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ORIGINAL PAPER

Mortality and risk factors among Israeli bullous pemphigoid patients

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Abstract

There are differences concerning reported mortality rates and prognostic factors of bullous pemphigoid (BP) patients in different studies. Our objectives were to evaluate the mortality rates and prognostic factors among Israeli BP patients compared to matched control subjects. Three age- and sex-matched patients without BP ($n=261$) who were treated in our clinic were selected and compared to BP patients ($n=87$). Mean survival period of the BP group was 4.1 years (95% CI: 3.3–4.8 years) and 5.9 years among the non-BP group (95% CI: 5.6–6.3 years). The 1-year mortality rate was 24.1% for the BP group and 6.5% for the control group. In multivariate analysis, age above 80 was a significant risk factor for mortality [HR 3.22 (95% CI, 1.15–8.96), $p=0.03$], while statins intake had a protective role [HR 0.36 (95% CI, 0.15–0.88), $p=0.03$]. In univariant analysis, dementia [HR 2.44 (95% CI, 1.02–5.99), $p=0.04$] was a risk factor. In conclusion, BP patients' mortality is correlated to increasing age at diagnosis, dementia, and statins use. Statins' protective role is newly discussed in the literature.

Keywords Bullous pemphigoid · Pemphigoid · Mortality · Prognosis

Introduction

Bullous pemphigoid (BP) is the most common autoimmune blistering disease among the elderly population [15]. Several studies investigated the incidence and mortality rate of BP patients among different populations. The incidence of BP in Israel has been previously described by Kirdin et al., as 11.4 cases per million inhabitants per year [8, 13, 18, 23, 24]. Reported worldwide mortality rates varied significantly, ranging from 11 to 41% in the first year following BP diagnosis [4, 9, 16, 19, 20, 23, 24, 26]. Only a few of the published studies were matched control studies [4, 25]. A study that investigated BP patients' mortality rates among US residents did not show increased mortality rate compared to the matched national population [25]. The great variability of the mortality rates reported in Europe compared to the United States was related by some authors to different practice patterns [25]. Multiple factors such as diabetes, hypertension, multiple medications, hospitalization, and residence in nursing homes are associated with aging populations, hence posing a difficulty in assessing the mortality contributed to BP solely, rather than to other confounders.

Therefore, BP mortality rate continues to be a puzzling issue. Since the general population continues to age and BP is the most frequent autoimmune blistering disease of the elderly population, it is of value to further investigate mortality rate and prognostic factors of BP. The aim of this study is to determine the 1-, 2-, and 3-year mortality rates, prognostic factors, and standardized mortality ratio (SMR) among BP patients in Israel diagnosed by Emek Medical Center in a retrospective matched case control study.

Methods

The study was approved by the local institutional review board of Emek Medical Center, a referral center for patients diagnosed with BP in northeast Israel, with an estimated population of 1M people [27]. It is the only center in the region to provide immune pathology service. The northern district population it serves is mostly urban mixed with rural. As for ethnicity, Jews and Arabs are combined within the region. About 7% of the district

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population is above 65 years old according to the 2008 census [27].

We searched the local health system database for residents of the north district of Israel first diagnosed with BP. These patients had been treated in Emek Medical Center between January 1, 2009 and December 31, 2016. For each patient, we randomly selected three control subjects without BP who visited our clinic for reasons other than BP such as skin tumors and inflammatory skin conditions. The control subjects were selected during their visit at our clinic based on residence in the north district and were matched by sex and age (within 2 years of the matched patient index date of diagnosis with BP).

