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# Mixed Individual-Aggregate Data on All-Cause Mortality in Bullous Pemphigoid
## A Meta-analysis

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**IMPORTANCE** The 1-year standardized mortality ratio (SMR) of bullous pemphigoid (BP) has been reported as 2.15 to 7.56 and lower in the US than in Europe.

**OBJECTIVE** To estimate the worldwide 1-year SMR of BP.

**DATA SOURCES** PubMed, Embase, Cochrane Library, Google Scholar, Lissa, and gray literature (eg, medRxiv) were screened for studies of BP published from inception to June 10, 2020, with review of reference lists.

**STUDY SELECTION** Retrospective and prospective studies reporting 1-year all-cause mortality rate in patients with BP and providing age statistics (eg, mean [SD]).

**DATA EXTRACTION AND SYNTHESIS** Two reviewers independently extracted the data. The 1-year SMR was computed in studies reporting 1-year mortality by combining information on age obtained from studies with aggregate data and individual data. Risk of representativity, misclassification, and attrition bias were assessed by a custom tool.

**MAIN OUTCOMES AND MEASURES** The primary end point was the worldwide 1-year SMR. Secondary analysis included comparison of 1-year SMRs between continents in a meta-regression.

**RESULTS** Three studies were performed in the US (n = 260), 1 in South America (n = 45), 16 in Asia (n = 1903), and 36 in Europe (n = 10 132) for a total of 56 unique studies and 12 340 unique patients included in the meta-analysis (mean [SD] age, 77.3 [12.7] years; 55.9% women). The mean (SD) patient age in the United States was 75.6 (13.7) years; in Asia, 73.8 (13.6) years; and in Europe, 78.1 (12.3) years. The worldwide 1-year SMR was estimated at 2.93 (95% CI, 2.59-3.28; $I^2$ = 85.6%) for all 56 studies. The 1-year SMR in the US was 2.40 (95% CI, 0.89-3.90; $I^2$ = 86.3%) for 3 studies; in Asia, 3.53 (95% CI, 2.85-4.20; $I^2$ = 86.3%) for 16 studies; and in Europe, 2.77 (95% CI, 2.35-3.19; $I^2$ = 86.3%) for 36 studies. After adjustment on the expected 1-year mortality rate, the European 1-year SMR did not differ significantly from the 1-year SMR in the United States (−0.48 vs Europe; 95% CI, −2.09 to 1.14; $P$ = .56) and Asia (0.51 vs Europe; 95% CI, −0.56 to 1.58; $P$ = .35). Risk of attrition bias was high (>10% censorship) in 16 studies (28.6%), low in 16 (28.6%), and unclear in 24 (42.9%). Only 4 studies (7.1%) had a sampling method guaranteeing the representativity of BP cases in a population.

**CONCLUSIONS AND RELEVANCE** Although heterogeneity was high and overall quality of follow-up was poor, this meta-analysis confirms the high mortality rate among patients with BP.

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Supplemental content

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Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin, which mainly affects elderly patients with frequent neurological comorbidities.[1] Bullous pemphigoid is associated with significant morbidity and an increased death rate that seems to differ throughout the world. In Europe, the 1-year death rate ranged from 0 to 52%,[2,3] whereas it ranged from 11% to 23% in the US[4,5] and from 0 to 42% in Asia.[6,7]

Some authors prefer to compute a standardized mortality ratio (SMR) to assess the extent to which the mortality of patients with BP is higher than the mortality due to diseases that come with old age in this population. The all-cause SMR of BP is the ratio between the observed all-cause mortality rate in patients with BP and the expected all-cause mortality rate in the general population with the same age and sex distribution as patients with BP. The SMR can be interpreted as a relative risk of death during a given period (eg, 1 year) compared with the general population. An SMR of greater than 1.00 means that there is an increased mortality rate relative to the general population, due to the disease (ie, BP), its treatments, or comorbidities. Major differences in the all-cause SMR of patients with BP have been reported from study to study and country to country, ranging from 2.15 to 7.56[8,9] for 1-year SMR and from less than 1.00 to 6.60 for global SMR.[4,10]

Older age, low Karnofsky score, hypoalbuminemia, high dose of oral corticosteroids, and neurological comorbidities (dementia, Parkinson disease, and stroke) have been reported to be associated with mortality in European series,[11-13] whereas the absence of hospitalization of patients with BP in the US has been suggested to explain the lower death rate of patients with BP in 1 US study.[5] To disentangle the discrepancies in the all-cause mortality of patients with BP among the different studies throughout the world, we performed a meta-analysis combining individual patient and aggregate data to estimate the all-cause 1-year SMR of patients with newly diagnosed BP (primary analysis), assess its heterogeneity, and compare it between continents.

