Rapid #: -19823793

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TYPE:	Article CC:CCG
JOURNAL TITLE:	JEADV. Journal of the European Academy of Dermatology and Venereology
USER JOURNAL TITLE:	Journal of the European Academy of Dermatology and Venereology
ARTICLE TITLE:	Mortality in eight autoimmune bullous diseases: A global large□scale retrospective cohort study
ARTICLE AUTHOR:	Boch, Katharina
VOLUME:	0
ISSUE:	0
MONTH:	
YEAR:	2022-11
PAGES:	-
ISSN:	0926-9959
OCLC #:	

Processed by RapidX: 11/7/2022 12:11:40 PM

Received: 21 August 2022 | Accepted: 25 October 2022

DOI: 10.1111/jdv.18700

LETTER TO THE EDITOR

Mortality in eight autoimmune bullous diseases: A global large-scale retrospective cohort study

Autoimmune bullous diseases (AIBDs) are typified by a life-threatening potential and long-term sequela.[1,2] The current knowledge about the prognosis of AIBDs is principally confined to the most prevalent diseases; pemphigus vulgaris (PV)[3–5] and bullous pemphigoid (BP).[4,6,7] Population-based estimates of mortality in other less frequent AIBDs remain to be delineated. Investigating the survival of patients with rare diseases is of great importance to better elucidate its burden and to tailor a convenient health policy enabling to improve its management.

The aim of this study is to assess the risk of mortality among patients with eight different AIBDs, namely BP, mucous membrane pemphigoid (MMP), epidermolysis bullosa acquisita (EBA), dermatitis herpetiformis (DH), lichen planus pemphigoides (LPP), PV, pemphigus foliaceus (PF) and paraneoplastic pemphigus (PNP).

This study was designed as a population-based, historical, retrospective cohort study utilizing the database of TriNetX, a global federated health research network providing access to electronic medical records across healthcare organizations (HCOs). The database of TriNetX was systematically screened for all prevalent cases with AIBDs. All 117.7 million health-insured individuals were screened for the presence of a diagnostic code compatible with AIBDs.

For each eligible patient with these eight AIBDs, a matched control individual lacking a diagnosis of any AIBD was recruited. Controls were matched to cases based on age, sex and race. A propensity score matching was additionally performed, ensuring an even distribution of confounders between groups, thereby increasing between-group comparability.[8]

This study included 17,919, 5747, 1.503, 10,661, 170, 14,716, 1115 and 179 patients with a diagnosis of BP, MMP, EBA, DH, LPP, PV, PF and PNP, respectively. A similar number of matched control individuals was allocated for each one of the aforementioned case populations (Table 1).

Table 2 delineates the risk of mortality among patients with each one of the eight AIBDs. In the subepidermal AIBDs subgroup, patients with BP (HR, 2.55; 95% CI, 2.39–2.71; $p < 0.001$) and EBA (HR, 2.52; 95% CI, 1.81–3.50; $p < 0.001$) experienced the highest risk of mortality relative to their matched control individuals. Correspondingly, patients with DH (HR, 1.91; 95% CI, 1.68–2.16; $p < 0.001$) and MMP (HR, 1.73; 95% CI, 1.51–1.99; $p < 0.001$) were at a significantly elevated risk of death as compared to their matched controls. LPP does not confer a significant risk of death (HR, 0.80; 95% CI, 0.28–2.28; $p = 0.681$).

When the pemphigus group was investigated, patients with PV (HR, 3.70; 95% CI, 3.40–4.02; $p < 0.001$) and PF (HR, 4.07; 95% CI, 2.94–5.62; $p < 0.001$) were found to possess an almost four-fold risk of mortality. Expectedly, PNP imposed the highest risk of mortality (HR, 8.03; 95% CI, 3.46–18.66; $p < 0.001$).

TABLE 1 Baseline characteristics of study participants

Disease	N of patients	N of controls	Mean age (SD), years	% of females	% of white race
Subepidermal autoimmune bullous disease group					
Bullous pemphigoid	17,919	17,919	72.4 (15.1)	52.4%	61.6%
Mucous membrane pemphigoid	5747	5747	65.2 (15.9)	45.3%	72.9%
Epidermolysis bullosa acquisita	1503	1503	57.7 (19.0)	41.3%	69.9%
Dermatitis herpetiformis	10,661	10,661	52.2 (20.8)	46.6%	74.0%
Lichen planus pemphigoides	170	170	56.3 (19.3)	61.8%	47.1%
Pemphigus group					
Pemphigus vulgaris	14,716	14,716	59.0 (20.1)	60.1%	67.3%
Pemphigus foliaceus	1115	1115	57.9 (21.2)	55.2%	60.1%
Paraneoplastic pemphigus	179	179	58.3 (18.2)	53.6%	67.0%

Abbreviations: N, number; SD, standard deviation.

TABLE 2 Risk of death among patients with AIBDs relative to matched controls

Disease	Cases		Controls		Risk difference (95% confidence interval), %	Hazard ratio (95% confidence interval)	*p* value
	N of outcomes	Risk, %	N of outcomes	Risk, %			
Subepidermal autoimmune bullous disease group							
Bullous pemphigoid	2994	17.4	1447	8.4	9.0 (8.4–9.8)	2.55 (2.39–2.71)	**<0.001**
Mucous membrane pemphigoid	481	8.4	346	6.0	2.4 (1.4–3.3)	1.73 (1.51–1.99)	**<0.001**
Epidermolysis bullosa acquisita	114	7.6	60	4.0	3.6 (2.0–5.3)	2.52 (1.81–3.50)	**<0.001**
Dermatitis herpetiformis	702	6.6	389	3.7	2.9 (2.4–3.5)	1.91 (1.68–2.16)	**<0.001**
Lichen planus pemphigoides	10	5.9	10	5.9	0.0 (−5.1–5.1)	0.80 (0.28–2.28)	0.681
Pemphigus group							
Pemphigus vulgaris	2193	15.0	769	5.2	9.7 (9.0–10.4)	3.70 (3.40–4.02)	**<0.001**
Pemphigus foliaceus	133	12.0	65	5.8	6.2 (3.8–8.5)	4.07 (2.94–5.62)	**<0.001**
Paraneoplastic pemphigus	37	20.7	10	5.6	15.1 (8.3–21.9)	8.03 (3.46–18.66)	**<0.001**

Abbreviations: N, number; AIBD, autoimmune bullous diseases.
Bold indicates significant values.

The rare nature of AIBDs considerably interferes with delineating their epidemiological characteristics.[6,9] Thus, our knowledge about the mortality of most AIBDs is very sparse and relies primarily on small hospital-based studies. Our study has several limitations to acknowledge. Diagnosis of AIBDs relied on ICD-10 codes rather than on immunopathological criteria. Yet, while defining the study cohorts, we excluded patients with diagnoses that might interfere with the validity of the index diagnosis. For example, in the definition of PV study population, eligible patients could not have a simultaneous diagnosis of pemphigoid. These measures guaranteed a higher precision of the diagnoses.

Our findings signify that the relative risk of mortality is greater among patients with pemphigus than those with subepidermal AIBDs, with PNP conferring eight-fold and PV and PF four-fold higher risk of death. Rather than LPP, all other investigated subepidermal AIBDs place individuals at a higher hazard of death. Patients with BP and EBA were at a 2.5-fold increased risk of death, whereas those with DH and MMP experienced 1.9-fold and 1.7-fold increased mortality, respectively. Physicians managing patients with AIBDs and health system decision-makers ought to be aware of these findings.

FUNDING INFORMATION
None.

CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, KK, upon reasonable request.

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