Epidemiological study of pemphigus vulgaris in the southwest of Iran: a 15-year retrospective study and a review of literature

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Background: Pemphigus vulgaris (PV) is a life-threatening autoimmune disease that affects the skin and mucosa. In most regions, little data is available on its epidemiology**.** This study aimed to present an overview of the worldwide epidemiology of pemphigus and evaluate the epidemiological features of PV in the southwest of Iran.

Methods: In this study, data including sex, age, time of disease onset, phenotype of the disease, geographic location of birth, geographic location of residence, level of education, and occupation of PV patients from 2004 to 2019 were collected from the records existing in the Oral Medicine Department of Shiraz Dental School and Shahid Faghihi Hospital, Shiraz, Iran.

Results: In total, 249 PV patients with a mean age of 42.72 ± 13.3 years were included. The female to male ratio was 1.74:1. The annual incidence of PV in Fars province was 2.7 per million people. In this region, the most frequent phenotype was the mucocutaneous phenotype in 204 patients (81.9%), followed by the mucosal dominant phenotype in 40 (16.1%) and the cutaneous phenotype in 5 (2%). Regarding the level of education, 43.4% had less than a high school diploma, 24.9% had a high school diploma, 17.3% had an associate diploma or higher, and 14.5 % were illiterate. Moreover, 55.8% were housewives, 21.7% were self-employed, 19.3 % were employed, and 3.2% were jobless.

Conclusion: The findings indicate that PV is a rare disease in the southwest of Iran compared with other regions. According to previous studies in this region, the incidence has decreased since 2005.

Keywords: pemphigus vulgaris, epidemiology, incidence, autoimmune disease

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INTRODUCTION

Pemphigus is a collective term referring to a rare group of blistering autoimmune diseases involving the skin and mucosa [1,2]. It has a long-term course and causes severe morbidity and considerable mortality [1,3]. Although systemic corticosteroid therapy has decreased the mortality rate [4], there is no cure for the disease, and it is still an important cause of significant mortality [3].

Pemphigus is classified into different subtypes based on clinical presentation, histological features, and the specific antigens targeted by circulating autoantibodies: pemphigus vulgaris

(PV), pemphigus foliaceus (PF), paraneoplastic pemphigus (PNP), pemphigus herpetiformis (PH), and IgA pemphigus [1].

The etiopathogenesis of PV is characterized by the formation of IgG autoantibodies against transmembrane desmosomal glycoprotein desmoglein (Dsg) 3, and in some cases, Dsg 1. The binding of autoantibodies to these desmosomal components causes acantholysis and intraepithelial blister formation [1]. The thin epithelial wall of small asymptomatic blisters ruptures easily, and flat painful and hemorrhagic erosions will arise [5].

There are two main variants of PV: mucocutaneous and mucosal dominant [6]. The oral mucosa is the first site of involvement in two-thirds of PV patients [7]. Other mucous membranes may be involved, including the conjunctiva, nasal mucosa, esophagus, larynx, pharynx, and genital mucosa [5].

Both genetic and environmental factors have a role in the etiopathogenesis of pemphigus, but most of which are unknown [6]. It may have a strong genetic basis due to more frequent occurrence of PV in certain racial groups such as individuals of Mediterranean descent and Ashkenazi Jews [3,6]. Besides genetic factors, environmental factors such as medications, stress, or viral infections seem to affect the initiation/triggering of the autoimmune response and the disease expression [3,4,7].

Although pemphigus is generally rare, it has a significant effect on the quality of life of patients. Therefore, the epidemiological study on the disease and its subtypes is important. Moreover, the epidemiology of PV has not been studied recently in Iran. This study aimed to present an overview of the worldwide epidemiology of pemphigus and evaluate PV patients' epidemiological features in the southwest of Iran from 2004 to 2019.

PARTICIPANTS AND METHODS

This descriptive-analytical study was conducted on the medical records of PV patients who visited Shiraz University of Medical Sciences (Shiraz, Iran) from 2004 to 2019. Data were collected from the records existing in the two largest related referral centers in southwest Iran, namely the Oral Medicine Department of Shiraz Dental School and the Dermatology Department of Shahid Faghihi Hospital (both inpatient and outpatient records). The study area is shown in Figure 1.