We collected data regarding demographic, hospitalization, and BP characteristics as well as treatment and comorbidities. Demographic characteristics included: age at diagnosis, gender, ethnicity, and nursing home residence during the 3 months prior to BP diagnosis. Hospitalization characteristics included hospitalization date and duration. BP characteristics consisted of head area involvement, mucous membranes involvement, treatment with topical corticosteroid (TCS) and/or systemic corticosteroids, symptoms duration, and diagnostic delay of more than 60 days from onset of symptoms until diagnosis. As for comorbidities we included: type 2 diabetes mellitus, hypertension, cerebrovascular accident (CVA), dementia, and other neurological diseases (multiple sclerosis, epilepsy, Parkinson's). Patients' medications were recorded, with specific attention to statins. We searched the pharmacy prescription database for statin prescription for at least 3 months during the 6 months prior to BP diagnosis.

Bullous pemphigoid diagnosis was based on findings that included review of the clinical presentation; for instance: pruritus, vesicles, bullae, and urticarial lesions, in conjunction with at least 2 of the following [28]:

- Histopathological findings suitable for BP such as subepidermal cleft with eosinophils.
- Direct immunofluorescence demonstrating a linear deposition of IgG and/or C3.
- Indirect immunofluorescence demonstrating circulating IgG antibodies against basement membrane proteins.
- Enzyme-linked immunosorbent assay with positive BP 230 and/or BP180 IgG antibodies.

Patients with predominantly oral disease were excluded from the study in order to avoid a possible confounder of other bullous diseases. The index date of BP diagnosis was determined as its first appearance in the medical records.

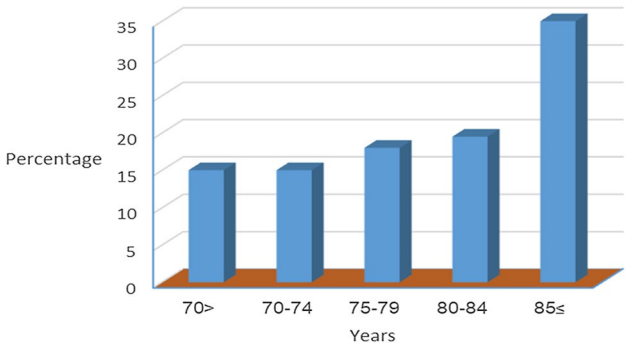

Fig. 1 Age distribution of newly diagnosed bullous pemphigoid patients in Emek Medical Center between 2009 and 2017

Statistical analysis

This study incorporated a matched case–control design, anchored to the diagnosis of BP. Categorical variables were frequencies and percentages. Continuous variables were presented as mean, standard deviation, median, and range. Any association between the study and control groups was estimated using conditional logistic regression, due to the matched case–control design. Follow-up duration was defined from the index date until the end of the study on 01.01.2017 or until the date of demise. The risk of death during follow-up period was compared between the 2 groups using Cox proportional hazards regression models and summarized with hazard ratios (HRs) and 95% CIs. Survival was estimated using the Kaplan–Meier survival analysis. In addition, univariate and multivariate Cox regression analyses were performed for the 1-year mortality rate. The standardized mortality rates (SMR) were calculated for the entire patient population and for specific groups based on age groups. The population data were taken from the Central Bureau of Statistics (Israel) based on the 2008 census. Approximate Poisson methods were used to calculate the 95% confidence interval (CI) for SMR, which represents the ratio between the observed to the expected number of deaths, using the OpenEpi program. All other statistical analyses were performed using SPSS 22 software. Significance was defined as p value < 0.05.

Results

General features of the study and control groups

Over the 8-year follow-up period, we identified 87 patients with BP (cases) and 261 matched controls without BP.

At the index date the mean age of the study group was 79.1 years (median 80.6, range 56.5–99.3) and 79.1 years (median 80.3, range 56.5–99.9) for the control group. Over 70% of the study group patients were above 75 years old at diagnosis, 32% were above 85 years (Fig. 1). Median follow-up period was 3.0 years. There was a majority of 54% males in both groups. Jewish ethnicity accounted for 74.7% of the BP patients and for 90.4% of the control subjects; 25.3% of the BP patients and 9.6% of the controls were Arabs. 13 of the BP patients (15.7%) were nursing home residents in the 3 months prior to BP diagnosis. The baseline characteristics were similar between the BP group and the control group. The baseline characteristics of the study group are presented in Table 1.

