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Epidemiology of interstitial lung disease in systemic lupus erythematosus in France: A nation-wide population-based study over 10 years

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Abstract

Background and objective: Data regarding interstitial lung disease (ILD) in the setting of systemic lupus erythematosus (SLE) are limited. We used a nationwide database to determine the incidence and the prevalence of ILD in SLE.

Methods: Characteristics of all SLE inpatients admitted between 2011 and 2012 in France were analysed through the French medico-administrative database. Features associated with the presence of ILD were studied. Cox hazard model was used to measure the impact of ILD on survival from the first stay to 2020. The incidence of ILD in SLE was estimated by analysing the onset of ILD from 2013 to 2020 in SLE patients who had no evidence of ILD in 2013.

Results: Between 2011 and 2012, 10,460 SLE patients had at least one hospital stay and could be traced until 2020. Among them, 134 (1.2%) had an ILD diagnosed at baseline. The frequency of ILD in SLE was higher in patients who had an associated autoimmune disease such as Sjögren's syndrome or systemic sclerosis (29.9% vs. 5.9%, $p < 0.0001$). ILD was associated with an increased risk of death in SLE in the multivariable analysis (hazard ratio [95% CI] 1.992 [1.420–2.794]; $p < 0.0001$). Among the 31,029 SLE patients with no evidence of ILD at baseline, ILD occurred in 795 (2.6%) between 2013 and 2020. The incidence rate of ILD in SLE was 10.26 for 1000 patient-years [95% CI: 10.24–10.28].

Conclusion: In SLE, ILD is exceedingly rare, often associated with another systemic autoimmune disorder and appears as a major risk factor for death.

KEYWORDS
death, epidemiology, interstitial lung disease, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) affects mostly women of child-bearing age and involves multiple organs.[1] Besides pleuritis—the most common thoracic manifestation of SLE—specific pulmonary manifestations mainly include acute pneumonitis, alveolar haemorrhage, organizing pneumonia, chronic interstitial lung disease (ILD), shrinking lung syndrome, bronchiolitis obliterans and pulmonary hypertension.[2,3] Little data are available regarding the prevalence and the severity of chronic ILD in SLE, most studies being limited to small and heterogeneous series.[4] The largest study in the field—an historical autopsy study by Haupt et al.[5]—reported interstitial lung fibrosis in 4% of 120 SLE patients, while chest radiographic abnormalities consistent with ILD have been reported in 6%–24% of unselected patients with SLE.[6,7]

We analysed the prevalence, incidence and outcome associated with chronic ILD in SLE patients using a French nation-wide hospital medical information database.

METHODS

Study population and data source

Data for all patients admitted between January 2011 and December 2020 in French hospitals with at least one SLE diagnosis were retrieved from the French nation-wide hospital medical information database PMSI (Programme de Médicalisation des Systèmes d'Informations, *Information System Medicalization Program*). PMSI database provides a summary with diagnosis and individual medical conditions at discharge of all French healthcare facilities. Information covers both medical and administrative data. Each facility produces its own anonymous standardized data, which are then compiled at the national level. The national database is built to link the medical data on each individual patient irrespective of which French healthcare facility is used. Medical data include main diagnosis, secondary diagnoses and procedures. Administrative data include age, sex, year, duration of the stay and location of the hospital. In-hospital death is reported. Diagnoses are coded according to the International Classification of Diseases, tenth revision (ICD-10, available at https://icd.who.int/browse10/2019/en). Procedures are coded according to the 'Classification Commune des Actes Médicaux' (CCAM). Regular checks are made by the social insurance authority to ensure that data are correctly imputed. The reliability and validity of PMSI data have been assessed elsewhere.[8,9] To select the SLE population, from the PMSI database, we first extracted all the records of patients for whom at least one ICD-10 M32 ('systemic lupus erythematosus') was reported. We excluded patients younger than 16 years old and patients admitted to hospital only for scheduled sessions (chronic haemodialysis, radiotherapy, chemotherapy). Hospital stays with ambiguous chaining were excluded.

