Phenotypes of organ involvement in sarcoidosis

SUPPLEMENT

Figure S1. Modified MCA including Belgrade as variable

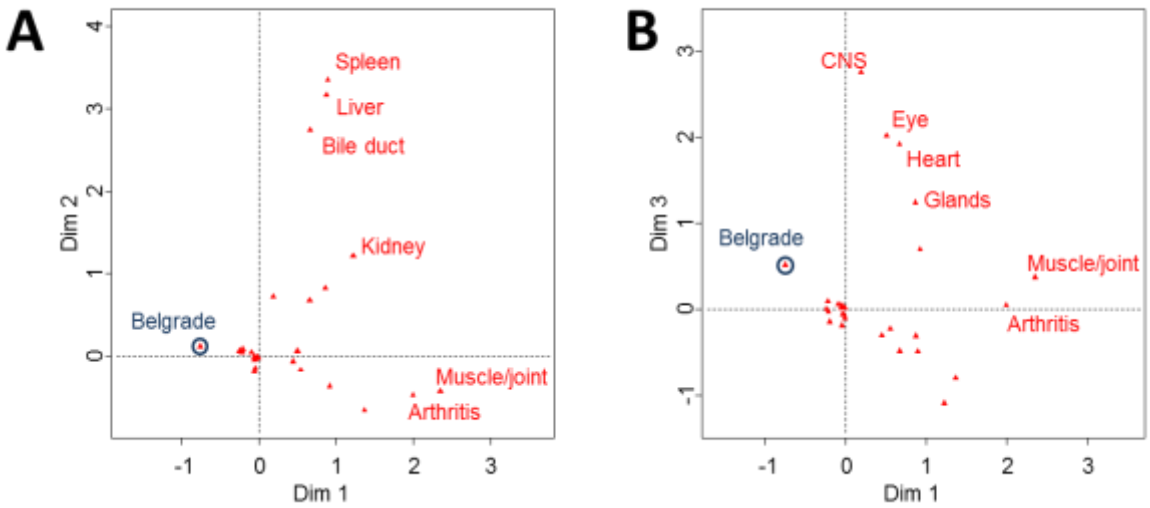

Figure S1: Factor maps of a modified MCA of organ involvement with inclusion of all original variables of organ involvement (as in figure 2) and additionally the recruiting centre "Belgrade" vs. the remaining study centres as variable. We calculated this modified MCA to evaluate a potential bias of the largest recruiting center. Dichotomization of the variable "Belgrade" vs. all other centers was necessary to achieve binary data as input for the modified MCA. A and B are scatter plots of variables contributing to different dimensions (MCA factor maps). Labelling of variables close to the zero-point was omitted due to narrowness. Factor loading of Belgrade on dimensions 1 to 3 is low as it arises near the zero-point (and none existent on dimension 2).

Square correlation ratio (R2) of the main variables contributing to the dimensions of the modified MCA for organ involvement and study centre Belgrade vs. the remaining centres:

Dimension 1	R2	p value
Muscle/Joint	0.55	0.00e+00
Arthritis	0.53	7.22e-315
Belgrade	0.34	1.48e-174

Dimension 3	R2	p value
Eye	0.41	6.55e-216
CNS	0.31	2.48e-155
Belgrade	0.16	1.59e-71