Patients born and residing in the southwest of Iran who had a confirmed diagnosis of PV based on clinical and histopathological findings were included in this study. Then, their documented information was retrospectively reviewed, and the following data were collected: sex, age and the year at the time of disease onset, the phenotype of the disease, geographic location of birth, geographic location of residence, level of education, and occupation. A telephone interview was conducted

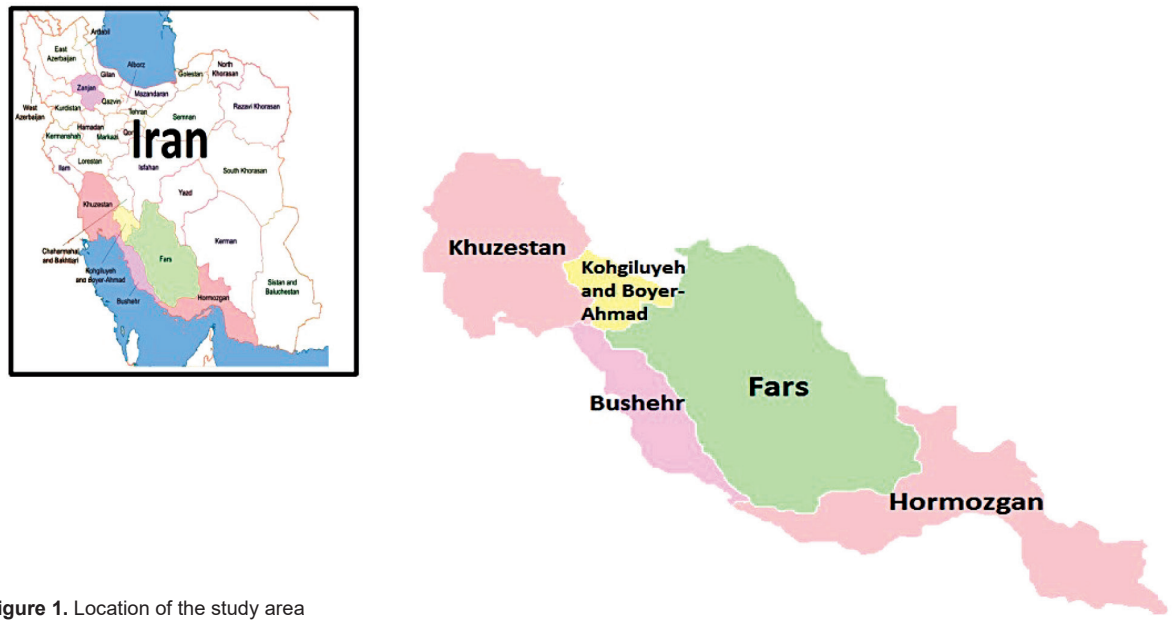


Figure 1. Location of the study area

for patients with incomplete or missing data. Records of patients who could not be contacted or did not answer the call were excluded. In the interviews, the study objectives were explained and informed consent was obtained before data were recorded. The protocol was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.DENTAL.REC.1399.073).

Data derived from their records were analyzed by the statistical software SPSS 2018 (Statistical Package for the Social Sciences) and Medcalc.

The annual incidence was estimated using the following equation:

$$\text{Annual incidence per 1,000,000 population} = \left[\frac{n}{P}\right] \times 1{,}000{,}000$$

where "n" is the mean annual number of new patients during a particular time period and "P" is the at-risk population (the population size in the middle year of the time period). Therefore, in this study, the annual incidence of PV was estimated as the ratios of the number of newly diagnosed PV patients in Fars province from 2004 to 2019 divided by 16 times the 2011 census population of the Fars province, obtained from the Statistical Center of Iran. It is worth noting that patients referring from other provinces (Khuzestan, Bushehr, etc.) were not considered in this calculation to avoid underestimations.

Descriptive statistics were used to measure the frequency, percentage, minimum, maximum, mean, and standard deviation. The Shapiro-Wilk test was used to test the normality of the frequency distribution of patients' age for females and males. Moreover, Pearson's chi-squared test and Fisher's exact test were used as tests of significance to determine non-random associations. P-values < 0.05 were considered significant.

RESULTS

Out of the total 451 PV patients referred to the study locations from 2004 to 2019, only 249 patients (55.2 %) were included in this study, as shown in Figure 2.

