Real-World Prevalence, Incidence and Management of Systemic Lupus Erythematosus in Germany: A Retrospective Claims Data Analysis

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SUPPLEMENTARY MATERIAL

Table S1 Additional criteria for patients included in the study based only on two outpatient SLE diagnoses

In addition to the two outpatient SLE diagnoses, at least one of the following criteria had to apply:
• At least one of the two outpatient SLE diagnoses was coded by a rheumatologist, nephrologist, internist, dermatologist, neurologist, pulmonologist or gynaecologist/obstetrician in 2012–2017 • At least one of the following combinations of supportive laboratory tests in 2011–2018 within ± 1 year of the index date: o ANA + anti-dsDNA antibodies, or o ANA + other ENA (antibodies against nuclear or cytoplasmic antigens such as Sm-B, U1-RNP, SS-A, SS-B, Scl-70, Jo-1, histone antibodies), or o ANA + cardiolipin antibodies, or o ANA + lupus anticoagulant (IgG and IgM), or o ANA + >1 C3 or C4 • At least one prescription in 2012–2017 o Antimalarials (chloroquine, hydroxychloroquine), or o Immunosuppressive medications (azathioprine, belimumab, cyclophosphamide, cyclosporine A, methotrexate, mycophenolate or mycophenolic acid, rituximab, systemic corticosteroids, tacrolimus) • At least one ICD-10-GM code (inpatient and/or outpatient) associated with organ involvement in 2012–2017 o N08.5 – glomerular diseases in systemic diseases of connective tissue

- N16.4 – tubulointerstitial kidney disease in systemic connective tissue diseases
- J99.1 – respiratory diseases in other diffuse connective tissue diseases
- I32.8 – pericarditis in other diseases classified elsewhere
- I39.x – endocarditis and valvular heart disease in other diseases classified elsewhere
- D59.1 – other autoimmune haemolytic anaemias
- K75.4 – autoimmune hepatitis
- G63.5 – polyneuropathy due to systemic diseases of connective tissue
- G05.8 – encephalitis, myelitis and encephalomyelitis in other diseases classified elsewhere
- G40.x – epilepsy

ANA antinuclear antibodies; *C3/4* complement component 3/4; *dsDNA* double-stranded DNA; *ENA* autoantibodies to extractable nuclear antigens; *ICD-10-GM* International Classification of Diseases, 10th revision, German modification; *IgG* immunoglobulin G; *IgM* immunoglobulin M; *SLE* systemic lupus erythematosus

Table S2 List of ICD-10-GM codes for subgroup allocation

Description	ICD-10-GM code associated with organ involvement
SLE only	NA
SLE + LN only	E321, E1321, M321, M350, N000-070, N072–074, N076-077, N08, N082, N084–085, N088, N12, N141, N150, N158–159, N16, N160–162, N164, N168, N170–703, N709, N171, N1711–1713, N1719, N172, N1721–1723, N1729, N178, N1718–1783, N1789, N179, N1791–1793, N1799, N18, N181–185, N188, N1880, N1889, N189, N19, R80
SLE + CNS only	F01, F010–013, F018–019, F03–05, F050–051, F058–060, F062–063, F068, F09, F129, F149, F159, F162, F169, F181, F189, F201–202, F205, F22, F229, F23, F231, F24, F251, F30, F302, F309, F314-315, F32, F322–323,F332–333, F349, F445, F53, F538–539, F840, F843, F848, G030, G04, G041, G048–049, G35, G360–361, G368–375, G378-379, G40, G400, G4000–4002, G4008–4009, G401-406, G408–409, I677, I778, R56, R560, R568
SLE + LN + CNS	A combination of at least one code of each of the SLE + LN–only and the SLE + CNS–only subgroups

CNS central nervous system; *ICD-10-GM* International Classification of Diseases, 10th revision, German modification; *LN* lupus nephritis; *NA* not applicable; *SLE* systemic lupus erythematosus

