

SUPPLEMENTAL MATERIAL

Study populations

This retrospective population-based study was conducted from January 1st, 2004 to December 31st, 2013 in 13 administrative regions in France (i.e.: Alpes Maritimes, Calvados, Finistère, Gironde, Haute Garonne, Haute Vienne, Ille et Vilaine, Loire Atlantique, Marne, Nord, Puy de Dôme, Seine Maritime and Somme). This administrative area corresponds to a combined population size of 13.75 million inhabitants according to the 2012 national census population obtained from the French National Institute of Statistics and Economic Studies (Insee). The Paris area was excluded since the population includes a high proportion of people who originate from other areas, particularly from Africa and North Africa, where high incidence rates of autoimmune pemphigus have been reported.

Patients and data collection

Inclusion criteria were the following: i) patient living in one of the 13 administrative regions during the time of the study; ii) newly diagnosed pemphigus based on clinical, histological, and immunological criteria, i.e. clinical features suggestive of pemphigus (cutaneous and/or mucosal blisters or erosions) with typical histological pattern (including an intraepidermal blister with acantholysis) and intercellular deposits of IgG and/or C3 by direct immunofluorescence. Since direct immunofluorescence is performed in France in hospital-based and in very few private practice pathology laboratories, cases of autoimmune pemphigus were identified using the computerized databases of the pathology laboratories of university and general hospitals and the private practice laboratories which perform direct immunofluorescence, in the 13 administrative regions of the study. Additionally, we used the databases from the 19 dermatology departments located in the corresponding regions. For patients who fulfilled all the inclusion criteria, demographic data and clinical features at diagnosis (i.e.: age, gender, medical history, clinical type of pemphigus) were recorded from

medical records. Clinical course, date and cause of death were recorded by contacting general practitioners and birthplace city halls.

Statistical analysis

Crude incidence rates were calculated for the whole population assuming a Poisson distribution. French-population-standardized incidence rates were calculated by geographical region using the French population age pyramid of 2009 as the reference population. In order to compare our results with those from previous studies, standardization of incidence rate was also performed on the basis of the world population (Ahmad *et al.*, 2001).

Standardized mortality ratios (SMR) of patients were estimated by the Ederer I method (Ederer *et al.*, 1961) from year-, administrative region-, age- and gender-specific general population mortality rates estimated from French death and census data from 2003 to 2015 smoothed by mixed-effects models. For each SMR, 95% Confidence Interval (CI) were estimated by BCa bootstrap (Efron, 1987). The overall survival rates were estimated by the Kaplan-Meier method. We used Cox regression to compare the mortality of patients and assess the association between comorbidities and mortality. Adjustment on age was performed by left-truncation from birth to age of diagnosis, guaranteeing that patients are compared at equal age, without hypothesis about the relation between age and mortality. Follow-up ended on June 1st, 2016 for SMR and Kaplan-Meier calculations. For all analyses, 2-sided p-values of less than 0.05 were considered statistically significant. The Student's t test was used to compare mean ages.

Statistical analyses were performed using R statistical software (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria).

This retrospective study was approved by the Institutional review board of Rouen University Hospital (registered number: E2016-10).

References

Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M (2001) Age Standardization of Rates: A New WHO Standard. Geneva: World Health Organization 31:1–14

Ederer F, Axtell LM, Cutler SJ (1961) The relative survival rate: a statistical methodology. Natl Cancer Inst Monogr 6:101–21

Efron B (1987) Better Bootstrap Confidence Intervals. J Am Stat Assoc 82:171

Insee, Populations légales 2012 des départements. <https://www.insee.fr/fr/statistiques>

Table 1. Overall and specific age- and gender-standardized incidence rates of pemphigus in 13 regions in France between 2004 and 2013

	Number of cases	Incidence rate (cases/million inhabitants/year)	95% CI ¹
Overall	249	1.85	1.63-2.08
Alpes Maritimes	38	3.18	2.33-4.21
Calvados	8	1.18	0.59-2.22
Finistère	13	1.38	0.74-2.32
Gironde	27	1.90	1.27-2.67
Haute Garonne	33	2.90	2.07-3.87
Haute Vienne	14	3.39	1.94-5.58
Ille et Vilaine	16	1.75	1.09-2.74
Loire Atlantique	21	1.74	1.08-2.56
Marne	11	2.01	1.09-3.47
Nord	23	0.99	0.64-1.45
Puy de Dôme	9	1.37	0.61-2.44
Seine Maritime	27	1.63	2.08-3.12
Somme	9	1.62	0.72-2.88

¹CI, confidence interval