### Key Points

**Question** Is bullous pemphigoid (BP) associated with increased mortality relative to the general population?

**Findings** This meta-analysis combining individual and aggregate data from 56 unique studies of 12 340 unique patients found that patients with BP had a 2.93-fold increased 1-year mortality rate compared with the general population. Mortality was associated with BP itself, adverse effects of treatment, and/or patients' comorbidities, with infections as the main cause of death.

**Meaning** These findings may help clinicians in the management of BP and suggest avoiding aggressive treatments.

## Methods

This systematic review and meta-analysis was registered on PROSPERO.[14] We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[15] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[16] Ethics committee approval was not required for this meta-analysis of published data.

### Eligibility Criteria

Inclusion criteria were either prospective or retrospective studies including patients with BP, for which the 1-year overall death rate could be extracted, and age distribution information of patients with BP was provided with at least 1 position statistic (eg, mean or median) or frequency by age class (eg, 20-40 years, 40-60 years, etc). Exclusion criteria were (1) massive inclusion (≥50%) of prevalent cases; (2) inclusion of specific BP populations that may have a different prognosis (eg, cancer, refractory BP); (3) inclusion of patients with other pemphigoid without possibility of isolating patients with BP; (4) reports of only cause-specific mortality; (5) case reports; and (6) systematic reviews. There was no exclusion based on methodology quality, diagnosis method, or number of patients.

### Information Sources and Literature Search

We performed a comprehensive systematic search in 15 different languages using PubMed, Embase, Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews), Google Scholar, Lissa, and gray literature (http://www.theses.fr and medRxiv) to screen studies published from inception to June 10, 2020 (first search in January 2020; updated in June 2020). The main search terms were *pemphigoid* AND *mortality*, *death*, *lethality*, *survival*, or *prognosis,* as described in eTable 1 in the Supplement. All prospective and retrospective studies were included with no language restriction, and the reference lists in relevant review articles were scanned manually as well. Two authors of this study (B.T. and A.G.) screened all eligible articles based on the title, abstract, and full text, with disagreements identified by software and solved by consensus (data screening in the eMethods in the Supplement).

### Data Extraction

Data extraction (eMethods in the Supplement) was conducted independently by 2 authors (B.T. and A.G.), with disagreements solved by consensus. The general characteristics of the studies were recorded: inclusion period, study area, and whether the follow-up of vital status was obtained passively (from medical records), actively (telephone calls or email to patients or family physician), or exhaustively (consultation of death registry). In addition, the mode of patient's inclusion (incident only or prevalent and incident), total number of patients, and sex ratio when available were recorded. The following statistics about age distribution were retrieved if available: mean, SD, minimum, maximum, median, quartiles, and frequency by age class (eg, 18-60 years, 60-79 years, etc). Sex-specific statistics were retrieved if available. The distribution of inclusion dates (eg, by 2-year periods) was recorded when available.

If possible, the Kaplan-Meier method was used for the estimation of the 1-year death rate (with graphical extraction from figures and pooling subgroups, if needed). Otherwise, the number of deaths, survivors, and censorships at 1 year were

recorded and the death rate was computed with a modified Kaplan-Meier estimator, assuming a uniform distribution of censorships (computation of SMRs in the eMethods in the Supplement).

Frequencies of each cause of death were extracted, counting either causes of deaths of all patients dying during the first year after BP diagnosis or causes of deaths of patients dying at any follow-up time that could be longer or shorter than 1 year or both. Causes of death were not extracted if they were only reported in a subgroup, such as treatment-related deaths.

