

ORIGINAL ARTICLE

Characteristics of patients with bullous pemphigoid: comparison of classic bullous pemphigoid to non-bullous pemphigoid

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Abstract

Background Bullous pemphigoid (BP) is the most common subepidermal autoimmune blistering disease. Patients occasionally present with a clinical picture of pruritus/urticaria alone for months and do not even develop blisters over time. Only few studies have investigated this subgroup of non-bullous pemphigoid (NBP).

Objective To evaluate the demographic and clinical characteristics of BP patients with or without blisters at the time of diagnosis.

Methods A retrospective study based on the medical records of 115 BP patients. Collected data included demographic characteristics, clinical presentation, treatment and response to treatment.

Results Thirty-six patients presented with pruritus/urticaria (31.3%), and 79 presented with blisters (68.7%), with mean ages of 77.5 and 76.0, respectively, at diagnosis and an equal female:male ratio. The level of immunoglobulin E (IgE) was 4.1 times higher, and the mean blood eosinophil count was significantly increased in the pruritus/urticaria group. Remission rate at 3 months and relapse rate were similar between the groups. Median follow-up period was 9 months (range 3–18). Only 23% of the patients with pruritus/urticaria developed blisters.

Conclusions A significant number of BP patients present without blisters. We found no significant epidemiological or clinical differences from the classic BP patients aside from significantly elevated IgE and blood eosinophil levels. Similar results in larger cohort studies might be the foundation for a change in clinical protocols regarding the diagnosis and recommended treatment for the elderly presenting with pruritus/urticaria only.

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Conflicts of interest

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Introduction

Bullous pemphigoid (BP) is the most common autoimmune bullous disease, and it mostly affects the elderly.¹ The typical histological findings are subepidermal separation with vesicle formation in association with immunoglobulin G (IgG) and/or C3 deposition along the basal membrane in immunohistochemistry. The disease is caused by autoantibodies directed against the 180-kDa BP (BP180) and 230-kDa BP (BP230)^{2,3} antigens and is associated with significant morbidity and an increased risk for mortality.

The disease occurrence correlates with older age, and its incidence rate is significantly higher after the age of 80, rising up to

150–330 new cases per million people per year.^{1,4–8} The disease is rather rare under the age of 50. During the years 2008–2012, an increase in the incidence rate by twofold to fivefold per decade has been noted in the United Kingdom, Germany, France^{1,4,7} and Israel,⁹ which may be associated with the increase in life expectancy and/or better availability of more sensitive and specific diagnostic tests.

The typical manifestation of BP consists of highly pruritic, tense serous or haemorrhagic bullae on normal or erythematous skin, frequently along with urticarial papules and plaques. Sites of predilection include inner thighs and arms, lower abdomen, groin and axillae. The involvement of the oral cavity is rare.

However, non-bullous forms of BP are well recognized. They always present with pruritus. Skin lesions include erythematous patches, urticarial plaques, papules, targetoid nodules, lichenoid plaques, eczema and erythroderma. Pruritus is rarely the sole manifestation, without any primary skin lesions.^{10–12} NBP may precede the bullous lesions of the disease. Nevertheless, in many cases, patients may never develop blisters over the course of their disease. Indeed, a recent systematic review found that only 9.8% of patients who presented with non-bullous lesions eventually progressed to bullous disease during follow-up.¹³

Currently, there is lack of consensus on the minimal diagnostic criteria of pemphigoid.¹⁴ The diagnosis of BP requires integration of clinical criteria, histological features, direct immunofluorescence (DIF) of perilesional skin and indirect immunofluorescence (IIF) for the presence of antibodies in the patient's serum. Still, all cases of atypical BP have the same immunopathological features of the classic form, ultimately allowing the correct diagnosis.

Because of the different, and sometimes confusing, clinical manifestation and the chronic course of the disease with only few reports describing the difference between BP patients suffering from blisters and NBP patients having only pruritus/urticarial lesions, we aimed to evaluate the clinical phenotype and the treatment outcomes of BP patients with bullous or non-bullous manifestation at the time of diagnosis.