Sex distribution and age at onset

Of 249 patients with PV, 158 (63.5%) were female, and 91(36.5%) were male. The number of females was more than males with a female to male ratio of 1.74:1. The mean age for all patients at the onset of the disease was 42.72 ± 13.3 (range: 14-87) years, with no significant difference between females and males (P = 0.456). It was 42.24 ± 12.78 (range: 14-69) years for females and 43.55 ± 14.2 (range: 17-87) years for males.

The age distribution at the onset of disease according to gender is illustrated in Figure 3. The majority of patients were in their fourth and fifth decades (124 cases, 49.8%), whereas 71 patients (28.5%) were older than 50 years, and 54 patients (21.7%) were less than 30 years of age. Few patients were observed in two age groups: less than 20 years of age (4.4%) and more than 60 years of age (8.8%).

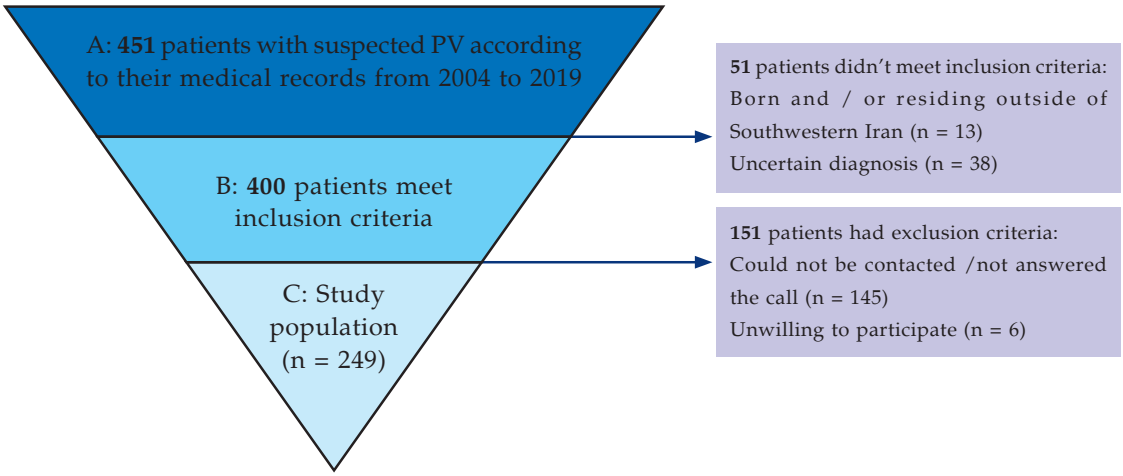
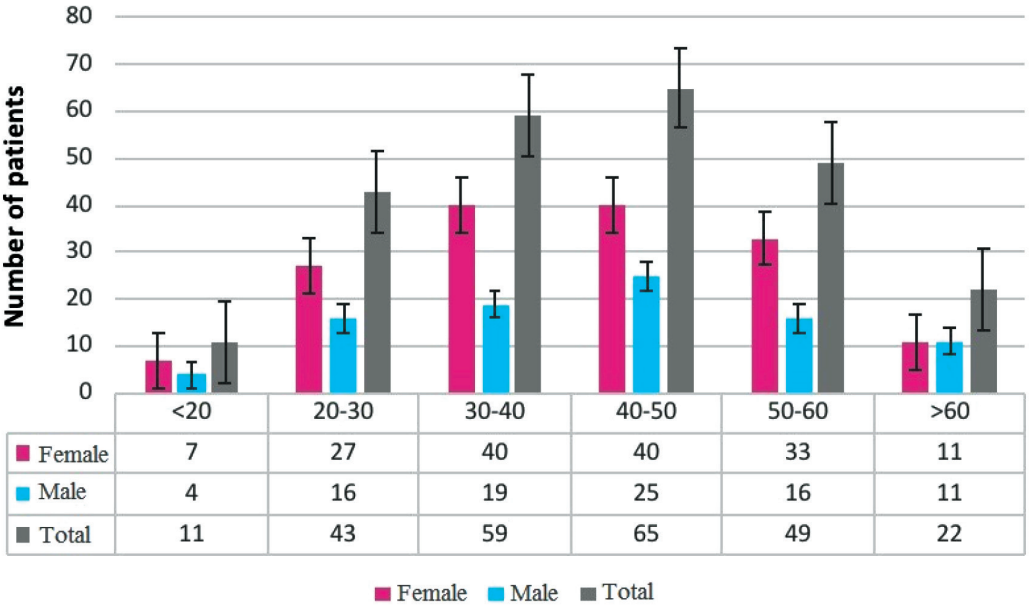