ILD was defined as having a chronic pulmonary disease with interstitial involvement (ICD-10 code J67.X, J84.1 or J84.8). Specific diagnostic codes were used for lupus-associated autoimmune diseases (AIDs) such as Sjögren's syndrome (ICD-10 M35.0), mixed connective tissue disorder (ICD-10 M35.1), systemic sclerosis (M34.X) or inflammatory myopathy (M33.X). For the exhaustive description of diagnosis and procedures codes, details are given in Appendix S1 in the Supporting Information.

SUMMARY AT A GLANCE

While exceedingly rare, interstitial lung disease (ILD) is a severe complication of systemic lupus erythematosus (SLE). In this French nation-wide population study, ILD is independently associated with death in SLE. The study reveals that another associated autoimmune disease is involved in many cases.

Statistical analysis

Categorical variables are presented as number (percentage). Quantitative variables are presented as median (first quartile–third quartile). For comparisons between groups, we used chi-square and Student's *t*-tests, as appropriate. Survival curves were plotted according to the ILD status at first stay according to the Kaplan–Meier method. Univariable and multivariable hazard ratios (HR) associated with the presence of ILD at first stay were calculated using Cox proportional hazard models. HRs are presented with their 95% CI as HR (95% CI). To perform the multivariable Cox proportional hazard model, we used all the variables that had a level of significance <0.05 in the univariable model as covariates. All tests were two sided, and *p*-values of <0.05 were considered to indicate a significant

TABLE 1 Baseline characteristics of SLE patients with or without ILD during 2011–2012

	ILD+, *n* = 134	ILD−, *n* = 10,326	*p*
Age (years), median (IQR)	55 (44–64)	44 (33–58)	<0.0001
Male gender, *n* (%)	28 (20.9%)	1384 (13.4%)	0.012
High blood pressure, *n* (%)	26 (19.4%)	1430 (13.8%)	0.065
Diabetes, *n* (%)	11 (8.2%)	428 (4.1%)	0.020
Chronic kidney disease, *n* (%)	4 (3.0%)	735 (7.1%)	0.064
Cancer, *n* (%)	5 (3.7%)	383 (3.7%)	0.989
APS, *n* (%)	3 (2.2%)	182 (1.8%)	0.678
Associated AID, *n* (%)	40 (29.9%)	607 (5.9%)	<0.0001
Sjögren's syndrome, *n* (%)	19 (14.2%)	461 (4.5%)	<0.0001
MCTD, *n* (%)	5 (3.7%)	33 (0.3%)	<0.0001
Systemic sclerosis, *n* (%)	15 (11.2%)	85 (0.8%)	<0.0001
Inflammatory myopathy, *n* (%)	7 (5.2%)	59 (0.6%)	<0.0001

Note: The analysis was performed on 10,460 SLE patients older than 16 years who had a hospital stay in France between 2011 and 2012. Comparisons were made between the patients who had ILD (ILD+) or did not have ILD (ILD−) at their first hospital stay.

Abbreviations: AID, autoimmune disease including Sjögren's syndrome, MCTD, systemic sclerosis or inflammatory myopathy; APS, antiphospholipid syndrome; ILD, interstitial lung disease; IQR, interquartile range; MCTD, mixed connective tissue disorder; SLE, systemic lupus erythematosus.

TABLE 2 Uni- and multi-variable analyses of risk factors for death in SLE patients

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.062	1.059–1.066	<0.0001	1.058	1.054–1.062	<0.0001
Male gender	2.224	1.949–2.538	<0.0001	1.493	1.306–1.706	<0.0001
High blood pressure	2.752	2.432–3.115	<0.0001	1.231	1.079–1.405	0.002
Diabetes	1.639	1.307–2.057	<0.0001	0.954	0.758–1.201	0.69
Chronic kidney disease	2.944	2.543–3.409	<0.0001	2.564	2.206–2.982	<0.0001
Cancer	4.889	4.129–5.789	<0.0001	2.963	2.498–3.514	<0.0001
APS	1.245	0.856–1.811	0.252	—	—	—
Associated AID	1.025	0.817–1.286	0.830	0.908	0.721–1.142	0.409
Sjögren's syndrome	0.971	0.743–1.270	0.832	—	—	—
MCTD	0.77	0.298–2.056	0.603	—	—	—
Systemic sclerosis	1.559	0.979–2.483	0.062	—	—	—
Inflammatory myopathy	0.593	0.246–1.428	0.240	—	—	—
ILD	2.448	1.749–3.426	<0.0001	1.992	1.420–2.794	<0.0001