Table S3 A list of drugs commonly used to treat patients with SLE

Drug class/type of therapy	Drug
Antimalarials	Chloroquine
	Hydroxychloroquine
	Mefloquine
	Primaquine
Biologics	Abatacept IV or SC[a]
	Belimumab IV or SC
	Rituximab IV only[a]
Immunosuppressants	Azathioprine
	Cyclophosphamide
	Cyclosporine
	Leflunomide
	Methotrexate
	Mycophenolate mofetil
	Mycophenolate sodium
	Tacrolimus
IVIg	
Combination therapy[b]	Antimalarial + azathioprine ± corticosteroid
	Antimalarial + methotrexate ± corticosteroid
	Antimalarial + belimumab ± corticosteroid
	Antimalarial + mycophenolate mofetil ± corticosteroid
	Antimalarial + any immunosuppressant (other than methotrexate, mycophenolate or azathioprine) ± corticosteroid

	Antimalarial + any biologic or IVIg ± corticosteroid
	Any drug + corticosteroid
	Any combination of 2 drugs[c]
	Any combination of ≥ 3 drugs[b]

IV intravenous; *IVIg* intravenous immunoglobulin; *SC* subcutaneous; *SLE* systemic lupus erythematosus; *SOT* sequence of therapy

[a]Off-label use

[b]Other additional agents or > 1 antimalarial were allowed if not explicitly excluded

[c]Antimalarials, biologics and immunosuppressants are differentiated by agents, and steroids are not counted as combination partners

Table S4 Predefined comorbid conditions assessed in the study

Comorbidity	ICD-10-GM codes associated with the predefined comorbidity
Rheumatoid arthritis and other inflammatory arthropathies	M05, M07, M09–14, E06.3
Ophthalmologic disorders	A185, A527, G360, H100–109, H470, H150–151
Osteoporosis	M80–82
Anaemia	D50–53, D55–64
Raynaud's syndrome	I73.0
Myositis/myalgia	M791, M797
Hypertension	I10–13, I15
Nephritis	E321, E1321, E1320, M321, M350, N000-085, N088, N08, N12, N140–142, N144, N150, N158–159, N16, N160–165, N168, N170–703, N709, N171, N1711–1713, N1719, N172, N1721–1723, N1729, N178, N1718–1783, N1789, N179, N1791–1793, N1799, N18, N181–185, N188, N1880, N1889, N189, N19, R80
Depression	F32, F33
Cardiac disease	I010-012, I020, I050–052, I058–062, I068–072, I078–083, I088-091, I092, I098–099, I10, I110, I119–120, I129–130, I1310–1311, I132, I150–152, I158–159, I200–201, I208–214, I21, I219–I221, I22,

	I228–229, I23, I230–236, I238, I240–241, I248–249, I25, I2510–2511, I252–256, I258–260, I269–272, I278–281, I288–301, I308–313, I31, I318–319, I32, I330, I339–342, I348–352, I358–362, I368–372, I378–379, I38, I39, I400, I408-409, I41, I421–424, I428, I440-447, I450–456, I458–459, I46, I469–472, I479–484, I491–495, I498–501, I50, I509, I514, I600–615, I616, I618–619, I6200–6202, I620–621, I629–636, I638–639, I660–663, I669–672, I675–680, I682, I688, I69, I690–693, I700–701, I7020–7025, I7029, I70, I708–709, I7100–I7103, I711–I716, I718–726, I728–731, I738–745, I748–749, I770–776, I77, I778–780, I788–791, I798–803, I809, I81, I82, I820–823, I8281, I828–832, I83, I830, I860–864, I868, I8700–8701, I870–872, I87, I878–879, I890–891, I898–899, I95, I950–952, I958–959, I970–972, I99
Pulmonary disease	J40–47
Hyperlipidaemia	E78, E78.0–78.5

ICD-10-GM International Classification of Diseases, 10th revision, German modification

Table S5 Treatment patterns according to the SOT in the SLE-only subgroup (incident cohort)