Materials and methods

This study was approved by the Institutional Review Board of Sheba Medical Center, Israel.

A retrospective cohort study included all BP patients who were diagnosed, treated and followed up between January 2011 and December 2016 in the Department of Dermatology and Outpatient Clinic at the Sheba Medical Center. Data were retrieved from patients diagnosed with BP on the basis of clinical presentation, compatible light microscopy findings (as defined by eosinophilic spongiosis, with or without subepidermal cleft) and positive DIF findings. Additional inclusion criteria included the fulfilling of one or more of the following features, as reported in previous studies¹⁵: (i) presence of three of the four clinical characteristics (aged > 70 years, absence of atrophic scars, absence of mucosal involvement and absence of bullous lesions on the head and neck); (ii) detection of circulating IgG antibasement membrane autoantibodies by IIF microscopy using NaCl-separated normal human skin; and (iii) detection of anti-BP180 IgG autoantibodies by enzyme-linked immunoassay.

Only patients who had positive DIF findings were included. The patients in the bullous group were included only if the clinical picture did not raise a suspicion of another pemphigoid disease such as mucous membrane pemphigoid, epidermolysis bullosa acquisita. As DIF being the gold standard for diagnosis, only few patients were sent for IIF or ELISA testing. In our study, only three patients did also IIF testing which was positive

– two patients from the bullous group and one patient from the NBP group.

Patients were defined as having NBP if they fulfilled the above criteria and presented with pruritus and/or urticarial lesions, but did not have blisters in their history and at presentation, whereas BP patients presented tense blisters at presentation.

Patients' data were processed from the computerized files of the Chameleon Electronic Medical Record at Sheba. The data collected included the following:

- Epidemiological data – age and sex
- Clinical data – pruritus
- Medical history – with an emphasis on the risk factors (cardiac, metabolic, neurological, autoimmune and neoplastic history)
- Medications – including beta-blockers, angiotensin-converting enzyme inhibitors, statins and diuretics
- Laboratory data – eosinophilia and IgE levels

Follow-up and treatment results were assessed 3 months after the first visit. According to consensus definitions,¹⁶ these included description of disease control/relapse in patients presenting with blisters and, according to patients' reports, presence/absence of pruritus in patients presenting without blisters.

Statistical analysis

Categorical variables were described as numbers and percentages. They were evaluated for normal distribution using a histogram and Q–Q plot. Normally distributed continuous variables were described as mean and standard deviation. Skewed variables were described using median and an interquartile range. Chi-squared and Fisher's exact tests were used to compare categorical variables between the groups. Continuous variables were compared between the groups using analysis of variance, independent-samples *t*-test, Kruskal–Wallis test or Mann–Whitney test. Disease relapse during follow-up period was described using the Kaplan–Meier curve, and the log-rank test was used to compare the groups. All statistical tests were two-tailed, and a *P*-value of less than 0.05 was considered statistically significant. SPSS v. 24 was used for all statistical analyses (IBM-Corp, released 2016, Armonk, NY).

Results

The study included 121 patients. Six patients were excluded because of missing data. Ultimately, the study included 115 patients diagnosed with BP through clinical presentation, biopsy and DIF performed in the Department of Dermatology and Outpatient Clinic at Sheba Medical Center between 2011 and 2016. At the time of diagnosis, 36 (31.3%) of these patients presented with pruritus/urticarial lesions and 79 (68.7%) presented with blisters. Patients' demographic clinical and laboratory characteristics are presented in Table 1. For NBP patients, the female: male ratio was 1.25, while for BP patients, it was 0.92 (Figure S1). The mean ages ($\pm$ SD) at presentation were 76 ($\pm$ 13.5) and 77.5

