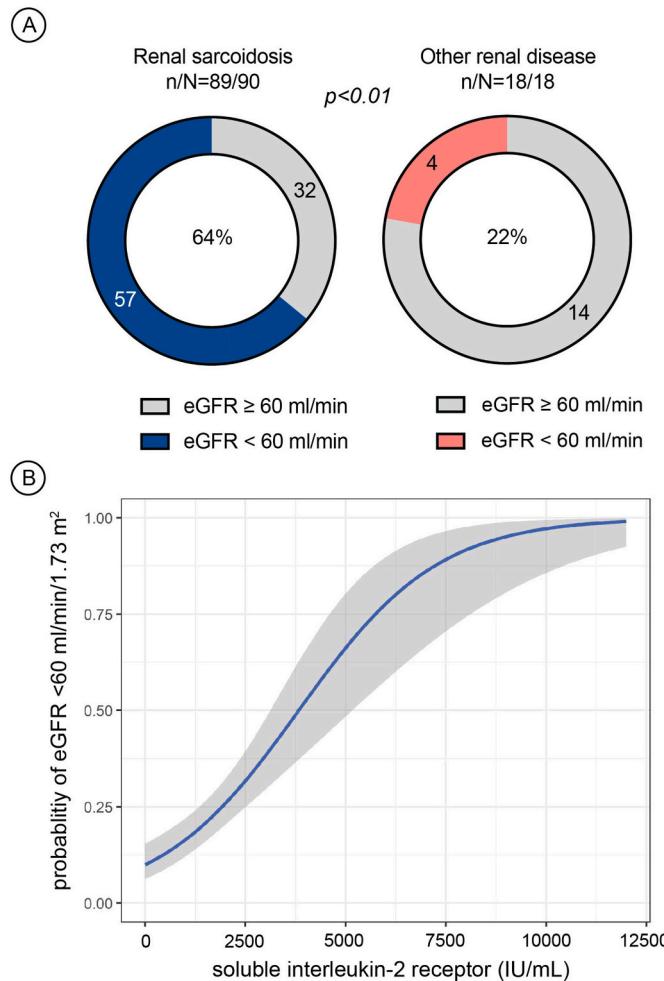


Fig. 3. Frequency of eGFR ranges in renal sarcoidosis versus other renal diseases (A). Association of eGFR <60/ml/min/1.73 m² with soluble interleukin-2 receptor (B).

n/N, number of patients with available data.

available. This was the case for 76/90 (84.4%) in renal sarcoidosis. In non-renal sarcoidosis, 138/197 (70.5%) had data for these parameters. In renal sarcoidosis (Figs. 5A), 15 (20%) patients had pathologic results in all four parameters. Of note, all but three patients with renal sarcoidosis had a combination of elevated sIL-2R plus any of the three abnormal findings. One patient had entirely normal parameters, and two patients only had pathologic urine sediment without any other abnormality.

By contrast, 55 (51.4%) patients with non-renal sarcoidosis had elevated sIL-2R levels. The most common finding in non-renal sarcoidosis patients was an abnormal urine sediment, present in 10 (9.3%) as the sole finding and 26 (24.3%) patients in combination with an elevation of sIL-2R (Fig. 5B).

3.4.2. Test characteristics of the evaluated parameters

To determine the test characteristics of the evaluated parameters, we calculated the sensitivity, specificity, and positive and negative predictive values. The results are shown in Table 3. Based on the individual parameters, the sIL-2R had the highest sensitivity (0.95 [95% confidence interval, CI 0.87 to 0.99]) but low specificity (0.33 [95% CI 0.26 to 0.42]), resulting in a negative predictive value (NPV) of 0.92 (95% CI 0.81 to 0.98). In this analysis, proteinuria >300 mg/g crea (or 300 mg/24 h) and an eGFR <60 ml/min/1.73 m² had the highest specificities

(0.93 [95% CI 0.88 to 0.97], and 0.93 [95% CI 0.87 to 0.96], respectively).