	SOT1 (*n* = 348)	**SOT2 (*n* = 111)**	**SOT3 (*n* = 49)**
Treatment gaps (> 60 days), *n* (%)	248 (71.3)	54 (48.6)	26 (53.1)
Monotherapy, *n* (%)	192 (55.2)	31 (28.0)	14 (28.6)
Corticosteroids	109 (31.3)	0	0
Antimalarials	76 (21.8)	18 (16.2)	6 (12.2)
Immunosuppressants	6 (1.7)	11 (9.9)	8 (16.3)
Biologics	0	4 (3.6)	0
Rituximab	0	1 (0.9)	0
Belimumab	0	0	0
Other	0	3 (2.7)	0
IVIg	1 (0.3)	0	1 (2.0)
Combination therapy, *n* (%)	156 (44.8)	80 (72.1)	35 (71.4)
Antimalarials + corticosteroids	112 (32.2)	22 (19.8)	9 (18.4)
Immunosuppressants + corticosteroids	22 (6.3)	32 (28.8)	8 (16.3)
Antimalarials + immunosuppressants + corticosteroids	15 (4.3)	21 (18.9)	11 (22.5)
Antimalarials + immunosuppressants	6 (1.7)	3 (2.7)	2 (4.1)
Antimalarials + biologics + corticosteroids	0	0	2 (4.1)

Immunosuppressants + biologics + corticosteroids	1 (0.3)	1 (0.9)	0
Antimalarials + immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + biologics	0	0	1 (2.0)
Immunosuppressants + biologics	0	0	1 (2.0)
Biologics + corticosteroids	0	1 (0.9)	1 (2.0)
Biologics used in combination therapies, *n* (%)			
Belimumab	0	1 (0.9)	4 (8.2)
Rituximab	1 (0.3)	1 (0.9)	1 (2.0)

IVIg intravenous immunoglobulin; *SLE* systemic lupus erythematosus; *SOT* sequence of therapy

Table S6 Treatment patterns according to the SOT in the SLE + LN–only subgroup (incident cohort)

	SOT1 (*n* = 249)	**SOT2 (*n* = 107)**	**SOT3 (*n* = 56)**
Treatment gaps (> 60 days), *n* (%)	157 (63.1)	57 (53.3)	31 (55.4)
Monotherapy, *n* (%)	357 (52.4)	57 (23.2)	25 (22.1)
Corticosteroids	72 (28.9)	0	0
Antimalarials	33 (13.3)	10 (9.4)	4 (7.1)
Immunosuppressants	7 (2.8)	9 (8.4)	5 (8.9)
Biologics	1 (0.4)	2 (1.9)	1 (1.8)
Rituximab	1 (0.4)	1 (0.9)	1 (1.8)
Belimumab	0	1 (0.9)	0
Other	0	0	0
IVIg	0	0	0
Combination therapy, *n* (%)	136 (54.6)	86 (80.4)	46 (82.1)
Antimalarials + corticosteroids	71 (28.5)	20 (18.7)	5 (8.9)
Immunosuppressants + corticosteroids	40 (16.1)	39 (36.5)	9 (16.1)
Antimalarials + immunosuppressants + corticosteroids	24 (9.6)	0	27 (48.2)
Antimalarials + immunosuppressants	1 (0.4)	23 (21.5)	0
Antimalarials + biologics + corticosteroids	0	1 (0.9)	1 (1.8)

Immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + immunosuppressants + biologics + corticosteroids	0	3 (2.8)	0
Antimalarials + biologics	0	0	0
Immunosuppressants + biologics	0	0	0
Biologics + corticosteroids	0	0	4 (7.1)
Biologics used in combination therapies, *n* (%)			
Belimumab	0	4 (3.7)	3 (5.4)
Rituximab	0	0	2 (3.6)

IVIg intravenous immunoglobulin; *LN* lupus nephritis; *SLE* systemic lupus erythematosus; *SOT* sequence of therapy

Table S7 Treatment patterns according to the SOT in the SLE + CNS–only subgroup (incident cohort)

