Incidence and Mortality of Pemphigus in France

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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Incidence and Mortality of Pemphigus in France

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TO THE EDITOR

The incidence of pemphigus varies from 0.5 to 34 cases/million inhabitants/year, with the highest incidence rates in Brazil (Hans-Filho et al., 1996; Ishii et al., 2008; Langan et al., 2008; Meyer and Misery, 2010). Additionally, although the prognosis of pemphigus patients is considered good in the literature, recent findings reported unusually high mortality rates (Almugairen et al., 2013; Langan et al., 2008).

We estimated the incidence and mortality of pemphigus among 13 regions in France (Figure 1a) over a 10-year period. Inclusion criteria were: (i) patient living in 1 of the 13 regions and (ii) newly-diagnosed pemphigus. Cases were identified using the computerized databases of the pathology laboratories of the university and general hospitals and private-practice laboratories that perform direct immunofluorescence. Statistical analyses are described in Supplementary Material online.

From January 2004 to December 2013, 629 patients were identified in included regions, which corresponded to a population size of 13.75 million inhabitants (Figure 1a). Among them, 380 were excluded: (i) diagnosis of pemphigus not confirmed (n = 74); (ii) patient not domiciled in the selected regions (n = 194), and (iii) diagnosis of pemphigus made before or after the study period (n = 112). A total of 249 incident cases (125 women, 124 men) were included. Mean age at diagnosis was 59.4 ± 18.7 years and was similar between male and female patients ($P = 0.93$). The age distribution of the population is shown in Figure 1b. Pemphigus types were pemphigus vulgaris (PV) (n = 155 [62%], pemphigus

Abbreviations: CI, confidence interval; IQR, interquartile range; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris

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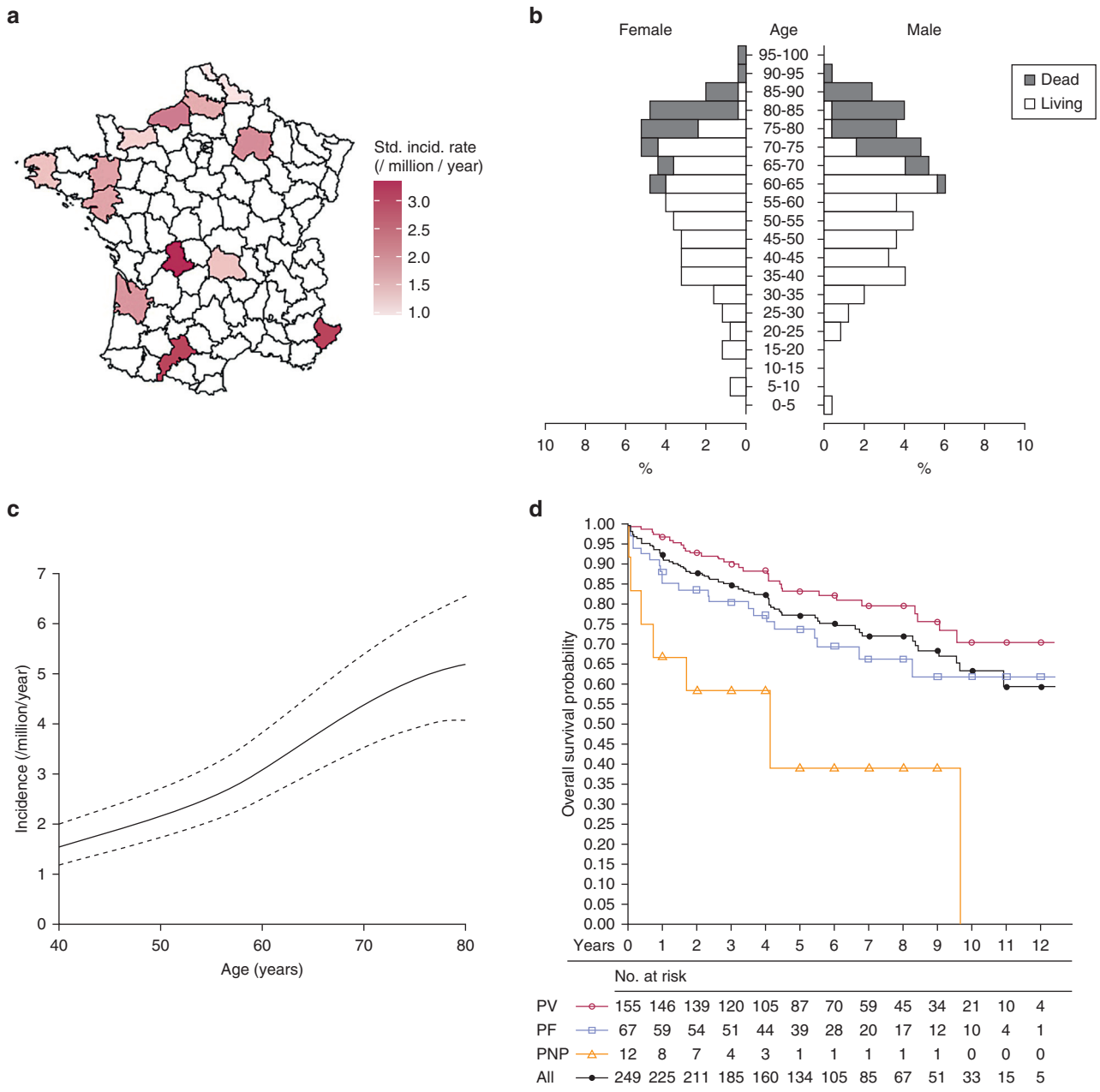