Figure 2. Inclusion and exclusion criteria of the study population



	<20	20-30	30-40	40-50	50-60	>60
Female	7	27	40	40	33	11
Male	4	16	19	25	16	11
Total	11	43	59	65	49	22

Figure 3. Frequency of patients' age at disease onset according to the sex

Level of education

Regarding the level of education, 108 (43.4%) patients had less than a high school diploma, 62 (24.9%) had a high school diploma, 43 (17.3%) had an associate diploma or higher, and 36 (14.5%) were illiterate. The number of PV patients was higher in the group of patients with less than a high school diploma compared with the other groups.

Occupation

According to the occupations, 139 (55.8%) were housewives, 54 (21.7%) were self-employed, 48 (19.3%) patients were government employed, and 8 (3.2%) were unemployed. Upon comparing different occupation groups, the number of PV patients who were housewives was higher.

The phenotype of the disease

In terms of phenotype, 204 (81.9%) patients had the mucocutaneous phenotype, 40 (16.1%) had the mucosal dominant phenotype, and 5 (2%) had the cutaneous phenotype. Also, there was no significant difference among mucosal dominant, cutaneous, and mucocutaneous phenotypes in terms of sex (P = 0.066), age at onset (P = 0.322), level of education (P = 0.931), and occupation (P = 0.898), as shown in Table 1.

Incidence and Geographic location

During the 16-year period (2004-2019), we observed 195 newly diagnosed patients in Fars province. Since the Fars province population was 4,596,658 (2011 census), the estimated annual incidence of PV in Fars province over this 16-year period (2004-2019) was 2.7 per 1,000,000 people.

Patients' geographic location of birth and residence is shown in Table 2.

Based on the results of our study, 209 (83.9%) patients were from the Fars province, and the remaining 40 (16.1%) were from the four adjacent provinces. Of the 209 PV patients from the Fars province, 107 (51.2%) were residents of Shiraz, and 102 (48.8%) were from other cities of Fars province.

DISCUSSION

In this study, a review of the previous epidemiological studies on pemphigus is presented (Table 3). Accordingly, pemphigus has an uneven geographical distribution worldwide. Moreover, it is worth noting that PV is the most common subtype of pemphigus disease globally except in some countries such as Finland [11,12], Tunisia (central and south region) [13], Mali [14], and Botswana [15]. Interestingly,

Table 1. Comparison of various phenotypes of pemphigus vulgaris

Patients' characteristics	Disease phenotype*			*P*
	Mucosal dominant	Cutaneous	Mucocutaneous	
Sex				
Female	31 (77.5)	2 (40)	125 (61.3)	0.066
Male	9 (22.5)	3 (60)	79 (38.7)	
Age at onset				
< 20	2 (5)	0 (0)	9 (4.4)	0.322
20-30	5 (12.5)	2 (40)	36 (17.6)	
30-40	9 (22.5)	1 (20)	49 (24)	
40-50	6 (15)	1 (20)	58 (28.4)	
50-60	11 (27.5)	1 (20)	37 (18.1)	
> 60	7 (17.5)	0 (0)	15 (7.4)	
Level of Education				
Illiterate	6 (15)	1 (20)	29 (14.2)	0.931
Less than a high school diploma	18 (45)	3 (60)	87 (42.6)	
High school diploma	11 (27.5)	1 (20)	50 (24.5)	
Associate diploma or higher	5 (12.5)	0 (0)	38 (18.6)	
Occupation				
Employed	9 (22.5)	1 (20)	38 (18.6)	0.898
Self-employed	7 (17.5)	2 (40)	45 (22.1)	
Housewife	23 (57.5)	2 (40)	114 (55.9)	
Jobless	1 (2.5)	0 (0)	7 (3.4)	

*Number of patients (%) is reported for all variables

Table 2. Top-ranked cities of Fars province in terms of pemphigus vulgaris patients' geographic location of birth and residence

Rank	Geographic location of birth	Number of patients (%)
1	Shiraz	80 (39.6)
2	Marvdasht	15 (7.4)
3	Fasa	14 (6.9)
4	Kazerun	13 (6.4)
5	Mamasani	12 (5.9)
Rank	**Geographic location of residence**	**Number of patients (%)**
1	Shiraz	107 (51.2)
2	Kazerun	13 (6.2)
3	Marvdasht	12 (5.7)
4	Fasa / Mamasani	11 (5.3)

the PV subtype was reported with a notably high ratio among all pemphigus cases in Iran (Table 3).