	SOT1 (*n* = 36)	**SOT2 (*n* = 12)**	**SOT3 (*n* = 4)**
Treatment gaps (> 60 days), *n* (%)	21 (58.3)	5 (41.7)	2 (50.0)
Monotherapy, *n* (%)	22 (61.1)	3 (25.0)	1 (25.0)
Corticosteroids	9 (25.0)	0	0
Antimalarials	12 (33.3)	0	0
Immunosuppressants	1 (2.8)	3 (25.0)	1 (25.0)
Biologics	0	0	0
Rituximab	0	0	0
Belimumab	0	0	0
Other	0	0	0
IVIg	0	0	0
Combination therapy, *n* (%)	14 (38.9)	9 (75.0)	3 (75.0)
Antimalarials + corticosteroids	12 (33.3)	2 (16.7)	1 (25.0)
Immunosuppressants + corticosteroids	1 (2.8)	5 (41.7)	1 (25.0)
Antimalarials + immunosuppressants + corticosteroids	1 (2.8)	1 (8.3)	1 (25.0)
Antimalarials + immunosuppressants	0	1 (8.3)	0
Antimalarials + biologics + corticosteroids	0	0	0

Immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + biologics	0	0	0
Immunosuppressants + biologics	0	0	0
Biologics + corticosteroids	0	0	0
Biologics used in combination therapies, *n* (%)			
Belimumab	0	0	0
Rituximab	0	0	0

CNS central nervous system; *IVIg* intravenous immunoglobulin; *SLE* systemic lupus erythematosus; *SOT* sequence of therapy

Table S8 Treatment patterns according to the SOT in the SLE + LN + CNS subgroup (incident cohort)

	SOT1 (*n* = 48)	**SOT2 (*n* = 16)**	**SOT3 (*n* = 4)**
Treatment gaps (> 60 days); *n* (%)	31 (64.4)	10 (62.5)	3 (75.0)
Monotherapy, *n* (%)	30 (47.9)	2 (12.5)	0
Corticosteroids	0	0	0
Antimalarials	8 (16.7)	0	0
Immunosuppressants	1 (2.1)	2 (12.5)	0
Biologics	0	0	0
Rituximab	0	0	0
Belimumab	0	0	0
Other	0	0	0
IVIg	0	0	0
Combination therapy, *n* (%)	18 (37.5)	14 (87.5)	4 (100)
Antimalarials + corticosteroids	10 (20.8)	6 (37.5)	0
Immunosuppressants + corticosteroids	5 (10.4)	4 (25.0)	2 (50.0)
Antimalarials + immunosuppressants + corticosteroids	2 (4.2)	4 (25.0)	2 (50.0)
Antimalarials + immunosuppressants	0	0	0
Antimalarials + biologics + corticosteroids	1 (2.1)	0	0

Immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + immunosuppressants + biologics + corticosteroids	0	0	0
Antimalarials + biologics	0	0	0
Immunosuppressants + biologics	0	0	0
Biologics + corticosteroids	0	0	0
Biologics used in combination therapies, *n* (%)			
Belimumab	1 (2.1)	0	0
Rituximab	0	0	0

CNS central nervous system; *IVIg* intravenous immunoglobulin; *LN* lupus nephritis; *SLE* systemic lupus erythematosus; *SOT* sequence of therapy