Note: The analysis was performed on 10,460 SLE patients older than 16 years who had a hospital stay in France between 2011 and 2012 with a median follow-up of 75.2 (30.7–96.7) months.

Abbreviations: AID, autoimmune disease including Sjögren's syndrome, MCTD, systemic sclerosis or inflammatory myopathy; APS, antiphospholipid syndrome; HR, hazard ratio; ILD, interstitial lung disease; MCTD, mixed connective tissue disorder; SLE, systemic lupus erythematosus.

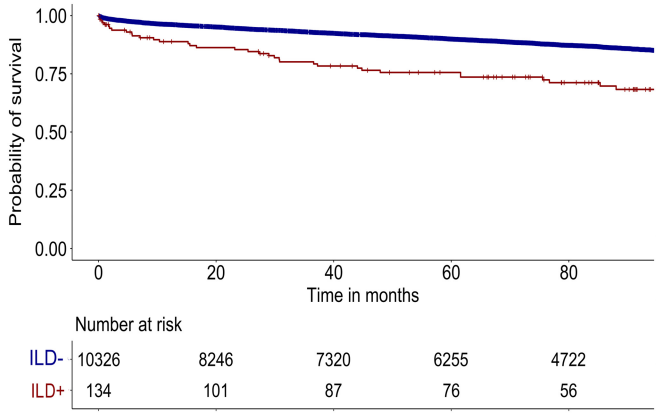

FIGURE 1 Survival according to the ILD status at baseline in SLE patients. Survival curve was plotted according to the ILD status (ILD+ vs. ILD−) at first stay using the Kaplan–Meier method. ILD, interstitial lung disease; SLE, systemic lupus erythematosus

association. All analyses were performed using SAS© software version 9.4 (SAS Inc., Cary, NC). Kaplan–Meier and cumulative incidence function curves were made with R software version 4.0.3, package 'survminer'.

RESULTS

Factors associated with ILD in SLE

Between 2011 and 2020, 37,393 SLE unique patients were hospitalized in France. Among them, 10,460 individuals older than 16 years had a stay between 2011 and 2012 and could be followed up from their first stay to 2020 (Figure S1 in the Supporting Information). As expected, most patients were female (9048 [86.5%] of 10,460 patients) with a median (interquartile range) age of 44 (33–58) years. Among the 10,460 SLE patients considered for the analysis, only 134 (1.2%) had an ILD code at baseline. SLE patients with ILD were significantly older (55 [44–64] vs. 44 [33–58] years; $p < 0.0001$) and more frequently male (20.9% vs. 13.4%; $p = 0.012$) than SLE patients without ILD. Interestingly, the frequency of ILD in SLE was higher in patients who had another AID—such as Sjögren's syndrome or systemic sclerosis—associated with SLE (29.9% vs. 5.9%; $p < 0.0001$; Table 1). The distribution of ILD prevalence in SLE appears to vary across the country (Figure S2 in the Supporting Information). We observed a higher incidence rate overseas, especially in the Caribbean islands and in the areas of big cities.