Next, we evaluated whether a combination of two abnormal parameters combined (“AND” combination) or a pair of two parameters with at least one abnormal value (“OR” combination) was superior to individual parameters. Here, the pair of sIL-2R and eGFR had the highest sensitivity (0.61 [95% CI 0.49 to 0.72]), whereas proteinuria and eGFR had the best specificity (0.98 [0.94 to 1.0]). Using “OR” combinations of two parameters, urine sediment paired with the sIL-2R yielded a sensitivity of 0.99 (95% CI 0.93 to 1.0). Still, proteinuria paired with the eGFR was the most specific (0.88 [95% CI 0.82 to 0.93]) for the presence of renal sarcoidosis.

Finally, we developed a prediction tree model including all of the continuous parameters to test whether a combination of three or all four parameters was even better. In this model, a decreased eGFR <60 ml/min/1.73 m² was the most significant differentiation, with a sensitivity of 0.69 (95% CI 0.59 to 0.77) and a specificity of 0.91 (95% CI 0.87 to 0.95), resulting in a positive predictive value (PPV) of 0.80 (95% CI 0.70 to 0.87) and an NPV of 0.85 (95% CI 0.80 to 0.90).

4. Discussion

Our data demonstrate a prevalence of biopsy-proven renal manifestations of sarcoidosis in 27.5% of patients. This prevalence exceeds the rates published in other large series [11,34–36]. The most frequent histopathological finding was IN, with or without granulomas, followed by NC alone or combined with other histological findings. SGN was found much less frequently. NC can occur with or without increased serum calcium levels. Whether the presence or absence of granulomas reflects a different pathology or is due to sampling errors in kidney biopsies is currently unknown. Since we do not show long-term follow-up data in our cohort, we cannot answer this question.

Importantly, renal sarcoidosis is not a trivial finding: Our findings demonstrate that almost two-thirds of the patients with biopsy-confirmed renal sarcoidosis had a reduced renal function with an eGFR <60 ml/min/1.73 m², potentially reflecting CKD, which is associated with an increased risk of cardiovascular disease (CVD) [37]. In our cohort, a renal manifestation of sarcoidosis was the most common reason for a significantly reduced eGFR in patients with systemic sarcoidosis. Although the urinary findings in most cases were only mildly abnormal, the disease burden of renal involvement is eminent.

A study by Yassari et al. described renal abnormalities in 33% of sarcoidosis patients but did not confirm the diagnosis by kidney biopsy [17]. However, other case series found a prevalence as high as 30–50% [15,16]. Thus, if systematically screened for, renal manifestations are likely present in up to 25–30% of all sarcoidosis patients. The results in our cohort with biopsy-proven renal involvement are similar to those published by Mahévas et al. [13], one of the most extensive series concerning proteinuria and pathological urine sediment. In the study by Mahévas et al., 29 out of 47 patients (62.5%) presented with chronic kidney disease (CKD) stages 4 or 5 [13]. Likewise, 37% of patients in the study by Löffler et al. had advanced CKD [14]. Further supporting this, a recent multicenter survey from Italy spanning 39 patients with renal sarcoidosis revealed that CKD developed in 65% of the patients with available follow-up data [38]. In the series of 47 patients with renal sarcoidosis by Mahévas et al., the median eGFR was 20.5 ml/min [13] compared to 41.5 ml/min in our patients. This difference may be explained by the fact that we only included patients with a recent diagnosis of sarcoidosis. Another reason could be a lower threshold to perform a kidney biopsy in the presence of any abnormality of renal function, proteinuria, or urine sediment in our cohort. Importantly, we found only a low to moderate proteinuria in most cases.

The relatively frequent finding of a pathologic result in urine sediments in patients with non-renal sarcoidosis is unexpected. This may be explained by an overlooked renal disease, such as nephroangiosclerosis or diabetic nephropathy. Alternatively, and more likely, it may