Table S9 Medications used in 2019 in the epidemiological analysis group

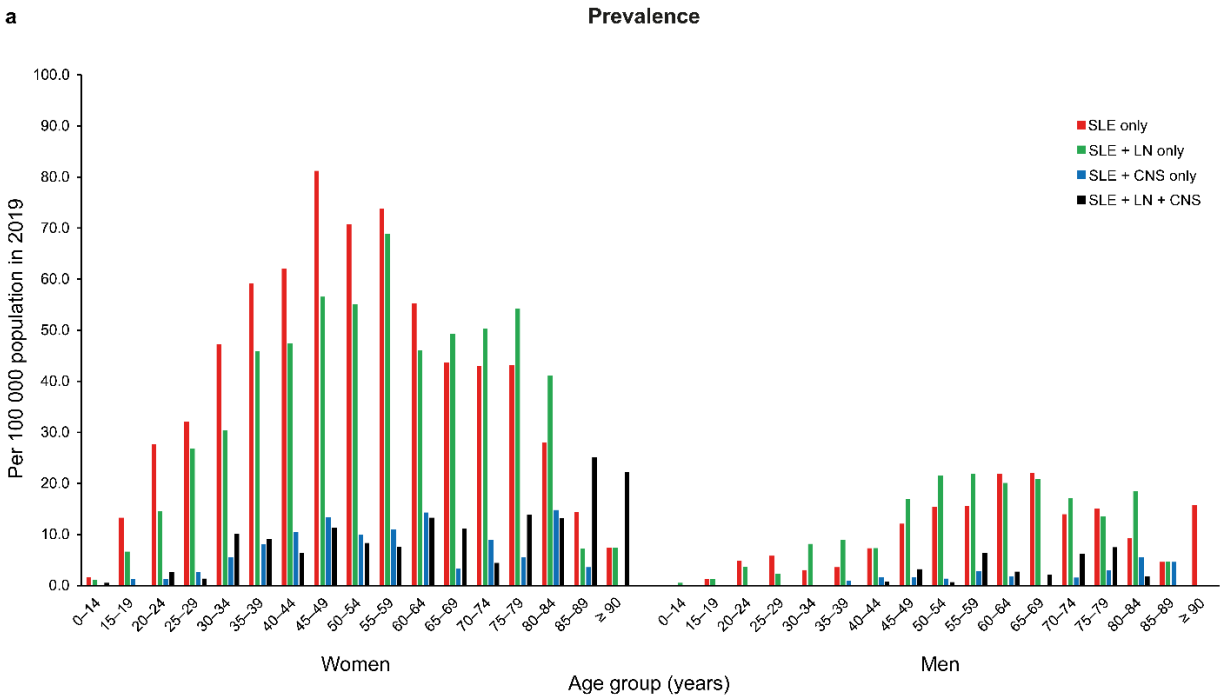
	Drugs used (*N* = 1802)
Abatacept[a]	1 (0.06)
Hydrocortisone	6 (0.33)
Ig	8 (0.44)
Cyclophosphamide	9 (0.50)
Betamethasone	11 (0.61)
Rituximab[a]	13 (0.72)
Leflunomide	15 (0.83)
Tacrolimus	19 (1.05)
Triamcinolone	19 (1.05)
Cyclosporine	24 (1.33)
Dexamethasone	33 (1.83)
Methylprednisolone	41 (2.28)
Belimumab	65 (3.61)
Chloroquine	65 (3.61)
Prednisone	94 (5.22)
Mycophenolate	168 (9.32)
Methotrexate	191 (10.60)
Azathioprine	249 (13.82)
Hydroxychloroquine	834 (46.28)
Prednisolone	841 (46.67)

Ig immunoglobulin

Data are presented as *n* (%)