Association of ILD with poor outcome in SLE

Among the 10,460 SLE patients identified between 2011 and 2012, 1277 (12.2%) died during a median follow-up of 75.2 (30.7–96.7) months. In the univariate analysis, death in SLE was associated with older age (HR [95% CI] 1.062 [1.059–1.066]; $p < 0.0001$), male gender (HR [95% CI] 2.224 [1.949–2.538]; $p < 0.0001$), high blood pressure (HR [95% CI] 2.752 [2.432–3.115]; $p < 0.0001$), diabetes (HR [95% CI] 1.639 [1.307–2.057]; $p < 0.0001$), chronic kidney disease (HR [95% CI] 2.944 [2.543–3.409]; $p < 0.0001$), cancer (HR [95% CI] 4.889 [4.129–5.789]; $p < 0.0001$) and ILD (HR [95% CI] 2.448

TABLE 3 Characteristics of SLE patients with or without ILD occurring during follow-up

	ILD+, *n* = 795	ILD−, *n* = 30,234	*p*
Age (years), median (IQR)	54 (44–65)	45 (33–59)	<0.001
Male gender, *n* (%)	125 (15.7)	4277 (14.2)	0.208
High blood pressure, *n* (%)	118 (14.8%)	3395 (11.2%)	0.002
Diabetes, *n* (%)	40 (5.0%)	1184 (3.9%)	0.111
Chronic kidney disease, *n* (%)	39 (4.9%)	1276 (4.2%)	0.344
Cancer, *n* (%)	21 (2.6%)	805 (2.7%)	0.971
APS, *n* (%)	7 (0.9%)	553 (1.8%)	0.047
Associated AID, *n* (%)	242 (30.4%)	1872 (6.2%)	<0.001
Sjögren's syndrome, *n* (%)	70 (8.8%)	975 (3.2%)	<0.001
MCTD, *n* (%)	140 (17.6%)	719 (2.4%)	<0.001
Systemic sclerosis, *n* (%)	53 (6.7%)	154 (0.5%)	<0.001
Inflammatory myopathy, *n* (%)	20 (2.5%)	94 (0.3%)	<0.001

Note: The analysis was performed on 31,029 SLE patients older than 16 years who had no evidence of ILD at baseline in 2013 in France. Comparison was made on characteristics at baseline (i.e., 2013) between patients with incident (ILD+) or no (ILD−) ILD between 2013 and 2020.
Abbreviations: AID, autoimmune disease including Sjögren's syndrome, MCTD, systemic sclerosis or inflammatory myopathy; APS, antiphospholipid syndrome; ILD, interstitial lung disease; IQR, interquartile range; MCTD, mixed connective tissue disorder; SLE, systemic lupus erythematosus.

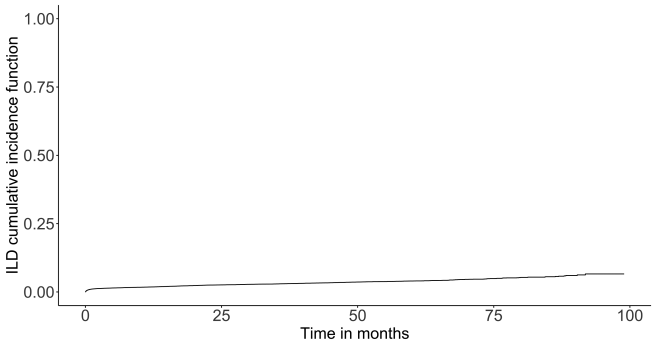

FIGURE 2 Cumulative ILD incidence in SLE. The cumulative incidence function of ILD in SLE from 2013 to 2020 is represented. To determine the incidence of ILD in SLE patients, we selected among the 37,393 SLE patients hospitalized in France between 2011 and 2020 those who (i) were older than 16 years, (ii) had no ILD diagnosed between January 2011 and January 2013 and (iii) had at least one hospital stay after January 2013. Accordingly, 31,029 SLE patients without evidence of ILD at baseline (i.e., January 2013) were studied. ILD, interstitial lung disease; SLE, systemic lupus erythematosus

[1.749–3.426]; $p < 0.0001$). In the multivariable analysis, ILD remained significantly associated with an increased risk of death (HR [95% CI] 1.992 [1.420–2.794]; $p < 0.0001$; Table 2 and Figure 1).