Table 1 Demographic, clinical and laboratory characteristics of study population

		NBP, n(%) (n = 36)	Blisters, n(%) (n = 79)	P
Gender	Male	16 (44.4%)	41 (51.9%)	NS
	Female	20 (55.6%)	38 (48.1%)	
Age at diagnosis		77.5 ± 11.3	76.0 ± 13.5	NS
Comorbidities	Cardiac disease	30 (83.3%)	61 (77.2%)	NS
	Diabetes	16 (44.4%)	36 (45.6%)	NS
	Neurological disease	9 (25%)	25 (31.6%)	NS
	Autoimmune thyroid disease	2 (5.6%)	0 (0%)	0.035
	Neoplasia	3 (8.3%)	16 (20.3%)	NS
Pharmacological treatments	ACE inhibitors	13 (36.1%)	26 (32.9%)	NS
	ARB	2 (5.6%)	10 (12.7%)	NS
	Beta-blockers	9 (25%)	31 (39.2%)	NS
	Diuretics	11 (30.6%)	27 (34.2%)	NS
	Statins	17 (47.2%)	38 (48.1%)	NS
	Insulin	3 (8.3%)	16 (20.3%)	NS
BSA	<20%	4 (11.1%)	9 (11.4%)	0.160
	20%–40%	4 (11.1%)	21 (26.6%)	
	>40%	28 (77.8%)	49 (62.0%)	
Mucous membrane involvement		6 (16.7%)	21 (26.6%)	0.245
IgE (IU/mL), mean (SD)		2389.2 (±3003.3), n = 12	413.3 (± 481), n = 15	0.019
Blood eosinophil count (/μL), mean (SD)		803.7 (±1542.4), n = 32	309.7 (±368.7), n = 72	0.012

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BSA, body surface area involved at the time of diagnosis; NBP, non-bullous pemphigoid.

(±11.3) for BP and NBP patients, respectively (Figure S2). There was no significant difference in gender, age at diagnosis or origin between the groups. Autoimmune thyroid disease was documented in two patients (5.6%) in the NBP group but in none in the BP group ($P = 0.035$). No significant difference was found in the rate of other comorbidities or pharmacological treatments (Table 1). There were significant differences in IgE and blood eosinophil levels. The IgE level was significantly increased in the NBP group compared to the BP group [2389.2 (3003.3) IU/mL vs. 413.3 (481) IU/mL, mean (SD), respectively, $P = 0.019$]. Blood eosinophil count was significantly increased in the NBP group compared to the BP group [(803.7 ± 1542.4)/μL vs. (309.7 ± 368.7)/μL, mean (SD), respectively, $P = 0.012$]. There was no significant difference between the groups in other clinical parameters such as the body surface area or mucous membrane involvement. All patients in the study were treated according to the same protocol that included potent topical corticosteroids for active lesions. In more resistant cases, patients were treated with a systemic regimen combined of 0.5 mg/kg/day prednisone plus 50–100 mg/day of minocycline, and in patients who did not achieve disease control with this treatment, steroid-sparing immunosuppressive therapy was added (azathioprine, cyclosporine, dapsone, methotrexate, or mycophenolate mofetil). Ten patients were treated with topical corticosteroid therapy only – three NBP patients (out of 36; 8.3%) and seven BP patients (out of 79; 8.9%). One hundred and five patients received systemic therapy – 33 NBP patients (out of 36; 91.7%) and 72 BP patients

(out of 79; 91.1%). Follow-up data were available only for 89 patients – 26 NBP patients (out of 36; 72.2%) and 63 BP patients (out of 79; 79.7%), of whom treatments are specified in Table 2. Mean follow-up time was 11.27 months (±11 months). Overall, 77 of 89 patients reached disease control (86.5%) – 23 NBP patients (out of 26; 88.46%) compared to 54 patients presenting with blisters (out of 63; 85.7%; $P = 0.837$). Of the NBP group, patients who did not achieve disease control until the end of follow-up were initially treated with topical potent corticosteroids (one patient), minocycline (one patient) and methotrexate (one patient), and of the BP group, all patients who did not achieve disease control until end of follow-up were initially treated with minocycline (nine patients). Sixty-four patients out of 77 continued follow-up after achieving disease control (13 patients were lost to follow-up). Of the NBP patients, 8 (19.1%) of 19