The annual incidence of PV found in the present study was 2.7 per million. Compared with epidemiological studies on PV in other world regions summarized in Table 4, the annual incidence in our area is similar with Malaysia [16], Poland [17], Tunisia [13], and Italy [18], higher than Germany [19,20] and France [13], and lower than Kuwait [21], Taiwan [22], United Kingdom [23], Greece [24], and Israel [25,26]. The present study's data were collected from the records of Shiraz Dental School and both the inpatient and outpatient records of Shahid Faghihi Hospital, while a great number of previous studies performed in Iran were only hospital-based [4, 27-31]. Therefore, the results of other studies may be less representative of pemphigus in the population. Nevertheless, the disease trend seems to be decreasing in Iran over time. However, further investigations on the trend of pemphigus in the population of Iran are needed.

Our study findings indicate an overall female predisposition (female to male ratio = 1.74:1). Apart from three studies originating from Malaysia [16], Kuwait [21], and Morocco [32], a female predisposition was observed in all remaining epidemiological studies on PV summarized in Table 4. The female to male proportion ranged from 1.07 in France [33] to 4.5 in Poland [17]. Although the reason for this sex difference is not clear, there are several explanations for this finding. One of the possible explanations may be the different effects of sex steroids on the immune system in females and males, with more immune responsiveness in females to autoimmunity [34]. On the other hand, HLA allele DQB1*03:02, which is associated with severe PV, is presented more frequently in females than in males [35]. Therefore, females are more likely to use healthcare services due to their disease severity.

In our study, PV onset was most often between 31-50 years of age. As shown in Table 4, our patients

Table 3. Epidemiological features of pemphigus disease in different countries of the world

Authors/Year of publication	Country, region	Pemphigus group			
		Ratio of PV to all pemphigus patients	Female to male ratio	Mean age at disease onset (years)	Annual incidence (pmp)
Simon *et al.* [46] /1980	United States, Connecticut	11/12	5	63.6	4.2
Hietanen and Salo [11]/1982	Finland (nationwide)	9/44	1.11	57.5	0.76
Bastuji-Garin *et al.* [13]/1995	Tunisia (nationwide)	75/198	4.1	36.7 ± 15.7	6.7
Bastuji-Garin *et al.* [13]/1995	France, Ile-de-France administrative area	63/87	1.2	52 ± 18.1	1.7
Mahe *et al.* [14]/1996	Mali, Bamako	4/30	4	NS	2.9
Micali *et al.* [18]/1998	Italy, eastern Sicily	63/84	1.6	55	6
Tsankov *et al.* [47]/2000	Bulgaria, Sofia	57/74	1.11	56.03 ± 4.25 (male) 54.31 ± 3.94 (female)	4.7
Tallab *et al.* [48]/2001	Saudi Arabia, southern region	18/19	0.45	43.1 ± 13.4	1.6
Seo *et al.* [49]/2003	Korea, Seoul	32/51	1.32	46.8	NS
Nanda *et al.* [21]/2004	Kuwait, Kuwait city	48/60	0.91	36.5 ± 11.36	4.57
Chams-Davatchi *et al.* [27]/2005	Iran, Tehran	1111/1209	1.5	42 ± 19	16
Golusin *et al.* [40]/2005	Serbia, Vojvodina	37/51	1.55	55.6	6.6
Uzan, *et al.* [37]/2006	Turkey, Adana and Antalya	128/148	1.35	43	2.4
Salmanpour *et al.* [28]/2006	Iran, southwestern region	194/221	1.33	38	6.7(in Shiraz)
Shamsadini *et al.* [50]/2006	Iran, Kerman Province	45/55	2.24	46 ± 17.9	NS
Kanwar *et al.* [36]/2006	India, northern region	302/328	1.2	39.27 ± 14.21 (male) 38.57 ± 13.43 (female)	NS
Brenner and Wohl [34]/2007	United States	NS	1.7	45.4 ± 12.9	NS
V`lckova-Laskoska *et al.* [51]/2007	Macedonia, Skopje (covering all the population)	103/133	1.3	52 ± 13.4	4.4
Ishii *et al.* [38]/2008	Japan, Kurume	28/55	2.1	55.3	NS
Kumar [52]/2008	India, Thrissur District	10/13	NS	NS	4.4
Marazza *et al.* [53]/2009	Switzerland (nationwide)	4/7	2.5	NS	0.6