Incidence of ILD in SLE

To estimate the incidence rate of ILD in SLE, we analysed the onset of ILD from 2013 to 2020 in SLE patients without ILD up to 2013. Thus, SLE patients who had (i) an ILD ICD code associated with any stays between January 2011 and December 2012 or (ii) no hospital stay after December 2012 were excluded from the analysis (Figure S3 in the Supporting Information). Accordingly, 31,029 SLE patients without ILD at baseline (i.e., 2013) were studied. Between 2013 and 2020, ILD occurred in 795 SLE patients (2.6%). ILD patients were older (54 [44–65] vs. 45 [33–59]; $p < 0.001$) and displayed more frequently another AID (30.4% vs. 6.2%; $p < 0.001$) associated with SLE at baseline (Table 3). Overall, the incidence rate of ILD in SLE was of 10.26 for 1000 patient-years (95% CI 10.24–10.28) (Figure 2).

DISCUSSION

By using a nation-wide healthcare database, we were able to analyse the burden of ILD in SLE and show that a very limited proportion of the SLE population admitted in hospital was affected by ILD (2.6% in a 7-year period). Such rate is lower than the 3%–13% of ILD prevalence previously reported in smaller clinical series of SLE patients.[2,10] On the other hand, a previous necropsy study identified pulmonary fibrosis in only four lung specimen from 120 SLE patients.[5] Consistent with the literature, ILD in SLE was related to age and other comorbid conditions.[11,12]

Indeed, almost a third of SLE patients with ILD had, in addition to SLE, another autoimmune disorder—such as Sjögren's syndrome, systemic sclerosis, mixed connective tissue disorder or inflammatory myopathy—which all are at specific risk for lung involvement. The frequency of ILD in SLE is thus exceedingly rare and a high proportion of SLE patients with ILD had an 'overlapping' SLE. Moreover, a direct link between SLE and ILD is difficult to ascertain because many confounding factors such as environmental factors—as suggested by the heterogeneous geographical distribution of ILD across the country—smoking or drugs exposure may intervene.

Although ILD was considered to have a limited impact on global outcome in previous reports,[4] it is independently associated with a premature death in our study, with an HR similar to chronic kidney disease in SLE.[13]

Our study suffers several limitations. First, as only inpatients were considered, our study was probably enriched in

SLE patients with a more severe phenotype and less severe outpatients with both SLE and ILD could be missed. Second, we had no access to many confounding factors, such as smoking habits. Third, we cannot determine if any ILD pattern—such as non-specific interstitial pneumonia, usual interstitial pneumonia, organizing pneumonia, diffuse alveolar damage and/or lymphocytic interstitial pneumonia—was specifically associated with SLE. Eventually, our database rely on the medico-administrative encoding of the hospital stays and the accuracy of the individual medical diagnoses could not be assessed.[14] The usual characteristics of the SLE population in our study were however consistent with previously published epidemiologic studies in France.[13,15]

In conclusion, ILD is rare, significantly associated with other systemic autoimmune disorders and has a poor prognosis in SLE.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Arthur Mageau: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); writing – original draft (equal). **Raphael Borie:** Conceptualization (equal); methodology (equal); supervision (equal); validation (equal); writing – original draft (equal). **Bruno Crestani:** Conceptualization (equal); supervision (equal); writing – original draft (equal). **Jean-François Timsit:** Conceptualization (equal); methodology (equal); writing – original draft (equal). **Thomas Papo:** Conceptualization (equal); supervision (equal); writing – original draft (equal). **Karim Sacre:** Conceptualization (equal); methodology (equal); project administration (equal); supervision (equal); validation (equal); writing – original draft (equal).

DATA AVAILABILITY STATEMENT

Data are available on reasonable request from authors.

HUMAN ETHICS APPROVAL DECLARATION

The institutional review board (Hôpitaux Universitaires Paris Nord Val de Seine, Paris Cité University, Assistance Publique Hôpitaux de Paris) gave approval for use of the patient database. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. This is a human non-interventional study and anonymized information was collected in the setting of clinical care. According to the Public Health French Law (Law no. 2012-300), written consent is not required for this type of study.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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