Table 2 Treatment modalities of study population

	Non-bullous pemphigoid (n = 26)	Bullous pemphigoid (n = 63)	P
Topical corticosteroids	3 (11.5%)	7 (11.1%)	NS
Prednisone and/or minocycline	18 (69.2%)	45 (71.4%)	NS
Immunosuppressive therapy	5 (19.2%)	11 (17.5%)	NS

(42.1%), vs. 15 of 45 (33.3%) of the BP patients ($P = 0.645$; Figure S3) experienced relapses. Over the follow-up period, only six NBP patients (out of 26; 23%) developed blisters, of which four presented with pruritus and two with urticarial lesions. Overall, bullous lesions developed in these patients after 8.3 ± 8.9 months (mean $\pm$ SD) from the diagnosis (range 1–24 months).

Discussion

Bullous pemphigoid is the most common autoimmune blistering disease. However, it can sometimes present without blisters and can be characterized by itching and/or urticaria for months and even years and sometimes as a preceding stage but in the vast majority of cases without the appearance of blisters. Pruritus as a clinical feature in itself is not sufficient to define the disease, and the diagnosis should also include positive characteristics of immunohistochemistry and immunofluorescence tests. ELISA and IIF testing are of important diagnostic value, though DIF still remains gold standard.¹⁷ Only sparse studies have dealt with this issue, and all of them have limited population size.¹³ In our retrospective study of 115 patients, the NBP group had similar demographic, clinical and laboratory characteristics, except for higher IgE and blood eosinophil levels and increased autoimmune thyroid disease. The mean age at diagnosis was similar to that previously reported in studies from Europe, United States and Singapore, but it was higher than the mean age reported in China, Kuwait and Arab population in Israel (Figure S2). Gender distribution was also similar to what is in the previous studies (Figure S1).

Furthermore, patients had a similar response to treatment. Interestingly, only 23% of patients developed blisters over the follow-up period. There was also a significant difference between the rate of autoimmune thyroid diseases among patients presenting with pruritus/urticaria at the initial diagnosis and those presenting with blisters (5.6% and 0%, respectively). BP has been reported to be associated with several autoimmune disorders, including rheumatoid arthritis, autoimmune thrombocytopenia, dermatomyositis, systemic lupus erythematosus, alopecia, vitiligo and autoimmune thyroid disease.¹⁸ This association most probably reflects genetic susceptibility to autoimmune diseases. The low number of patients (two in total) with an autoimmune thyroid disease makes it difficult to draw conclusions; thus, larger studies are needed to establish whether patients presenting with NBP have higher incidence of other autoimmune diseases.

There is a well-known relationship in the literature between BP and high IgE levels (75%–80% of cases).¹⁹ Associations were found between IgE levels and disease activity, as well as decrease in IgE levels during remission. In this study, we found significantly higher IgE levels in the NBP group than the levels in the BP group. As in the studies conducted by van Beek *et al.*, there was a relationship between IgE and itch levels and urticaria.^{19,20} In

the study by Cozzani *et al.*, higher IgE levels were found in patients with blisters, although no significant association was found with the severity of the disease.²¹ As we tested only for total IgE and not for serum levels of IgE autoantibodies against BP180, the question remains open whether NBP patients differ from BP patients regarding these specific antibodies. No significant difference was found between the NBP group and the BP group in terms of relapse rate over time. The percentage of relapsing patients in both the groups is quite similar, suggesting that the treatment options should be considered in the same way for both the groups to keep patients from relapsing (see Figure S3).

No significant difference was found between the NBP group and the BP group in terms of disease control over time. The percentage of patients in remission in both the groups is quite similar, suggesting that prognosis is the same and treatment options during remissions should be considered in the same way for both the groups.

The mean blood eosinophil count was significantly increased in the NBP group in comparison with the BP group ($803.7 \pm 1542.4/\mu\text{L}$ vs. $309.7 \pm 368.7/\mu\text{L}$, respectively). Peripheral eosinophilia has been reported in 50%–60% of BP patients^{22,23} and correlated with the severity of the disease. Kridin *et al.*⁹ have recently reported that BP patients with serum eosinophilia were significantly older and had higher palmoplantar involvement. Our study shows that both IgE and eosinophilia are more pronounced in the NBP group, possibly reflecting the severity of their disease and the older age of the patients in our study group.