Figure 1. (**a**) Map of France showing the French population standardized annual incidence rate in the 13 administrative regions that participated in the study. France is characterized by a Mediterranean climate in the Southern regions and a continental climate in the Northern regions. (**b**) Age at diagnosis (years), sex distribution and mortality of patients with pemphigus in the 13 administrative areas in France. (**c**) Incidence rate of pemphigus by age (in plots: 95% confidence interval). (**d**) Kaplan-Meier survival curves of patients with newly diagnosed pemphigus between 2004 and 2013. PV, pemphigus vulgaris; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus.

foliaceus (PF) (n = 67 [27%]), paraneoplastic pemphigus (n = 12 [5%]; and other subtypes, n = 15 [6%]) (Table 1).

The mean annual crude incidence of pemphigus was 1.85 cases/million inhabitants/year (95% confidence interval [CI] = 1.63−2.08). The mean world-population standardized incidence was 1.45 cases/million inhabitants/year (95% CI = 1.11−1.79). Mean annual French population-standardized incidence rates ranged from 0.99 cases/million inhabitants/year (95% CI = 0.64−1.45) in the North region of France to 3.39 cases/million inhabitants/year (95% CI = 1.94−5.58) in the Haute-Vienne region. The linear North-South gradient was significant ($P = 0.004$) with an incidence rate ratio estimated to 1.11 (95% CI = 1.04−1.18) for a move of 100 km to the South (Figure 1a and Supplementary Material online). The annual incidence rate ratio per calendar year over the study period was 1.05 (95% CI = 0.97−1.06), showing no significant increase of incidence over the study period ($P = 0.45$). Otherwise, the incidence rate of pemphigus increased with age (Figure 1c).

The median follow-up duration of the cohort was 5.4 years (interquartile range [IQR] = 3.0−8.1 years). Thirteen patients were lost to follow-up (5.2%). A total of 66 (27%) patients died during

Table 1. Baseline characteristics and evolution of the 249 patients with newly diagnosed pemphigus