Table 3. Continued

Authors/Year of publication	Country, region	Pemphigus group			
		Ratio of PV to all pemphigus patients	Female to male ratio	Mean age at disease onset (years)	Annual incidence (pmp)
Yazdanfar [4]/2010	Iran, Hamedan Province	178/200	1.04	41.4	16
Baican *et al.* [54]/2010	Romania, northwestern region	55/68	NS	NS	4
Thomas *et al.* [55]/2010	France, southwestern region	21/37	1.18	Age at diagnosis: 62 ± 4.5	2.7
Zaraa *et al.* [56]/2011	Tunisia, northern region	56/92	2.06	50	8.62
Marinovic *et al.* [57]/2011	Croatia, Zagreb (covering northern and eastern regions)	NS	1.93	NS	3.7
Noorbala *et al.* 29/2012	Iran, Yazd	69/89	1.23	Age at diagnosis: 44.19 ± 20.30	9.8
Bozdag and Bilgin [58]/2012	Turkey, western region	81/87	1.64	48.3 ± 12.6	1.8
Sobhan *et al.* [30]/2016	Iran, Hamedan Province	NS	1.11	43.3 ± 17.2	NS
Kridin *et al.* [59]/2016	Israel, northern region	159/180	1.7	54.7 ± 16	7.2
Milinkovic *et al.* [60]/2016	Serbia, Central Serbia	384/478	1.44	NS	4.35
Parmar and Patel [61]/2017	India, central Bhuj	12/24	0.41	NS	7.2
Yayli *et al.* [62]/2017	Turkey (covering twenty provinces in different geographic regions)	192/220	1.41	48.92 ± 15.02	4.7
Jelti *et al.* [33]/2019	13 regions in France	155/249	1.01	Age at diagnosis: 59.4 ± 18.7	1.85
Forsti *et al.* [12]/2019	Finland, northern region	12/46	1.7	Age at diagnosis: 62	2.8
Madu *et al.* [15]/2019	Botswana, south and southeastern regions	5/15	NS	NS	1.7
Chiu *et al.* [63]/2020	Taiwan (nationwide)	NS	1.17	52.5 ± 16.3	4

Abbreviations: PV, pemphigus vulgaris; pmp, per million per year; NS, not stated.

had an earlier age at onset (42.72 ± 13.3 years) than the PV patients in most studies. Although the exact explanation for the earlier age at onset is not clear, this might have resulted from a warmer or more humid climate seen in the southwest of Iran relative to other locations.

We also found that the majority of patients (81.9%) presented mucocutaneous lesions. This finding is similar to the results of the studies from India [36], Turkey [37], Japan [38], Slovakia [39], Italy [18], Iran [27], France [33], Morocco [32], Serbia [40], and China [41], in which more than half of PV patients had mucocutaneous involvement during the course of the disease. Conversely, in a study conducted by Michailidou *et al.* [24] in northern Greece, 86.1% of PV patients only featured oral involvement. Although the reasons were unknown, Amagai *et al.* [42] found that the clinical phenotype of PV was associated with the Dsg auto-antibody profile. Consequently, Harman *et al.* [43] reported that the genetic background of PV patients might be important in determining the auto-antibody profile.

We found that most PV patients had indoor activities due to their occupations. Therefore, they

Tables 4. Epidemiological features of pemphigus vulgaris in different countries of the world