Our study has several limitations. It was retrospective, with a relatively small sample of patients representing one medical centre. In addition, the follow-up period was short in some of the patients. A small number of patients were tested for IIF or ELISA, serum tests which might provide higher sensitivity and specificity. This could hamper the distinction between the different pemphigoid diseases.¹⁷

In conclusion, although BP is a bullous disease, a significant proportion of patients present with pruritus/urticaria, without blisters. The clinical, epidemiological, laboratory and immunohistological characteristics of patients in both groups did not differ, except for IgE and eosinophil levels. Clinicians should be alert of this subgroup of patients especially in older patients having only symptoms of pruritus/urticaria.

Further, larger prospective studies are needed in order to establish clinical guidelines for the diagnosis and treatment of BP patients presenting with or without bullae.

References

- 1 Joly P, Baricault S, Sparsa A *et al.* Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012; **132**: 1998–2004.
- 2 Stanley JR, Tanaka T, Mueller S, Klaus-Kovtun V, Roop D. Isolation of complementary DNA for bullous pemphigoid antigen by use of patients' autoantibodies. *J Clin Invest* 1988; **82**: 1864–1870.

- 3 Sawamura D, Li K, Chu ML, Uitto J. Human bullous pemphigoid antigen (BPAG1). Amino acid sequences deduced from cloned cDNAs predict biologically important peptide segments and protein domains. *J Biol Chem* 1991; **266**: 17784–17790.
- 4 Bertram F, Brocker EB, Zillikens D, Schmidt E. Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia. *J Dtsch Dermatol Ges* 2009; **7**: 434–440.
- 5 Gudi VS, White MI, Cruickshank N *et al*. Annual incidence and mortality of bullous pemphigoid in the Grampian Region of North-east Scotland. *Br J Dermatol* 2005; **153**: 424–427.
- 6 Jung M, Kippes W, Messer G, Zillikens D, Rzany B. Increased risk of bullous pemphigoid in male and very old patients: a population-based study on incidence. *J Am Acad Dermatol* 1999; **41**: 266–268.
- 7 Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337**: a180.
- 8 Marazza G, Pham HC, Scharer L *et al*. Incidence of bullous pemphigoid and pemphigus in Switzerland: a 2-year prospective study. *Br J Dermatol* 2009; **161**: 861–868.
- 9 Kridin K, Bergman R. Ethnic variations in the epidemiology of bullous pemphigoid in Israel. *Int J Dermatol* 2018; **57**: 34–39.
- 10 Bakker CV, Terra JB, Pas HH, Jonkman MF. Bullous pemphigoid as pruritus in the elderly: a common presentation. *JAMA Dermatol* 2013; **149**: 950–953.
- 11 Cozzani E, Gasparini G, Burlando M, Drago F, Parodi A. Atypical presentations of bullous pemphigoid: clinical and immunopathological aspects. *Autoimmun Rev* 2015; **14**: 438–445.