33 BP patients (37.9%) were hospitalized through the follow-up period. Hospitalization duration was 1–57 days (mean 10.2 ± 9.8 SD, median 8). Among the study group 8 patients (9.3%) had oral mucous involvement and 16 patients (18.4%) had head region involvement. Itching was present in all 87 cases. 42 patients had neurological disorders (48.3%), 37 had type 2 diabetes mellitus (42.5%), hypertension was reported in 74 patients (85.1%), statins intake during the 3 months prior to BP diagnosis was noted in 58 patients (66.7%).

Table 1 Baseline characteristics of the study group

Total	$N=87$
Male	47 (54.0%)
Female	40 (46.0%)
Mean age at diagnosis, years (median, SD)	79.1 (80.6, 56.5–99.3)
Arabs	22 (25.3%)
Jews	65 (74.7%)
Hospitalization	33 (37.9%)
Nursing home residence	13 (15.7%)

SD standard deviation

Mortality and prognostic factors

During the follow-up period, 39 of the BP patients died (44.8%), while 57 of the control group died (21.8%). The 1-year mortality rate was 24.1% for the study group compared to 6.5% for the control group. The 2-year mortality rate among the BP group was 37.9% (95% CI: 28.4–48.4%) compared to 13.0% (95% CI: 9.5–17.6%) among the control group; the 3-year mortality rate among the BP group was 42.5% (95% CI: 32.7–53.0%), whereas it was 15.7% (95% CI: 11.8–20.6%) in the control group. The mortality rate during the follow-up period was statistically significantly different between the 2 groups (HR: 2.76; 95% CI: 1.84–4.16), Cox proportional hazards assumptions were met. Mean survival time of the BP group was 4.1 years (95% CI: 3.3–4.8 years) and 5.9 years for the non-BP group (95% CI: 5.6–6.3 years). There was a statistically significant difference in survival time between the 2 groups (log rank test: Chi-square = 25.89, $p < 0.001$). Figure 2 shows the Kaplan–Meier survival curves of patients with and without BP. Table 2 presents mortality status of the study group at 1-year intervals, comparing it by demographic characteristics. Table 3 compares the study and control groups' characteristics with further separation into deceased or alive by the end of the follow-up period.

The SMR of the study group ranged from 2.12 to 26.5 varying between age groups. Based on this data the mortality rate of the study group was not higher than mortality

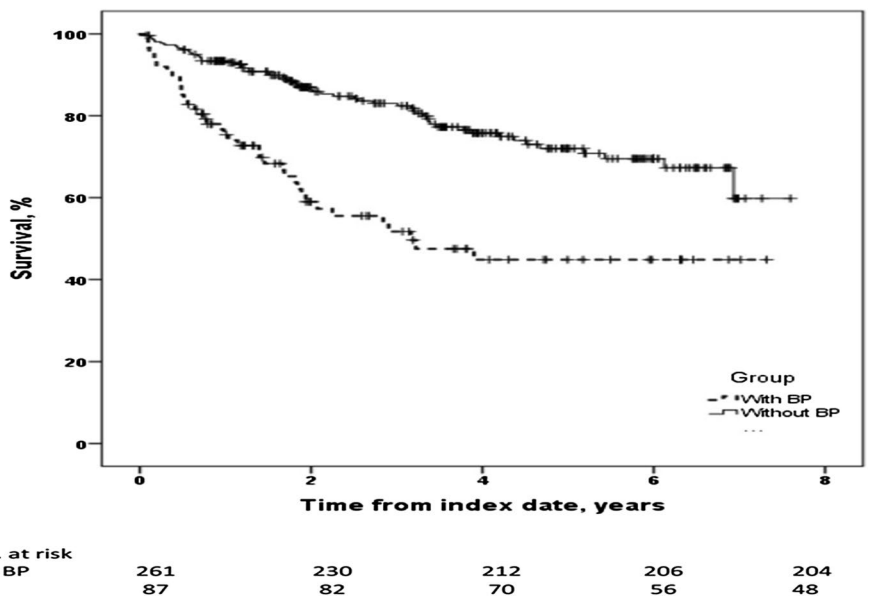

Fig. 2 Kaplan–Meier survival curves of patients with and without bullous pemphigoid

rate of the population of northern Israel with one exception. The SMR value of patients aged 80–84 years at diagnosis was 6.25; this value is more than six times higher than the SMR value of the general population (CI 95%, 2.50–12.88). Table 4 shows the observed and expected 1-year mortality rates and the calculated SMR among the BP patients.