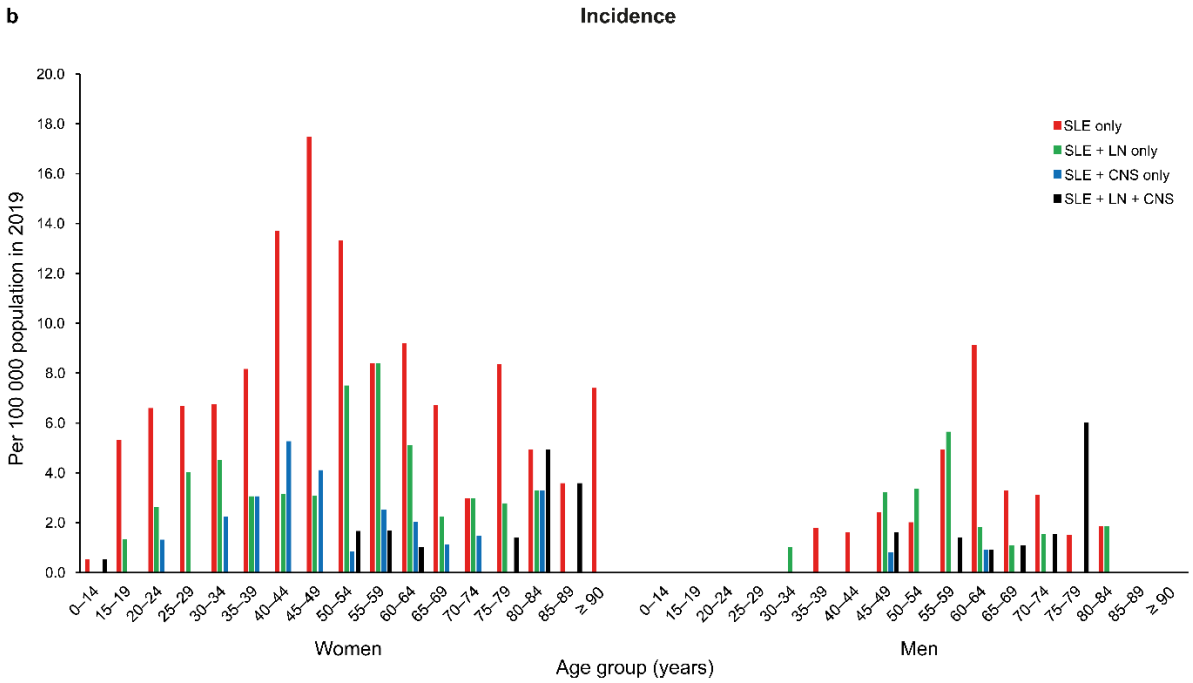
[a]Off-label use

a



Age group, years	SLE only	SLE + LN only	SLE + CNS only	SLE + LN + CNS
Women				
0–14	1.61	1.07	–	0.54
15–19	13.27	6.64	1.33	–
20–24	27.70	14.51	1.32	2.64
25–29	32.14	26.79	2.68	1.34
30–34	47.25	30.37	5.62	10.12
35–39	59.19	45.93	8.16	9.19
40–44	62.14	47.39	10.53	6.32
45–49	81.22	56.55	13.37	11.31
50–54	70.83	55.00	10.00	8.33
55–59	73.87	68.83	10.91	7.56
60–64	55.20	46.00	14.31	13.29
65–69	43.63	49.23	3.36	11.19
70–74	42.95	50.36	8.89	4.44
75–79	43.16	54.29	5.57	13.92
80–84	27.95	41.10	14.80	13.15
85–89	14.37	7.18	3.59	25.14
≥ 90	7.40	7.40	–	22.21

Age group, years	SLE only	SLE + LN only	SLE + CNS only	SLE + LN + CNS
Men				
0–14	–	0.51	–	–
15–19	1.24	1.24	–	–
20–24	4.82	3.62	–	–
25–29	5.81	2.32	–	–
30–34	3.05	8.14	–	–
35–39	3.60	8.99	0.90	–
40–44	7.31	7.31	1.62	0.81
45–49	12.11	16.96	1.61	3.23
50–54	15.46	21.50	1.34	0.67
55–59	15.52	21.88	2.82	6.35
60–64	21.91	20.08	1.83	2.74
65–69	22.00	20.90	–	2.20
70–74	13.96	17.06	1.55	6.21
75–79	15.05	13.54	3.01	7.52
80–84	9.26	18.51	5.55	1.85
85–89	4.62	4.62	4.62	–
≥ 90	15.75	–	–	–



Age group, years	SLE only	SLE + LN only	SLE + CNS only	SLE + LN + CNS
Women				
0–14	0.54	–	–	0.54
15–19	5.31	1.33	–	–
20–24	6.60	2.64	1.32	–
25–29	6.70	4.02	–	–
30–34	6.75	4.50	2.25	–
35–39	8.16	3.06	3.06	–
40–44	13.69	3.16	5.27	–
45–49	17.48	3.08	4.11	–
50–54	13.33	7.50	0.83	1.67
55–59	8.39	8.39	2.52	1.68
60–64	9.20	5.11	2.04	1.02
65–69	6.71	2.24	1.12	–
70–74	2.96	2.96	1.48	–
75–79	8.35	2.78	–	1.39
80–84	4.93	3.29	3.29	4.93
85–89	3.59	–	–	3.59
≥ 90	7.40	–	–	–