Figure S2. Modified MCA including disease duration as variable

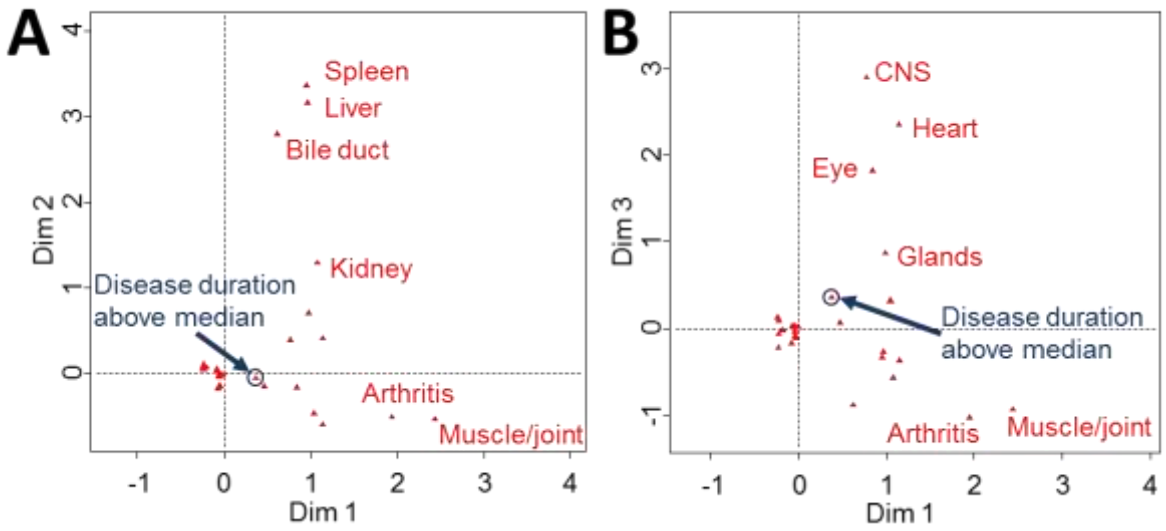

Figure S2: Factor maps of a modified MCA of organ involvement with inclusion of all original variables of organ involvement (as in figure 2) and additionally disease duration above the median of 12 months. We calculated this modified MCA to evaluate a potential bias of disease duration. Dichotomization of the variable "disease duration" was necessary to

achieve binary data as input for the modified MCA. A and B are scatter plots of variables contributing to different dimensions (MCA factor maps). Labelling of variables close to the zero-point was omitted due to narrowness. Factor loading of disease duration on dimensions 1 to 3 is low as it arises near the zero-point (and none existent on dimension 2).

Square correlation ratio (R2) of the main variables contributing to the dimensions of the modified MCA for organ involvement and disease duration:

Dimension 1	R2	p value	
Muscle/joint	0.583	0.00E+00	
Arthritis	0.495	5.24E-288	[…]
Disease duration above the median	0.098	3.47E-44	

Dimension 3	R2	p value	
CNS	0.338	7.12E-174	
Eye	0.326	1.17E-166	[…]
Disease duration above the median	0.088	1.74E-39	

Dimension 2 is omitted as “disease duration” has no influence on dimension 2.

Table S1. Recruiting centres

Recruiting consortium members	**Affiliation**	**Number of included patients**
Prof. Dr. V. Mihailović-Vučinić Prof. Dr. D. Jovanovic S. Filipovic J. Videnovic-Ivanovic	University Hospital, Belgrade, Serbia	916
Prof. Dr. J. Müller-Quernheim	Departement of Pneumology, University Medical Center, Killianstr. 5, 79106 Freiburg, Germany	176