In order to recognize risk factors for BP patients' prognosis, we used univariate and multivariate Cox analysis. Univariate analysis examined factors that were found to be correlated to higher 1-year mortality rate: age above 80 at diagnosis and dementia, while oral use of statins had a protective role. Dementia was statistically significantly correlated to 1-year mortality [HR, 2.48 (95% CI, 1.02–5.99), $p = 0.04$]. Multivariate factors correlated to 1-year mortality were age above 80 at diagnosis [HR, 3.22

Table 2 Mortality status of the study group at 1-year interval

Characteristic	*N* (%) deceased at 1 year (*n* = 21)	N (%) alive at 1 year (*n* = 66)	OR (95% CI)	*p* value
Mean age (SD) (median, CI)	83.9 ± 7.2 (84.2, 67.8–99.3)	77.6 ± 9.1 (76.8, 55.5–92.2)		0.005
Gender			0.92 (0.34–2.45)	0.86
Male	11 (52.4%)	36 (54.5%)		
Female	10 (47.6%)	30 (45.5%)		
Ethnic group			1.70 (0.58–4.98)	0.33
Arab	7 (33.3%)	15 (22.7%)		
Jew	14 (66.7%)	51 (77.3%)		
Hospitalization	8 (38.1%)	25 (37.9%)	1.00 (0.37–2.78)	0.99

Comparison by demographic characteristics

CI confidence interval, *SD* standard deviation

Table 3 Study and control group characteristics with further separation of deceased or alive at the end of the follow-up period

	Study group		Control group	
	Deceased (*N* = 39)	Alive (*N* = 48)	Deceased (*N* = 57)	Alive (*N* = 204)
Mean age (median, CI)	83.5 (84.2; 56.6–99.3)	75.6 (75.4; 56.5–92.1)	85.2 (86.3; 68.5–99.2)	77.4 (78.4; 55.4–99.9)
Gender				
Male	20 (51.3)	27 (56.3)	25 (43.9)	116 (56.9)
Female	19 (48.7)	21 (43.7)	32 (56.1)	88 (43.1)
Ethnic group				
Jew	26 (66.7)	39 (81.3)	50 (87.7)	186 (91.2)
Arab	13 (33.3)	9 (19.7)	7 (12.3)	18 (8.8)
Comorbidity				
Diabetes mellitus type 2	18 (46.2)	19 (39.6)	29 (50.9)	78 (38.4)
Hypertension	34 (87.2)	40 (83.3)	48 (84.2)	163 (80.3)

CI confidence interval

Table 4 Observed and expected 1-year mortality rates and calculated standardized mortality ratio (SMR) among the BP patients

Age group	Total (*n*)	Mortality (*n*)	Expected	Observed	SMR
55–59	3	0	0.0048	0.0000	–
60–64	7	0	0.0075	0.0000	–
65–69	3	1	0.0126	0.3333	26.46 (0.35–147.20)
70–74	13	1	0.0212	0.0769	3.63 (0.05–20.19)
75–79	16	3	0.0383	0.1875	4.89 (0.98–14.28)
80–84	17	7	0.0662	0.4176	6.25 (2.50–12.88)
85+	28	9	0.1513	0.3214	2.12 (0.97–4.03)
All	87	21	0.0431	0.2414	3.50 (2.17–5.35)

(95% CI, 1.15–8.96), $p = 0.03$] and statins intake [HR, 0.36 (95% CI, 0.15–0.88), $p = 0.03$].