- 12 Strohal R, Rappersberger K, Pehamberger H, Wolff K. Nonbullous pemphigoid: prodrome of bullous pemphigoid or a distinct pemphigoid variant? *J Am Acad Dermatol* 1993; **29**: 293–299.
- 13 Lamberts A, Meijer JM, Jonkman MF. Nonbullous pemphigoid: a systematic review. *J Am Acad Dermatol* 2018; **78**: 989–995.e2.
- 14 Lipsker D, Borradori L. “Bullous” pemphigoid: what are you? Urgent need of definitions and diagnostic criteria. *Dermatology* 2010; **221**: 131–134.
- 15 Zhang Y, Luo Y, Han Y, Tian R, Li W, Yao X. Non-bullous lesions as the first manifestation of bullous pemphigoid: a retrospective analysis of 181 cases. *J Dermatol* 2017; **44**: 742–746.
- 16 Joly P, Roujeau JC, Benichou J *et al*. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; **346**: 321–327.
- 17 Eckardt J, Eberle FC, Ghoreschi K. Diagnostic value of autoantibody titers in patients with bullous pemphigoid. *Eur J Dermatol* 2018; **28**: 3–12.
- 18 Ljubojevic S, Lipozencic J. Autoimmune bullous diseases associations. *Clin Dermatol* 2012; **30**: 17–33.
- 19 van Beek N, Luttmann N, Huebner F *et al*. Correlation of serum levels of IgE autoantibodies against BP180 with bullous pemphigoid disease activity. *JAMA Dermatol* 2017; **153**: 30–38.
- 20 van Beek N, Schulze FS, Zillikens D, Schmidt E. IgE-mediated mechanisms in bullous pemphigoid and other autoimmune bullous diseases. *Expert Rev Clin Immunol* 2016; **12**: 267–277.
- 21 Cozzani E, Parodi A, Rebora A *et al*. Bullous pemphigoid in Liguria: a 2-year survey. *J Eur Acad Dermatol Venereol* 2001; **15**: 317–319.
- 22 Bernard P, Venot J, Constant F, Bonnetblanc JM. Blood eosinophilia as a severity marker for bullous pemphigoid. *J Am Acad Dermatol* 1987; **16**: 879–881.
- 23 Bushkell LL, Jordon RE. Bullous pemphigoid: a cause of peripheral blood eosinophilia. *J Am Acad Dermatol* 1983; **8**: 648–651.
- 24 Tan SK, Tay YK. Bullous pemphigoid: Profile and outcome in a series of 100 cases in Singapore. *J Dermatol Dermatol Surg* 2018; **22**: 12–15.
- 25 Thorslund K, Seifert O, Nilzén K *et al*. Incidence of bullous pemphigoid in Sweden 2005–2012: a nationwide population-based cohort study of 3761 patients. *Arch Dermatol Res* 2017; **309**: 721.
- 26 Nanda A, Al-Saeid K, Al-Sabah H, Dvorak R, Alsaleh QA. Clinicoepidemiological features and course of 43 cases of bullous pemphigoid in Kuwait. *Clin Exp Dermatol* 2006; **32**: 339–342.
- 27 Brick KE, Weaver CH, Lohse CM *et al*. Incidence and mortality rates of bullous pemphigoid in Olmsted County, Minnesota, over 6 decades. *J Am Acad Dermatol* 2014; **71**: 92–99.
- 28 Li J, Zuo Y, Zheng H. Mortality of bullous pemphigoid in China. *JAMA Dermatol* 2013; **149**: 106–108.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Gender distribution of BP patients.