Characteristics	Pemphigus Vulgaris (n = 155)	Pemphigus Foliaceus (n = 67)	Paraneoplastic Pemphigus (n = 12)	Other Pemphigus Subtypes[1] (n = 15)
Sex ratio, female/male	1.07/1	0.68/1	2/1	2/1
Age at diagnosis, years, mean ± SD	57.5 ± 17.3	61.3 ± 20.4	71.1 ± 11.0	61.3 ± 25.8
Distribution by age category, n (%)				
<40 years	30 (19.4)	10 (14.9)	0	3 (20.0)
40–59 years	50 (32.3)	20 (29.9)	0	2 (13.3)
60–74 years	50 (32.3)	15 (22.4)	8 (66.7)	3 (20)
75–89 years	24 (15.5)	21 (31.3)	3 (25.0)	7 (46.7)
≥90 years	1 (0.6)	1 (1.5)	1 (8.3)	0
Clinical presentation, n (%)				
Mucosal and skin lesions	105 (67.7)	4[2] (6.0)	10 (83.33)	8 (53.3)
Exclusive skin lesions	9 (5.8)	63 (94.0)	1 (8.33)	7 (46.7)
Exclusive mucosal lesions	41 (26.5)	0	1 (8.33)	0
Comorbidities, n (%)				
Malignancy	15 (9.7)	5 (7.5)	8 (66.7)	3 (20.0)
Cardiovascular disorder	28 (18.1)	17 (25.4)	5 (41.7)	6 (40.0)
Hypertension	43 (27.7)	15 (22.4)	8 (66.7)	6 (40.0)
Pulmonary disorder	23 (14.8)	7 (10.4)	3 (25.0)	2 (13.3)
Diabetes mellitus	20 (12.9)	4 (6.0)	5 (41.7)	4 (26.7)
Neurological disorder	6 (3.9)	5 (7.5)	0	4 (26.7)
First-line treatment regimens, n (%)				
Oral prednisone alone	95 (61.3)	25 (37.3)	7 (58.3)	4 (26.7)
Oral prednisone + IS	36 (23.2)	9 (13.4)	1 (8.3)	1 (6.7)
Rituximab + oral prednisone	9 (5.8)	1 (1.5)	0	1 (6.7)
Dapsone without oral prednisone	5 (3.2)	21 (31.3)	0	5 (33.3)
Topical corticosteroid	10 (6.5)	11 (16.4)	4 (33.3)	4 (26.7)
Follow-up duration, years mean ± SD	5.9 ± 3.2	5.5 ± 3.4	2.7 ± 2.7	5.0 ± 4.0
Lost to follow-up, n (%)	9 (5.8)	3 (4.5)	0	1 (6.7)
Deaths, n (%)	30 (19.4)	21 (31.1)	7 (58.3)	8 (53.3)
Males	15 (20.0)	17 (42.5)	1 (25.0)	3 (60.0)
Females	15 (18.8)	4 (14.8)	6 (75.0)	5 (50.0)
Oral prednisone alone	17 (17.9)	8 (32.0)	4 (57.1)	2 (50.0)
Oral prednisone + IS	6 (16.7)	6 (66.7)	1 (100.0)	—
Rituximab + oral prednisone	0	1 (100.0)	0	1 (100.0)
Dapsone without oral prednisone	0	2 (9.5)	0	3 (60.0)
Topical corticosteroid	7 (70.0)	4 (36.4)	2 (50.0)	2 (50.0)
Causes of death, n (%)				
Malignancy	7 (23.3)	3 (14.3)	4 (57.1)	3 (37.5)
Cardiovascular disorder	8 (26.7)	6 (28.6)	1 (14.3)	1 (12.5)
Infectious disorder	2 (6.7)	4 (19.0)	1 (14.3)	1 (12.5)
Dementia	3 (10.0)	2 (9.5)	0	2 (25.0)
Pulmonary disorder	1 (3.3)	2 (9.5)	1 (14.3)	0
Digestive disorder	1 (3.3)	1 (4.8)	0	0
Alcoholic hepatitis	0	1 (4.8)	0	0
Hyponatremia	0	1 (4.8)	0	0
Diabetes mellitus	1 (3.3)	—	0	0
Unknown cause	7 (23.3)	1 (4.8)	0	1 (12.5)

Abbreviations: SD, standard deviation; IS, immunosuppressant.

[1]Other pemphigus subtypes: IgA pemphigus (n = 7); pemphigus vegetans (n = 4); pemphigus herpetiformis (n = 3); drug-induced pemphigus (n = 1).