12 of the 33 hospitalized patients (36.4%) died during the follow-up period, compared to 27 (50.0%) of the non-hospitalized patients ($p > 0.22$). No significant difference was found between shorter and longer than 5-day hospitalization duration. Three out of nine (33.3%) patients hospitalized for less than 5 days died, compared to 8 of 22 (36.4%) patients hospitalized for more than 5 days ($p > 0.99$). Table 5 summarizes the risk factors for 1-year mortality of the BP patients using univariate and multivariate analysis.

Patients' division based on treatment

BP patients' mortality risk can be further divided based on therapeutic regimen. 29 patients received only topical glucocorticosteroids (high-potency clobetasol propionate 0.05%), of whom 5 (17.2%) died during the first-year interval, 13 (44.8%) died by the end of the follow-up period. 24 patients were treated with only oral prednisone therapy, of whom, 8 patients (33.3%) died within 1 year while 12 patients (50.0%) died by the end of the follow-up period. 34 patients were treated with both topical and oral prednisone; 8 (23.5%) died within the first year of follow-up, while 14 (41.2%) died by the end of the follow-up period ($p = 0.46$).

Discussion

This study investigated the mortality rate, SMR, and prognostic factors of BP patients in northeast Israel by a retrospective cohort case-controlled manner for the first time. We found significant findings regarding various prognostic factors such as statins intake, age at diagnosis, and dementia. The longer observation period enabled an insightful observation regarding treatment management and mortality prevention.

Our study design included a control group matched by geographic area, gender, and age in order to reinforce the results. When comparing the study and control groups, the mean survival time was 4.1 years compared to 5.9 years, respectively. These findings altogether are compatible with earlier studies' results as presented in Table 6, which compares the 1-year mortality rate between the current study and prominent studies published in recent years. Previous studies that tried to determine the contribution of BP to mortality rate lacked comorbidity-matched control subjects. In order to minimize it in our study, we examined both BP patients and control subjects matched by age, sex, and geographical area. The mortality rate measured in the study of Roujeau et al., which investigated BP among the French population, was higher compared to our measured rate, despite similar age at diagnosis [2, 25]. On the other hand, the study of Brick et al., which examined BP patients in Minnesota, US, showed lower age at diagnosis and lower mortality rate than reported in our study [4]. Most studies reported just a 1-year mortality rate, with only a few studies reporting longer time periods such as 3-year survival rates as described in the studies of Kalinska and Cortés [9, 16].

The 1-year SMR values were 3.50 (CI, 2.17–2.50) for all 87 patients and 6.25 (CI, 2.50-12.88) for patients aged 80–84, allowing us to determine that the survival rate of BP patients aged 80–84 was 6.25 times lower than the general Israeli population survival rate, in line with previous reported SMR rates among BP populations in Europe and Asia [6, 16, 19]. It should be noted that the SMR values in the United States were lower than reported values in Asia and Europe and ranged between 0.4 and 0.7 [16, 19, 23].

Investigating the prognostic factors among BP patients demonstrated several significant findings including the poor prognosis of patients aged above 80 years at diagnosis and those diagnosed with dementia. On the other hand, the protective role of statins use was also significant by multivariate analysis. Advanced age at BP diagnosis was related to decreased survival rate in the first year following diagnosis by both univariate and multivariate analysis ($p = 0.03$) as reported by previous studies [9, 11]. Rzany et al. found that increasing age, lower serum levels of albumin, and increased dosage of systemic glucocorticoids treatment were associated with higher mortality rate [26].

We also found dementia to be a poor prognostic factor for BP using the univariate analysis ($p = 0.04$) but not by multivariate analysis, similar to previous reports that demonstrated lower survival rates during the first year of observation [3, 16, 19, 23, 25]. A recent meta-analysis found dementia patients to be twice more likely to die [21]. This connection has been a curiosity among dermatologists, and today speculations are that autoimmune reaction against BP antigens in the brain cross-reacts with BP antigens in the skin [5].