Figure S2. Age of BP patients.

Figure S3. Relapse rate over time.

eFigure 1.

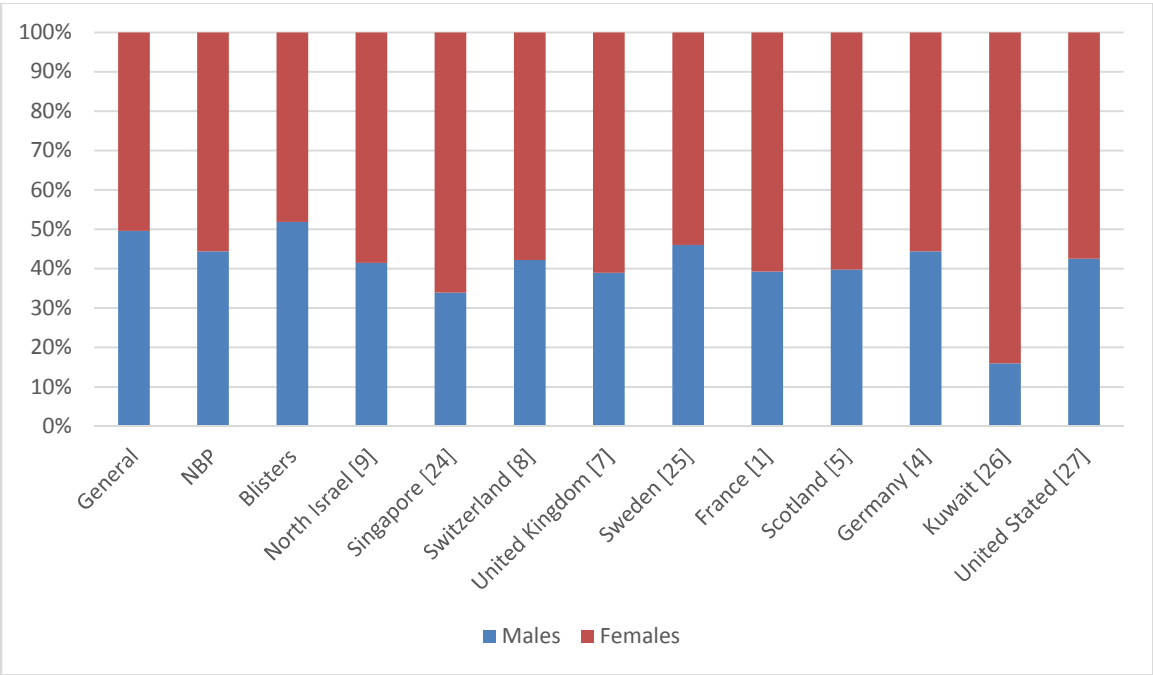


Figure 2.

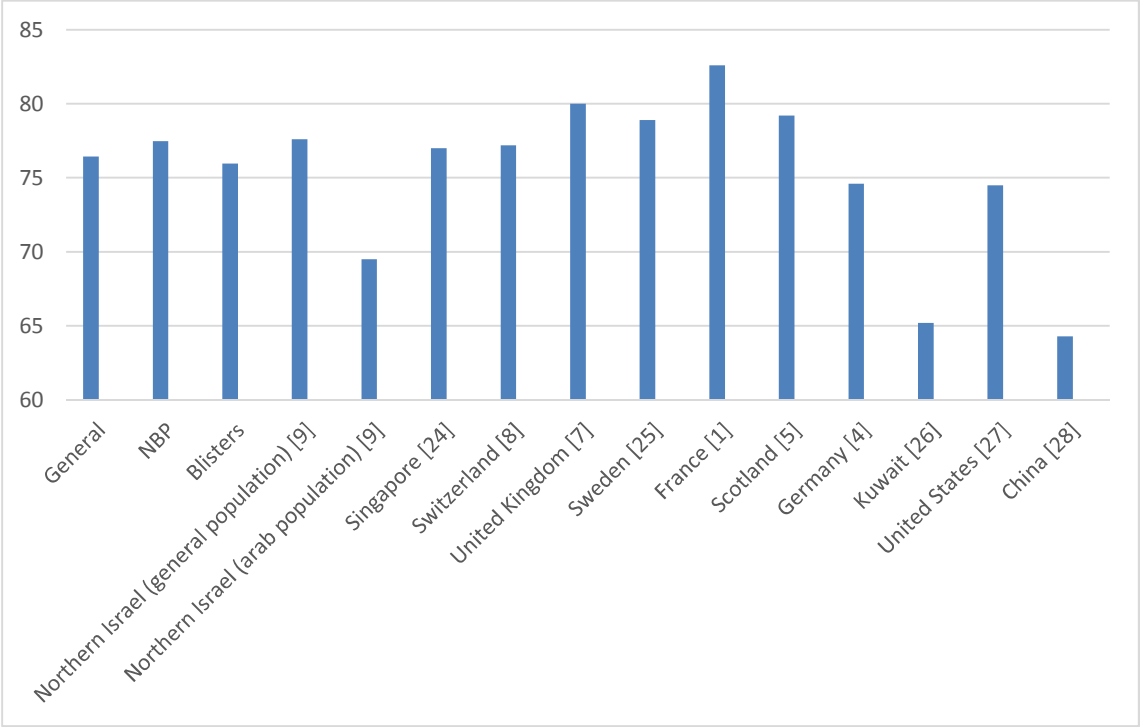


Figure 3.