[2]These four patients were classified as pemphigus foliaceus because they mainly presented skin lesions. The histologic examination of a skin biopsy showed an acantholysis in the upper layers of the epidermis. Three of these four patients had negative serum anti-DSG3 antibodies, and one had very low (22 U) anti-DSG3 antibody ELISA values (n < 20), whereas all these four patients had elevated anti-DSG1 antibody ELISA values.

the study period (Table 1). The 1-, 2-, and 5-year overall survival rates were 92% (95% CI = 88–95%), 88% (95% CI = 83–91%), and 77% (95% CI = 71–82%), respectively, in the whole population; 97% (95% CI = 92–99%), 93% (95% CI = 87–96%), and 83% (95% CI = 76–89%), respectively, in PV patients; 88% (95% CI = 78–94%), 84% (95% CI = 72–91%), and 74% (95% CI = 61–83%), respectively, in PF patients; and 67% (95% CI = 34–86%), 58% (95% CI = 27–80%), and 39% (95% CI = 8–70%), respectively, in paraneoplastic pemphigus patients (Figure 1d). Relative to expected age-, sex-, and region-specific overall death rates in the general

population in France, the standardized mortality ratio of pemphigus patients was 1.67 (95% CI = 1.46−1.93). The median age of death was 82.4 years (IQR = 76.9−87.5 years) in the whole pemphigus population, corresponding to 82.3 years (IQR = 76.6−86.0 years) in PV patients, 87.4 years (IQR = 81.6-88.5 years) in PF patients, 74.9 years (IQR = 67.7−80.7 years) in paraneoplastic pemphigus patients, and 80.7 years (IQR = 77.4−82.9 years) in patients with other pemphigus subtypes. All deaths were observed in patients older than 60 years at diagnosis. Interestingly, the proportion of PF patients older than 75 years at diagnosis (22 of 67 [32.8%]) was twofold higher than that of PV patients (25 of 155 [16.1%]). The cause of death could be recorded in 57 of the 66 deceased patients. Main causes of death were malignancy (n = 17 [29.8%]), cardiovascular disease (n = 16 [28.1%]), infection (n = 8 [14.0%]), and dementia (n = 7 [12.3%]) (Table 1). Older age at diagnosis and association with neoplasia were statistically associated with mortality. Indeed, the risk of mortality in patients older than 75 years corresponded to a hazard ratio of 16.3 (95% CI = 9.4−28.3) relative to younger patients, and the risk of mortality in patients with neoplasia adjusted on age by left truncation from birth to diagnosis, corresponded to a hazard ratio of 2.44 (95% CI = 1.35−4.40; $P = 0.005$). The left-truncated age-adjusted mortality rate of PF was not significantly higher than that of PV mortality (hazard ratio = 1.55; 95% CI = 0.84−2.84; $P = 0.16$).

The crude incidence rate of PV was estimated at 1.15/million inhabitants/year, which is more than sixfold lower than the crude incidence rate of PV reported by Langan et al. (2008) in the United Kingdom and lower than that reported from Southern European countries, ranging from 4 to 4.4 cases/million inhabitants/year (Baican et al., 2010; V'lckova-Laskoska et al., 2007). Interestingly, we observed higher incidence rates of pemphigus in Southern regions of France compared to Northern regions, which is in accordance with the North to South gradient of pemphigus incidence in Europe. We observed an increasing incidence of pemphigus with age, with the highest incidence in people aged older than 80 years.

Importantly, the 92%, 88%, and 77% 1-, 2- and 5-year survival rates calculated in the present study suggest that the prognosis of pemphigus is worse than the 5% mortality rate usually reported in general reviews (Bystryn et al., 2005; Chams-Davatchi et al., 2005).

Our data suggest that the high mortality rate observed in our population of pemphigus patients was mainly related to the old age of patients because the median age at death of PF and PV patients was 87.4 and 82.4 years, respectively. Indeed these elderly patients poorly tolerated corticosteroids and immunosuppressant side effects, as demonstrated by their main causes of death.