A newly reported association was found between statins use and BP patients' mortality rate. Statistical significance was achieved using both univariate and multivariate analysis ($p = 0.03$). This finding strengthens previous reports of Garin et al., who conducted a prospective case–control study that included 201 French BP patients and 345 control subjects [1]. They investigated various risk factors including different medications and showed that chronic intake of lipid-lowering drugs had a protective role on mortality rate regarding overall lipid-lowering drugs use [OR, 0.56 (95% CI, 0.35–0.92), $p = 0.02$] and statins use [OR, 0.66 (95% CI, 0.39–1.12), $p = 0.10$]. Although the protective role of statins was suggested, it was not statistically significantly correlated to BP patients' mortality rate. To the best of our knowledge, our study is the first to demonstrate a statistically significant role of statins use on BP patients' mortality rate.

Table 5 Univariate and multivariate analysis of patients with bullous pemphigoid within 1-year of follow-up period

Characteristic	No. patients (%)	No. deaths (%)	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Age				**0.01**	3.22 (1.15–8.96)	**0.03**
≥ 80	45 (51.7)	16 (35.6)	3.54 (1.29–9.66)			
< 80	42 (48.3)	5 (11.9)				
Gender				0.84		
Male	47 (54.0)	11 (23.4)	0.91 (0.39–2.15)			
Female	40 (46.0)	10 (25.0)				
Ethnic group				0.41		
Arab	22 (25.3)	7 (31.8)	1.47 (0.59–3.64)			
Jew	65 (74.7)	14 (21.5)				
Diabetes mellitus				0.90		
Yes	37 (42.5)	9 (24.3)	1.06 (0.44–2.50)			
No	50 (57.5)	12 (24.0)				
Hypertension				0.26		
Yes	74 (85.1)	16 (21.6)	0.56 (0.21–1.54)			
No	13 (14.9)	5 (38.5)				
Statin intake				**0.01**	0.36 (0.15–0.88)	**0.03**
Yes	58 (66.7)	9 (15.5)	0.34 (0.14–0.81)			
No	29 (33.3)	12 (41.4)				
Neurological diseases				0.12		
Yes	42 (48.3)	13 (31.0)	2.01 (0.83–4.86)			
No	45 (51.7)	8 (17.8)				
CVA				0.31		
Yes	15 (17.2)	5 (33.3)	1.69 (0.62–4.60)			
No	72 (82.8)	16 (22.2)				
Dementia				**0.04**	1.57 (0.63–3.92)	0.33
Yes	20 (23.0)	8 (40.0)	2.48 (1.02–5.99)			
No	67 (77.0)	13 (19.4)				
Hospitalization admission				0.92		
Yes	33 (37.9)	8 (24.2)	1.04 (0.43–2.52)			
No	54 (62.1)	13 (24.1)				
Blisters present on diagnosis				0.83		
Yes	70 (80.5)	17 (24.3)	1.12 (0.38–3.34)			
No	17 (19.5)	4 (23.5)				
Head involvement				0.99		
Yes	16 (18.4)	4 (25.0)	1.01 (0.34–2.99)			
No	71 (91.6)	17 (23.9)				
Mucous involvement				0.98		
Yes	8 (9.3)	2 (25.0)	1.02 (0.24–4.36)			
No	78 (90.7)	19 (24.4)				
Corticosteroid treatment				0.46		
Topical	29 (33.3)	5 (17.2)	1.00 (ref)			
Systemic	24 (27.6)	8 (33.3)	2.02 (0.66–6.17)			
Both	34 (39.1)	8 (23.5)	1.41 (0.46–4.30)			
Symptoms after 6 months				0.59		
Yes	32 (36.8)	7 (21.9)	0.78 (0.32–1.93)			
No	55 (63.2)	14 (25.5)				
Diagnostic delay				0.40		
≥ 60 days	46 (52.9)	13 (28.3)	1.46 (0.60–3.53)			
< 60 days	40 (46.0)	8 (20.0)				