Authors	Country, region	Pemphigus vulgaris			
		Number of patients	Female to male ratio	Mean age at disease onset (years)	Annual incidence (pmp)
Pisanti *et al.* [26]/1974	Israel, Jerusalem	76	1.62	NS	16.1
Kyriakis *et al.* [44]/1989	Greece, Athens	NS	1.7	56.8 ± 17.1 (male) 52.1 ± 17 (female)	NS
Adam *et al.* [16]/1992	Malaysia, Kuala Lumpur	84	1	NS	2
Bastuji-Garin *et al.* [13]/1995	Tunisia (nationwide)	75	NS	NS	2.5
Bastuji-Garin *et al.* [13]/1995	France, Ile-de-France administrative area	63	NS	NS	1.3
Micali *et al.* [18]/1998	Italy, eastern Sicily	63	2.2	56	2.5
Hahn-Ristic *et al.* [19]/2002	Germany, Lower Franconia and Mannheim	14	1.3	NS	0.98
Seo *et al.* [49]/2003	South Korea, Seoul	32	1.5	44.3	NS
Nanda *et al.* [21]/2004	Kuwait, Kuwait city	48	0.71	36.53 ± 11.08	3.66
Asilian *et al.* [31]/2006	Iran, Isfahan Province	188	1.6	41.1 ± 13.7	5
Michailidou *et al.* [24]/2007	Greece, northern region	129	2.15	59.6 ± 12.7 (male) 55.8 ± 10.1 (female)	8
Ishii *et al.* [38]/2008	Japan, Kurume	28	2.1	52.8	NS
Langan *et al.* [23]/2008	United Kingdom (nationwide)	138	1.94	NS (median=71)	6.8
Kumar [52]/2008	India, Thrissur District	10	2.33	58 (male) 37 (female)	NS
Bertram *et al.* [20]/2009	Germany, Lower Franconia	1	NS	62	0.5
Chmurova and Svecova [39]/2009	Slovakia, Bratislava	31	1.4	49 ± 16.2	NS
Baican *et al.* [54]/2010	Romania, the northwestern region	55	1.75	53 ± 1.9	NS
Huang *et al.* [22]/2012	Taiwan (nationwide)	853	1.33	52.5 ± 15.9	4.7
Zhu *et al.* [41]/2014	China, Harbin	221	1.4	44.19 ± 21.45	NS
Baum *et al.* [64]/2016	Israel	290	1.54	49.7 ± 16.1	NS
Kridin *et al.* [25]/2017	Israel, Haifa and the northern regions	207	1.76	Age at diagnosis: 52.9 ± 16	6.4
Serwin *et al.* [17]/2018	Poland, Podlaskie Province	44	4.5	54.69 ± 12.58	2.44 ± 1.57
Lee *et al.* [65]/2018	South Korea (nationwide)	1033	1.18	NS	2.06
Jelti *et al.* [33]/2019	France, 13 regions in France	155	1.07	Age at diagnosis: 57.5 ± 17.3	NS
Madu *et al.* [15]/2019	Botswana, south and southeastern region	5	NS	NS	0.6
Hicham *et al.* [32]/2020	Morocco, Rabat	31	0.41	54 ± 14.2	NS

Abbreviations: pmp, per million per year; NS, not stated.

were not frequently sun-exposed. Conversely, Kyriakis *et al.* [44] found that PV was more common in occupations with sun exposure. Wohl and Brenner [45] subsequently reported a possible correlation between occupational exposure to ultraviolet radiation and pemphigus induction. The reason for this contradictory result is not completely clear, but this was probably a result of referral bias.

In the current study, there were differences in the level of education among our patients. Significantly, patients with less than a high school diploma constituted the majority of our study population. Previous studies have shown that stress, anxiety, and depression are among the initiating factors of various autoimmune reactions implicated in the pathogenesis of PV [7]. Furthermore, there is a consistent relationship between lower levels of education and higher stress levels [66]. Hence, our results also confirm this relationship that PV, an autoimmune disease which is triggered by stress, is seen in patients with lower education and higher stress levels. Further studies would be needed to determine exactly how the level of education affects PV induction.

It is plausible that two limitations could have influenced the results obtained. Missing data is

the first limitation of our study, though telephone interviews were conducted to minimize the impact of this issue. Another possible limitation was the fact that some patients may have been referred to other centers or treated in private practice, especially in other provinces of the southwest of Iran rather than Fars province. Shiraz is the capital of Fars. It is most likely that the majority of patients are referred to this city, which has specialized centers for PV diagnosis and treatment. In other southwest provinces, referral to different centers and private practice has probably occurred. That is why we solely calculated the annual incidence of Fars to avoid underestimation in other provinces.

CONCLUSION

The findings of this study indicate that, in Iran, PV mainly affects females in the fourth and fifth decades of life and manifests mucocutaneous lesions. Moreover, individuals with lower levels of education are more susceptible to PV. We also found that the majority of our PV patients did not have occupational sun exposure. What is important is that the disease seems to be decreasing over time when comparing the incidence found in our results with other studies in Iran. However, further investigations on the trend of pemphigus in other populations are needed.

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