Dr. J. Schupp Prof. Dr. A. Prasse Dr. A. Grubanovic Dr. A. Müller		
Prof. Dr. P. Rottoli E. Bargagli C. Oliveri	University Hospital, Siena, Italy	156
Priv.-Doz. Dr. S. Pabst	University Hospital, Bonn, Germany	73
Dr. P. Bresser Dr. R. E. Jonkers	Pulmonology Department, Academic Medical Center Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands	70
Prof. Dr. P. Zabel Priv.-Doz. Dr. K.I. Gaede	Medical Hospital, Research Center Borstel, Parkallee 25, 23845 Borstel, Germany Leibniz Center for Medicine and Biosciences, Airway Research Center North, Member of the German Center for Lung Research (DZL), Borstel, Germany.	62
Prof. A. Dubaniewicz	Department of Pulmonology, Medical University of Gdansk, Poland	61
Prof. Dr. B. Marshall K. O'Reilly	University Hospital, Southampton, UK	60
Dr. R. Kieszko, MD PhD Prof. Dr. J. Milanowski	Department of Pneumonology, Oncology and Allergology, Medical University of Lublin, Lublin, Poland	52
Prof. Dr. A. Günther	University Hospital, Giessen, Germany	45
Dr. A. Weihrich	Neuruppin, Germany	40
Prof. Dr. M. Petrek V. Kolek	Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Czech Republic	37
Prof. Dr. M. P. Keane Dr. S. O'Beirne Prof. Dr. S. Donnelly	University College Dublin and St Vincent's University Hospital, Dublin, Ireland	32
Dr. S. Haraldsdottir K. B. Jorundsdottir	University Hospital, Reykjavik, Iceland	32
Prof. Dr. U. Costabel Dr. F. Bonella	Ruhrlandklinik, Westdeutsches Lungenzentrum am Universitätsklinikum Essen gGmbH, Universitätsklinik Essen, Tüschener Weg 40, 45239 Essen, Germany	30
Prof. Dr. B. Wallaert	University Hospital, Lille, France	31
Dr. C. Grah	Hospital Berlin-Havelhöhe, Germany	31
Prof. Dr. T. Peroš-Golubičić	University Hospital Jordanovac, Zagreb, Croatia	29
Prof. Dr. M. Luisetti Dr. Z. Kadija	Foundation IRCCS Policlinico San Matteo - Pulmonology Unit, Pavia, Italy	28
Prof. Dr. C. Grohé	Evangelische Lungenklinik, Lindenberger Weg 27, 13125 Berlin, Germany	28
Prof. Dr. J. Strausz	National Koranyi Institut, Pihenő út 1, Budapest 1122,, Hungary	25
Prof. Dr. M. Vasakova Assist. Prof. M. Sterclova	Thomayer Hospital and 1st Faculty of Medicine, Charles University, Kateřinská 32, 121 08 Praha 2, Czech Rebublic	23
Prof. Dr. A. Millar	University Hospital, Bristol, UK	23
Prof. Dr. J. Homolka	Prague General Hospital, Charles University, Prague, Czech	20

Assist. Prof. A. Slováková	Republic	
Prof. Dr. L. Ho, Dr Y. Kendrick, Dr A. Crawshaw	Oxford Sarcoidosis Servic, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Old Rd, Headington, Oxford OX3 7LE, United Kingdom	20
Prof. Dr. W. Wuyts	University Hospital, Leuven, Belgium	18
Dr. L. Spencer	Aintree University Hospital, Liverpool, UK	14
Prof. Dr. M. Peifer	University Hospital, Regensburg, Germany	9
Prof. Dr. D. Valleyre	Groupe Hospitalier Avicenne-Jean Verdier-René Muret, Service de Pneumologie, 125, rue de Stalingrad, 93017 Bobigny, Franc	9
Prof. Dr. V. Poletti	Pulmonary Unit, Department of Thoracic Diseases, Azienda USL Romagna, GB Morgagni-L-Pierantoni Hospital, Via Carlo Forlanini, 34 - Pavilion Morgagni, Forlì, Italy	8
Prof. Dr. H. Wirtz	University Hospital, Department of Pneumology, Liebigstraße 20, 04103 Leipzig, Germany	5
Present affiliations		
Priv.-Doz. Dr. S. Pabst	Pneumologische Gemeinschaftspraxis, Am Burgweiher 54, 53123 Bonn, Germany	
Dr. K. O'Reilly	Consultant Respiratory and Acute Medicine Physician, Assistant Professor of Medicine, University College Dublin, Department of Respiratory Medicine, Mater Misericordiae University Hospital, Eccles St., Dublin 7, Ireland	
Prof. Dr. J. Strausz	County Hospital, Törökbálint, Munkácsy Mihály 70, Törökbálint H-2045, Hungary	

Table S2. Gender differences

	Male n=873	**Female n=1290**	**p values**
Age [years]	44.0 ± 11.5	49.5 ± 12.1	< 1*10^-6
Body height [cm]	177.5 ± 7.1	163.2 ± 7.0	< 1*10^-6
Body weight [kg]	86.2 ± 14.5	73.1 ± 15.1	< 1*10^-6
Smoking history [never / previously / currently in %]	63.4 / 25.4 / 11.1	76.5 / 14.3 / 9.2	< 1*10^-6
Packyears of cigarettes	7.7 ± 10.8	5.4 ± 9.4	< 0.01
Chest X-ray type [0 / I / II / III / IV in %]	12.6 / 33.8 / 39.7 / 10.7 / 3.3	18.9 / 37.6 /28.6 / 10.6 / 4.3	< 1*10^-6
TLC [% predicted]	92.2 ± 15.1	101.3 ± 16.5	< 1*10^-6
FEV1 [% predicted]	89.6 ± 21.1	94.9 ± 19.7	< 1*10^-6