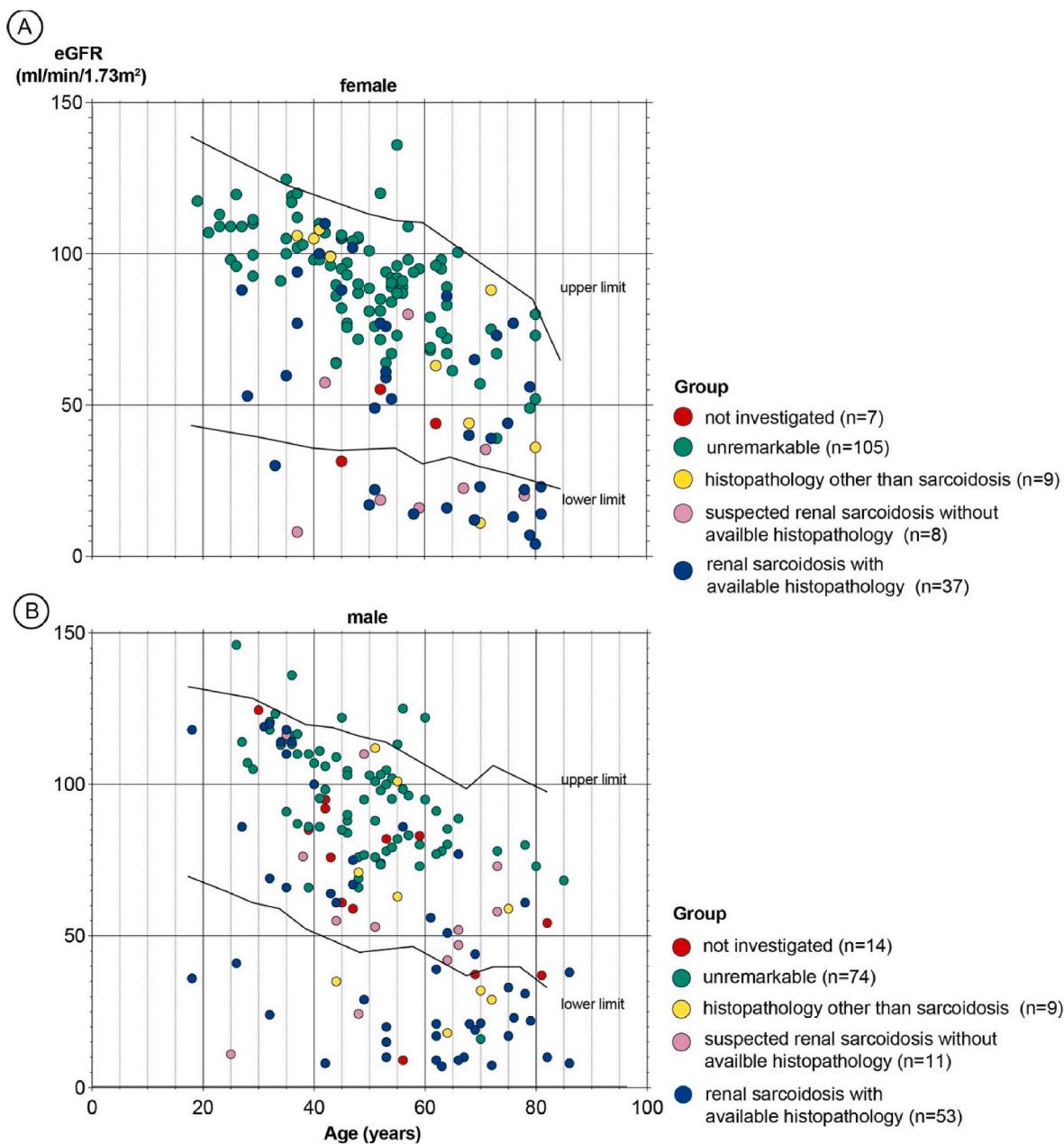


Fig. 4. Age-related renal function in the study cohort stratified according to diagnostic assessment (colored dots). A. eGFR of female patients (n = 166, 50.8%). B. eGFR of male patients (n = 161, 49.2%). eGFR, estimated glomerular filtration rate. Normal ranges for females and males are adapted from Ref. [33].

represent an overinterpretation of leukocyturia (the most frequent abnormality) as pathologic when, in fact, it was not.