Age group, years	SLE only	SLE + LN only	SLE + CNS only	SLE + LN + CNS
Men				
0–14	–	–	–	–
15–19	–	–	–	–
20–24	–	–	–	–
25–29	–	–	–	–
30–34	–	1.02	–	–
35–39	1.80	–	–	–
40–44	1.62	–	–	–
45–49	2.42	3.23	0.81	1.61
50–54	2.02	3.36	–	–
55–59	4.94	5.65	–	1.41
60–64	9.13	1.83	0.91	0.91
65–69	3.30	1.10	–	1.10
70–74	3.10	1.55	–	1.55
75–79	1.50	–	–	6.02
80–84	1.85	1.85	–	–
85–89	–	–	–	–
≥ 90	–	–	–	–

Fig. S1 a Prevalence and **b** incidence of SLE based on disease manifestation subgroups in the SHI population, stratified by sex and age (2019). *CNS* central nervous system; *LN* lupus nephritis; *SHI* statutory health insurance; *SLE* systemic lupus erythematosus

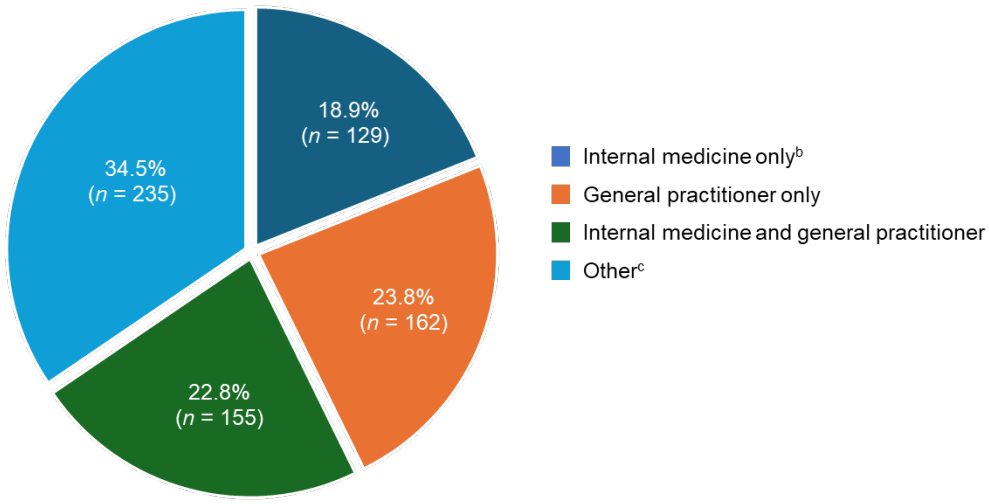


Fig. S2 Specialities visited for SLE-specific treatment[a]

ICD-10-GM International Classification of Diseases, 10th revision, German modification; *SLE* systemic lupus erythematosus

[a]SLE-specific treatment refers to patient visits coded with ICD-10 M32.

[b]Internist, rheumatologist or nephrologist.

[c]Any other specialities visited or patient visits not coded with ICD-10-GM M32.

Supplementary Methods

Statistical Analysis, Data Management and Quality Control

To estimate the projected sample size for the final study analysis, a feasibility assessment using WIG2 data from approximately 3500 patients with at least one SLE diagnosis between 1 January 2012 and 31 December 2017 was conducted, with an expectation of the same size for 2018–2019.

Completely anonymised analysis datasets were created using information from the full WIG2 benchmark database. The acquisition of data followed a predefined statistical data collection plan, which involved checks related to compliance and completeness of data acquisition, data processing, the processed data and quality assurance. All analyses were conducted at the site of the data provider due to German data protection requirements. Data quality management was built into the core processing systems, with the structured query language (SQL)/R used to process data to determine quality metrics.

To minimise misclassification of SLE, all available historical claims data were utilised and key variables assessed. The likelihood of missing data was minimal, owing to the inclusion criterion for patients to be continuously enrolled for a minimum of 12 months prior to the index date. To reduce selection bias, the selection of patients was not based on a sampling method, and the entire study population underwent observation, regardless of factors such as treatment received and patient health status. Medication data were limited to drugs administered in the outpatient setting only. Confounding is not applicable to this study, given that there were no assessments of causality, and no comparisons were made between exposure cohorts.