Lung involvement [%]	91.9	93.1	n.s., 0.4
Bronchial involvement [%]	67.8	72.7	n.s., 0.7
Intrathoracic lymph nodes [%]	81.4	74.0	< 0.001
Extrathoracic lymph nodes [%]	12.1	10.9	n.s., 0.56
Skin involvement [%]	11.9	18.9	< 1*10^-4
Eye involvement [%]	5.6	9.2	< 0.01
CNS involvement [%]	3.0	3.6	n.s., 0.52
Gland involvement [%]	2.6	4.7	< 0.05
Cardiac involvement [%]	3.2	3.2	n.s., 1
Hepatic involvement [%]	5.9	4.3	n.s., 0.11
Splenic involvement [%]	4.3	3.6	n.s., 0.46
Renal involvement [%]	3.8	2.9	n.s., 0.28
Musculoskeletal involvement [%]	6.7	8.1	n.s., 0.29
Gastrointestinal involvement [%]	0.4	0.8	n.s., 0.34
Genital involvement [%]	0.1	0.2	n.s., 0.93
Arthritis [%]	9.9	9.4	n.s., 0.79
Need for therapie [%]	60.3	61.9	n.s., 0.47
Fatigue [%]	55.0	66.4	< 1*10^-4
Fever [%]	23.0	18.5	< 0.05
Night sweat [%]	12.6	13.1	n.s., 0.84
Weight loss [%]	10.5	9.1	n.s., 0.37
Arthralgia [%]	41.5	54.7	< 1*10^-6
Cough [%]	49.1	47.0	n.s., 0.41
Dyspnoea [%]	43.0	45.3	n.s., 0.35
Chest pain [%]	18.6	23.4	< 0.05
Haemoptoea [%]	1.1	1.7	n.s., 0.43

Table S2: Data are presented as mean ± SD or percentages. TLC = total lung capacity; FEV1 = forced expiratory volume in 1 second; CNS = central nervous system.

Table S3. Age differences

	Age ≤ 40 years n=712	**Age > 40 years n=1445**	**p values**
Sex [male / female]	53.4/ 46.6	34.0 / 66.0	< 1*10^-6

Body height [cm]	173.3 ± 9.6	166.9 ± 9.4	< 1*10^-6
Body weight [kg]	79.3 ± 17.8	78.0 ± 15.3	n.s., 0.14
Smoking history [never / previously / currently in %]	61.9 / 22.1 / 15.9	75.8 / 17.2 / 6.9	< 1*10^-6
Packyears of cigarettes	5.7 ± 7.5	8.7 ± 12.2	n.s., 0.45
Chest X-ray type [0 / I / II / III / IV in %]	12.7 / 45.8 / 32.4 / 5.8 / 3.5	18.3 / 31.5 /33.1/ 13.0 / 4.2	< 1*10^-6
TLC [% predicted]	96.6 ± 15.9	98.4 ± 16.8	n.s., 0.05
FEV1 [% predicted]	92.1 ± 20.1	93.2 ± 20.6	n.s., 0.24
Lung involvement [%]	92.8	92.5	n.s., 0.88
Bronchial involvement [%]	78.2	66.4	< 1*10^-4
Intrathoracic lymph nodes [%]	85.0	72.7	< 1*10^-6
Extrathoracic lymph nodes [%]	12.6	10.5	n.s., 0.29
Skin involvement [%]	15.3	16.5	n.s., 0.53
Eye involvement [%]	5.5	8.9	< 0.05
CNS involvement [%]	3.9	3.2	n.s., 0.46
Gland involvement [%]	3.4	4.0	n.s., 0.57
Cardiac involvement [%]	1.9	3.9	< 0.05
Hepatic involvement [%]	4.9	4.9	n.s., 1
Splenic involvement [%]	3.7	4.0	n.s., 0.88
Renal involvement [%]	2.7	3.6	n.s., 0.36
Musculoskeletal involvement [%]	8.1	7.2	n.s., 0.50
Gastrointestinal involvement [%]	0.6	0.7	n.s., 1
Genital involvement [%]	0.2	0.2	n.s., 1
Arthritis [%]	11.3	8.7	n.s., 0.08
Need for therapie [%]	60.9	61.4	n.s., 0.87
Fatigue [%]	63.3	61.0	n.s., 0.38
Fever [%]	29.7	15.4	< 1*10^-6
Night sweat [%]	11.4	13.6	n.s., 0.23
Weight loss [%]	10.4	9.3	n.s., 0.54
Arthralgia [%]	50.4	49.0	n.s., 0.61
Cough [%]	49.3	47.1	n.s., 0.42
Dyspnoea [%]	37.7	47.5	< 1*10^-4
Chest pain [%]	23.3	20.4	n.s., 0.18
Haemoptoea [%]	1.6	1.3	n.s., 0.70