We found significantly higher levels of sIL-2R in renal sarcoidosis compared to non-renal sarcoidosis patients. While it has been shown that sIL-2R is slightly elevated in renal allograft patients [39], diminished renal clearance is probably not the only explanation for higher levels. The highest levels are observed in patients undergoing maintenance hemodialysis, where persistent inflammation can be observed [40]. This certainly requires further investigation. Our analysis of the test characteristics of the four evaluated parameters sIL-2R, proteinuria, eGFR, and urine sediment, showed that a normal sIL-2R had an excellent NPV for the presence of renal sarcoidosis. In clinical practice, one would consider more than one abnormal parameter to perform a kidney biopsy. Our results confirm that combinations of two parameters had either a high sensitivity or specificity (Table 3). To our knowledge, this is the

first analysis of renal sarcoidosis regarding these clinically relevant and applicable parameters.

Furthermore, no kidney biopsy was performed in some patients with suspected renal sarcoidosis based on urine abnormalities, such as tubular proteinuria. Indeed, the actual prevalence might be higher than we report here, and 21 patients did not even have a record of investigation regarding a renal manifestation.

A Swedish population-based study demonstrated increased overall mortality in sarcoidosis patients compared to matched controls (hazard ratio [HR] 1.88; [95%CI 1.56 to 2.26]) [41]. A Korean study showed similar mortality rates, which were significantly higher than those of the general population (standardized mortality rate 1.91, [95%CI 1.62–2.25]). The major comorbidities of sarcoidosis patients were diseases of the respiratory system (17.6%), heart (5.4%), eyes (4.3%), and cancer (2.3%) [42]. In addition, approximately 1–5% of patients with

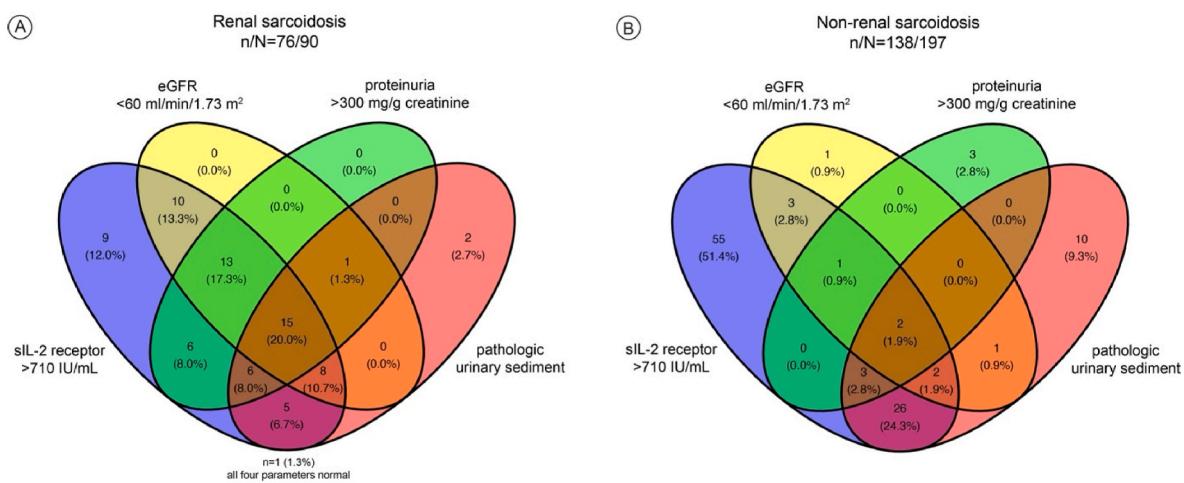


Fig. 5. Venn diagrams assessing a combination of the four parameters eGFR <60 mL/min/1.73 m², proteinuria >300 mg/g creatinine or 300 mg/24 h, pathologic urine sediment, and elevation of sIL-2R. **A.** Patients with biopsy-proven renal sarcoidosis. **B.** Patients with non-renal sarcoidosis. eGFR, estimated glomerular filtration rate; n/N, number of patients with available data; sIL-2R, soluble interleukin-2 receptor.

Table 3

Test characteristics of abnormal parameters and their combinations for the presence of renal sarcoidosis. Estimates are shown with 95%-confidence interval.