Table 5 (continued)

Characteristic	No. patients (%)	No. deaths (%)	Univariate HR (95% CI)	*p*	Multivariate HR (95% CI)	*p*
Unknown	1 (1.1)	–				

Bold values indicate $p < 0.05$

Table 6 Comparing major bullous pemphigoid cohort's mortality studies

Authors	1-year mortality rate (%)	Average age	No. of patients	Country	Year
Bernard et al. [2]	38	80	78	France	1995
Roujeau et al. [26]	41	79	217	France	1998
Rzany et al. [25]	29	77	369	Germany	2002
Colbart et al. [8]	11	77	37	United States	2004
Parker et al. [23]	23	75	223	United States	2008
Cortes et al. [9]	21	80	115	Switzerland	2011
Li et al. [20]	13	64	140	China	2013
Brick et al. [4]	19	75	87	United States	2014
Lee and Kim [19]	19	69	168	Korea	2014
Kalinska et al. [16]	22	76	205	Poland	2017

There are several explanations for this association; statins might take a role in modulation of the inflammatory process due to their 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibition. Statins are also known to have a protective role in inflammatory conditions by blocking the L-mevalonate pathway and decreasing metabolites such as farnesyl pyrophosphate, which is essential for the attachment of GTPases like RhoA and Ras to the cell membrane, which plays an important role in the immune response of migration, immune cell activation, and survival of immune cell [29]. The role of statins use has already been investigated in different autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and graft-versus-host disease [7, 10, 17, 22].

Another subject we addressed was the association between different treatment managements and BP patients' mortality rates. The mortality rate among patients treated with TCS in the first year following diagnosis was 17.5%, while the mortality rate of those treated with oral prednisone was 33.3%. Yet, the mortality rate at the end of follow-up period was found to be similar between the two groups (44.8%).

The large prospective trial by Joly et al. compared the mortality rate of patients treated with oral prednisone and patients treated with topical clobetasol [12]. This study showed higher first year mortality rate among the oral intake group compared to the topical treatment group. This result was achieved in the current study as well; nonetheless, the longer follow-up period of our study compared to the French study allowed us to demonstrate that mortality rate tends to equalize through longer follow-up periods. This observation should be taken into account when considering a treatment regimen for BP patients.

In addition to the findings above, analyzing hospitalization admission and duration could reflect a more severe disease. We did not find a significant difference in mortality rate during the follow-up period between hospitalized and non-hospitalized patients ($p > 0.22$). The impact of hospitalization on mortality rate is debated in the literature. Hospital admission rate in Europe differs from that in the United States, and therefore can cause a selection bias [6, 14]. Emek Medical Center is the only tertiary center with an immunopathological lab in northeastern Israel, treating almost all BP patients as community dermatologists are unlikely to treat these patients without immunopathological confirmation. Therefore, the results based on the database of our study are more likely to reflect the actual clinical picture among the BP population. Compared to other studies that tend to miss mild cases treated on an outpatient basis, this study narrows the chance for selection bias.

The limitations of our study include a retrospective design, which limits the assessment of disease severity. However, the treatment regimen could be a surrogate marker for disease severity, assuming that oral treatment would be given for the more severely ill patients. In addition, the study covers a small geographic area in a single tertiary center with patients being mostly of Jewish origin and might not represent the overall population.

In conclusion, the study emphasizes that the mortality rate among BP patients is higher than the mortality rate of

the overall papulation in Israel and is similar to reported mortality rates of BP patients around the world. In addition, we emphasized risk factors such as age and dementia and demonstrated for the first time that statins may play a protective role in BP patients' prognosis. We also demonstrated that although patients with oral treatment of glucocorticoids had higher 1-year mortality rate compared to TCS as reported previously, the overall mortality rate was similar.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interests.

Research involving human participants and/or animals Reviewed and approved by Emek Medical Center IRB (institutional review board), approval number: 151-15.

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