Table S3: Data are presented as mean ± SD or percentages. TLC = total lung capacity; FEV1 = forced expiratory volume in 1 second; CNS = central nervous system.

Table S4. Patients' characteristics – symptoms and comorbidities

	All sarcoid patients	Acute onset n=829	Subacute onset n=1286	p values
Fatigue [%]	61.8	67.6	57.9	< 1*10^-4
Fever [%]	20.3	32.6	10.9	< 1*10^-6
Night sweat [%]	12.9	15.3	11.1	< 0.05
Weight loss [%]	9.7	9.7	9.8	n.s., 1
Arthralgia [%]	49.5	63.7	38.6	< 1*10^-6
Cough [%]	47.9	44.9	49.9	< 0.05
Dyspnoea [%]	44.4	35.9	50.1	< 1*10^-6
Chest pain [%]	21.5	21.6	21.4	n.s., 0.95
Haemoptoea [%]	1.5	1.3	1.6	n.s., 0.69
Familial sarcoidosis [%]	3.1	2.6	3.4	n.s., 0.38
Hemoglobin [g/dl]	12.3 ± 4.1	12.5 ± 3.5	12.3 ± 4.4	< 0.001
Leukocytes [10^6/µl]	6.6 ± 3.0	7.0 ± 2.7	6.4 ± 3.2	< 1*10^-4
Thrombocytes [10^6/µl]	264 ± 76	278 ± 87	258 ± 71	< 0.01
History of:				
Oncologic disease [%]	4.8	3.8	5.3	n.s., 0.13
Rheumatic disease [%]	2.5	2.6	2.5	n.s., 1
Ulcerative colitis [%]	0.5	0.5	0.5	n.s., 1
Crohn's disease [%]	0.6	0.7	0.5	n.s., 0.65
Cardiovascular disease [%]	23.4	21.1	24.5	n.s., 0.08

Table S4: Data are presented as mean ± SD or percentages. #Significance levels comparing acute vs. subacute onset.

Table S5. Basic characteristics of patients not included in MCA due to missing values

	Included patients n=1932	Not included patients n=231	p values
Age [years]	46.7 ± 12.1	49.5 ± 11.7	< 0.01

Sex [male / female]	41.3 / 58.7	32.5 / 67.5	< 0.05
Body height [cm]	169.2 ± 10.0	166.7 ± 9.4	< 0.001
Body weight [kg]	78.5 ± 16.3	77.4 ± 14.7	n.s., 0.4
Smoking history [never / previously / currently in %]	70.2 / 19.6 / 10.1	79.6 / 11.7 / 8.7	< 0.001
TLC [% predicted]	97.0 ± 16.7	103.9 ± 14.4	< 1*10^-6
FEV1 [% predicted]	91.9 ± 20.4	100.6 ± 19.1	< 1*10^-6

Table S5: Data are presented as mean ± SD or percentages. TLC = total lung capacity; FEV1 = forced expiratory volume in 1 second.