Parameter(s)	Sensitivity				Specificity				Positive predictive value		Negative predictive value	
Single parameters												
sIL-2R (>710 IU/mL)	0.87	0.95	0.99	0.26	0.33	0.42	0.36	0.44	0.52	0.81	0.92	0.98
Proteinuria (>300 mg/g crea)	0.42	0.54	0.65	0.88	0.93	0.97	0.69	0.82	0.91	0.72	0.79	0.85
eGFR (<60 mL/min/1.73 m ²)	0.50	0.62	0.73	0.87	0.93	0.96	0.70	0.82	0.91	0.75	0.82	0.87
Abnormal urine sediment	0.37	0.49	0.60	0.60	0.68	0.76	0.35	0.46	0.57	0.62	0.71	0.78
Two parameters "AND" combinations												
Urine sediment + proteinuria	0.19	0.29	0.40	0.92	0.96	0.99	0.62	0.81	0.94	0.64	0.71	0.78
Urine sediment + sIL-2R	0.33	0.45	0.57	0.68	0.76	0.83	0.38	0.51	0.63	0.63	0.71	0.79
Urine sediment + eGFR	0.21	0.32	0.43	0.92	0.96	0.99	0.64	0.83	0.94	0.65	0.72	0.78
Proteinuria + sIL-2R	0.41	0.53	0.64	0.91	0.96	0.98	0.74	0.87	0.95	0.72	0.79	0.85
Proteinuria + eGFR	0.27	0.38	0.50	0.94	0.98	1.0	0.75	0.91	0.98	0.67	0.74	0.80
sIL-2R + eGFR	0.49	0.61	0.72	0.89	0.94	0.97	0.73	0.85	0.93	0.74	0.81	0.87
Two parameters "OR" combinations												
Urine sediment OR proteinuria	0.62	0.74	0.83	0.57	0.65	0.73	0.44	0.54	0.64	0.73	0.82	0.89
Urine sediment OR sIL-2R	0.93	0.99	1.0	0.18	0.25	0.33	0.35	0.42	0.50	0.85	0.97	1.0
Urine sediment OR eGFR	0.68	0.79	0.87	0.56	0.64	0.72	0.45	0.55	0.65	0.76	0.85	0.91
Proteinuria OR sIL-2R	0.89	0.96	0.99	0.24	0.31	0.40	0.36	0.51	0.43	0.82	0.93	0.99
Proteinuria OR eGFR	0.67	0.78	0.86	0.82	0.88	0.93	0.68	0.79	0.87	0.81	0.88	0.93
sIL-2R OR eGFR	0.89	0.96	0.99	0.24	0.32	0.40	0.36	0.44	0.52	0.82	0.94	0.99
Recursive prediction tree model												
eGFR <60 mL/min/1.73 m ²	0.59	0.69	0.77	0.87	0.91	0.95	0.70	0.80	0.87	0.80	0.85	0.90

Crea, creatinine; eGFR, estimated glomerular filtration rate; sIL-2R, serum interleukin-2 receptor.

sarcoidosis die from complications of sarcoidosis [43]. Nevertheless, data demonstrating the potential impact of renal sarcoidosis on the mortality rate of sarcoidosis are missing. Still, CKD may be an overlooked contributor to the increased cardiovascular mortality in sarcoidosis [44].

In patients with coronary artery disease, the cumulative 5- and 10-year survival rates decreased gradually from 88% to 70%,

respectively, for those with normal renal function to 43% and 33% for those with an eGFR <30 mL/min/1.73 m² [45]. Compared to patients with normal renal function, the multivariable-adjusted hazard ratios for all-cause mortality among patients with mild, moderate, and severe renal impairment were 1.33 (95% CI 1.21–1.48), 1.67 (95% CI, 1.44–1.93), and 3.38 (95% CI, 2.73–4.19), respectively [45].

Low eGFR and high albuminuria have been associated with increased

mortality. For example, the adjusted HR for all-cause mortality at an eGFR of 45 mL/min/1.73 m² was 1.77 [95% CI 1.57–1.99] in non-hypertensive people. Similarly, for an albumin-creatinine ratio of 300 versus 5 mg/g crea, the HR was 2.30 (1.98–2.68) [46]. These data may also apply to patients with sarcoidosis without and with renal involvement, independent from other organ manifestations.

Renal insufficiency may also impact the therapeutic options. Some drugs are not approved in patients with reduced renal function, e.g., methotrexate (MTX). Indeed, renal sarcoidosis patients in our cohort were more frequently treated with GC and AZA or MMF and less frequently with MTX. This is in line with the published recommendations, which are, however, based on a paucity of data explicitly addressing this question [47].