We observed an unexpectedly high mortality rate in PF patients, which was likely related to the high proportion (32.8%) of patients older than 75 years among PF patients.

The second prognostic factor was the association with neoplasia, although the 58% mortality rate of paraneoplastic pemphigus patients in the present series was lower than the 75−90% mortality rate reported in the literature (Wieczorek et al., 2016).

In conclusion, this study highlights the high mortality of pemphigus in elderly patients, including PF, which is often presented as a more benign subtype than PV (Bystryn et al., 2005).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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Influenza Vaccination Rates in Adults with Psoriasis Compared to Adults with Other Chronic Diseases

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TO THE EDITOR

Psoriasis is a chronic inflammatory skin disease affecting about 3% of the population (Rachakonda et al., 2014). Over the past decade, more evidence has been published suggesting that psoriasis is not just a disease of the skin, but a disease of systemic inflammation, predisposing patients to other medical comorbidities. Previous large, population-based studies have found that patients with psoriasis have higher rates of serious infections requiring hospitalization compared to adults without psoriasis, with lower respiratory tract infections, including pneumonia, being most common (Kao et al., 2014; Takeshita et al., 2018; Wakkee et al., 2011). Some respiratory infections are preventable through vaccination, but little is known about vaccination rates in psoriatic patients in the United States. Therefore, the objective of this study was to measure the rate of seasonal influenza vaccination in psoriasis patients in the United States and compare it to the rate of influenza vaccination in patients with other chronic diseases—rheumatoid arthritis and hypertension. Additionally, in psoriasis patients only, we sought to examine patient factors associated with receipt of a vaccination.

We performed a cohort study using US-based administrative and commercial claims data from OptumInsight Clinformatics Data Mart (Optum, Eden Prairie, MN), including all adults (≥18 years of age) with a diagnosis of psoriasis, rheumatoid arthritis, or chronic hypertension requiring oral antihypertensive therapy and continuous enrollment during the 2010–2011 influenza season and 24 months prior (September 2008–March 2011). Because this was an analysis of de-identified data, the study was granted exempt status by the Institutional Review Board at the University of Pennsylvania. The primary outcome was an inpatient, outpatient, or pharmacy claim for an influenza vaccine during the 2010–2011 flu season (September 2010–March 2011). This flu season was selected because it was considered "typical," by the Centers for Disease Control and Prevention (2011). Measured covariates were age, sex, region of residency, and a history of any of the following medical comorbidities considered to confer higher risk for developing complications of influenza: asthma, congestive heart failure, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, HIV, smoking, history of solid organ transplantation, and history of malignancy. A previously validated algorithm designed to identify smoking history in medical claims data was used (Chen et al., 2013). For patients with psoriasis and rheumatoid arthritis, information about treatments (including phototherapy) in the 3 months prior to the start of flu season (June 1, 2010–August 31, 2010) was also collected. Logistic regression was used to estimate the odds of vaccination in patients with chronic hypertension and rheumatoid arthritis compared to those with psoriasis, controlling for age, sex, and treatment (rheumatoid arthritis only). Finally, in psoriasis patients only, patient factors associated with receipt of a vaccine were identified using multivariable logistic regression.

There were 17,078 patients with psoriasis, 21,832 with rheumatoid arthritis, and 496,972 with chronic hypertension requiring oral therapy (Table 1). Patients with psoriasis were younger than those with rheumatoid arthritis and chronic hypertension. As expected, 73% of patients with rheumatoid arthritis were female compared to 49.8% and 50.6% of patients with psoriasis and chronic hypertension, respectively. A history of psoriatic arthritis was present in 11% of psoriasis patients, and the prevalence of comorbidities was similar to what has been reported in the literature previously (Shah et al., 2017).

After controlling for age and sex, patients with chronic hypertension had similar odds of receiving an influenza vaccination as patients with psoriasis (odds ratio = 0.98, 95% CI = 0.94–1.02). Adults with rheumatoid arthritis were approximately 10% more likely to receive a flu vaccination

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