Table S6. MCA Organ involvement

Dimension 1	**R2**	**p value**
Musculoskeletal involvement	0.6196	0.00E+00
Arthritis	0.5409	0.00E+00
Skin involvement	0.2487	7.11E-121

Dimension 2	**R2**	**p value**
Liver involvement	0.5884	0.00E+00
Spleen involvement	0.5195	0.00E+00
Bile duct involvement	0.0818	1.44E-36
Kidney involvement	0.0639	1.88E-28

Dimension 3	**R2**	**p value**
Eye involvement	0.4131	1.15E-224
CNS involvement	0.3544	1.35E-184
Cardiac involvement	0.1760	4.35E-82
Glands involvement	0.0849	5.35E-38

Dimension 4	**R2**	**p value**
Lung involvement	0.4231	7.37E-232
Bronchial involvement	0.1646	2.73E-76

Table S6: Square correlation ratio (R2) of the main variables contributing to the dimensions of the multiple correspondence analysis for organ involvement.

Table S7. Musculoskeletal phenotype

	Arthritis	**Musculoskeletal**

		involvement
Acute onset	63.1 % vs. 38.9 % ***	59.3 % vs. 39.0 % ***
Lung involvement [%]	84.3 % vs. 93.8 % *	87.8 % vs. 93.6 % *
Bronchial involvement [%]	51.2 % vs. 72.7 % **	51.7 % vs. 72.0 % **
Intrathoracic lymph nodes [%]	90.0 % vs. 75.6 % *	90.3 % vs. 76.4 % *
Skin involvement [%]	41.9 % vs. 12.8 % ***	47.6 % vs. 13.4 % ***
Eye involvement [%]	16.3 % and 7.3 % **	11.4 % vs. 7.1 %, p = 0.057
Renal involvement [%]	6.7 % vs. 2.8 % *	7.0% vs. 2.6 % *
Fever / subfebrile [%]	42.2 % vs. 18.8 % ***	29.8 % vs. 19.9 % *
Night sweat [%]	25.2 % vs. 11.2 % ***	23.1 % vs. 11.5 % **
Weight loss [%]	14.8 % vs. 8.1 % *	15.1 % vs. 8.8 % *
Arthralgia [%]	90.7 % vs. 47.6 % ***	89.4 % vs. 47.4 % ***

Table S7. Data are presented as percentages. All frequencies are given as with arthritis/musculoskeletal involvement vs. without arthritis/musculoskeletal involvement (for significance levels: * $p < 0.05$, ** $p < 0.001$, *** $p < 0.000001$).

Table S8. Pulmonary-lymphonodal and Extrapulmonary phenotype

	Pulmonary involvement	**No pulmonary involvement**	**p values**
TLC [% predicted]	96.5 ± 16.4	105.1 ± 17.2	< 1*10^-5
FEV1 [% predicted]	91.0 ± 19.9	98.4 ± 17.6	< 1*10^-4
Intrathoracic lymph nodes [%]	89.7 %	80.2 %	< 0.05
Skin involvement [%]	15.6 %	26.0 %	< 0.01
Musculoskeletal involvement [%]	6,9 %	16.9 %	< 1*10^-4
Arthritis [%]	8.8 %	17.7 %	< 0.01
Fatigue [%]	69.4 %	37.8 %	< 1*10^-6
Cough [%]	56.4 %	33.3 %	< 1*10^-4
Dyspnoea [%]	51.8 %	33.3 %	< 0.01
Chest pain [%]	25.8 %	11.6 %	< 0.01

Table S8: Data are presented as mean ± SD or percentages. TLC = total lung capacity; FEV1 = forced expiratory volume in 1 second.

Table S9. Basic characteristics of Serbians and non-Serbians

	Serbians n=916	**Non-Serbians n=1247**	**p values**
Age [years]	46.2 ± 11.2	47.6 ± 12.7	n.s., 0.06
Sex [male / female]	31.6 / 68.4	46.8 / 53.2	< 1*10^-6
Body height [cm]	167.4 ± 9.7	170.1 ± 9.9	< 1*10^-6
Body weight [kg]	78.0 ± 14.9	78.6 ± 17.1	n.s., 0.60
Smoking history [never / previously / currently in %]	77.3 / 10.2 / 12.6	66.7 / 25.2 / 8.1	< 1*10^-6

Table S9: Data are presented as mean ± SD or percentages.