The role of systemic glucocorticoids in the management of renal diseases in sarcoidosis patients is unclear. On the one hand, several case series demonstrated an improvement of renal function in sarcoidosis patients treated with GC [12,13,48], but relapses can occur when GC treatment is stopped [12]. On the other hand, GC treatment for potential renal sarcoidosis without histological evidence may increase the rate of infections due to unnecessary treatment.

Our study has several limitations. First, due to its retrospective cross-sectional design and analysis of routine data, data capture may be incomplete, and the different centers did not follow a specific protocol for assessing all potential organ manifestations. Thus, some organ manifestations may have been present although not reported, which may explain the difference in extrapulmonary lymph node affection in the renal versus non-renal groups. Second, we did not report a follow-up for renal sarcoidosis. Thus, we do not know how immunosuppressive treatment influences the long-term course of renal sarcoidosis, but this was not the purpose of the present study. In addition, we included only patients with a recent diagnosis of sarcoidosis. Therefore, the course of kidney dysfunction was not known in all cases. Furthermore, since all patients were evaluated in centers with nephrology expertise, mere acute kidney injury was not present in the cohort. Lastly, the high number of renal sarcoidosis may be due to selection bias. Still, we also report a pulmonary manifestation in 85% of the patients, which is slightly lower than other reports (reviewed in Ref. [36]).

Our report has several strengths. First, we analyzed a considerable number of sarcoidosis patients treated at different centers with long-standing experience in evaluating systemic diseases, including sarcoidosis. In addition, we report a very high number of renal biopsies, which is, to our knowledge, the highest number ever reported. Further, we have a relatively complete dataset regarding renal findings allowing for robust analyses.

5. Conclusions

Based on our data, renal manifestations of sarcoidosis are more prevalent than reported previously, and urinary findings are variable and often mild. Thus, a dedicated diagnostic renal workup is mandatory in patients with newly diagnosed sarcoidosis.

We recommend performing a renal workup as published previously in all patients with sarcoidosis [49]. In patients with elevated sIL-2R and any urine abnormality suggesting renal involvement, especially eGFR <60 mL/min/1.73 m² and proteinuria >300 mg/g crea or 300 mg/24 h, a kidney biopsy should be performed by an experienced nephrologist. Hilderson et al. published recommendations for additional immunosuppressive therapies [47]. In our cohort, the most frequently used second-line immunosuppressive therapies were AZA and MMF.

Unrecognized renal sarcoidosis may lead to CKD, which has been demonstrated as an independent cardiovascular risk factor potentially contributing to increased mortality in sarcoidosis.

Availability of data

All original data can be obtained from the authors upon reasonable

request.

Funding

The authors report no funding for this article.

CRediT authorship contribution statement

Raoul Bergner: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. **Stefan M. Weiner:** Data curation, Writing – review & editing. **Gabriele Kehl:** Data curation, Investigation, Writing – review & editing. **Kirsten de Groot:** Data curation, Writing – review & editing. **Sandra Tielke:** Data curation, Investigation, Writing – review & editing. **Thomas Asendorf:** Formal analysis, Software, Visualization, Writing – review & editing. **Peter Korsten:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

RB has received speaker fees from Abbvie, Bristol-Myers-Squibb, Chugai, Galapagos, GlaxoSmithKline, and Novartis, all unrelated to this paper. In addition, RB research grants from Vifor, to this paper. PK has received honoraria or travel support from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers-Squibb, Chugai, Galapagos, GlaxoSmithKline, Janssen-Cilag, Lilly, Novartis, and Pfizer, all unrelated to this paper. In addition, PK received research grants from GlaxoSmithKline and Diamed Medizintechnik GmbH, all unrelated to this paper.

All other authors declare no conflicts of interest.

Acknowledgment

Peter Korsten appreciates fruitful discussions with Maarten Boers (Department of Epidemiology and Data Science, Amsterdam UMC, Vrije Universiteit, Amsterdam, Netherlands) about the principles of graph and table design used in this paper (described in detail in Boers, M. *Data Visualization for Biomedical Scientists*, 1st edition, VU University Press).

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