Individual patient data were searched for 12 studies[4,5,10,17-25] in a previous meta-analysis.[26] The authors, contacted by email, returned deidentified individual data regarding birthdate, sex, date of diagnosis, date of death, and optionally cause of death. In addition, published data of 4 studies containing detailed individual data tables were considered as individual data studies.[2,27-29] Risk of bias was assessed using a 3-dimensional custom tool created for this meta-analysis, remotely based on Newcastle-Ottawa Scale,[30] but adapted to noncomparative studies, to assess representativity, misclassification, and attrition bias (eMethods in the Supplement).

## Statistical Analysis

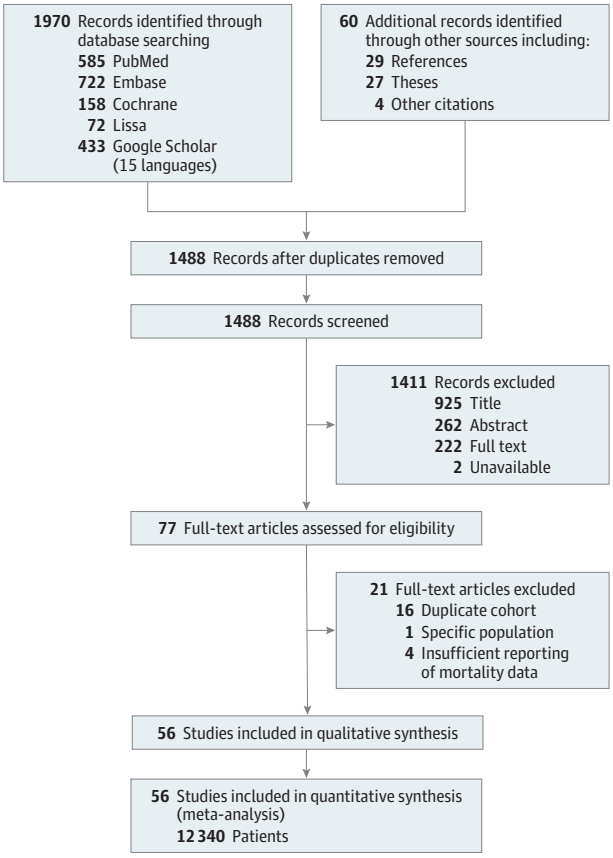
### Computation of SMRs for Each Study

The SMRs have been computed as the rate between the crude 1-year death rate and the expected death rate for a general population of the same country, period, and age pyramid. For individual data studies, the exact age pyramid was available. For aggregate data studies, an approximate age pyramid was estimated by distortion of all individual-data studies pooled together until it fit the aggregate statistics. A nonlinear spline-based model fitted on the individual patient data was used to describe the association of the sex-ratio with age (eMethods in the Supplement). In aggregate data studies, the age-sex distribution was derived from this nonlinear model and from the global sex-ratio of the study. The United Nations mortality table of each nation was retrieved in October 2019 from the estimates and standard projection variants data sets.[31] The 5-year precise age-, sex-, and period-specific death rates were interpolated to get 1-year precision assuming a local Gompertz distribution (eMethods in the Supplement).[32] With the 1-year death rate, joint age-sex distribution, distribution of inclusions and country of inclusions, the SMR was computed (eMethods in the Supplement).

### Estimation and Comparison of Pooled SMRs

The worldwide SMR (primary analysis) was pooled in a random-effects linear model without transformation. Continent-specific death rates and SMRs (secondary preplanned analyses) were estimated in single mixed-effects meta-regression DerSimonian-Laird linear models. A comparison of SMRs between continents was performed in a meta-regression with linear adjustment on the expected 1-year death rate of the study (denominator of the SMR, quantitative variable). For subgroup analyses (eg, by age class), the variance-stabilizing square root transformation was applied to the random-effects model, to adapt to small samples with a strong covariance between variance and the proportion (post hoc decision).[33]

Figure 1. Flowchart According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for the Systematic Literature Search




### Estimation and Comparisons of Crude Death Rates and Directly Standardized Rates

The worldwide crude 1-year death rate was pooled (post hoc analysis) in a random-effects linear model, without transformation. The eMethods in the Supplement provides details of the post hoc multivariate analyses of factors associated with death rates. Death rates directly standardized on the pooled age-sex distribution of individual data studies were computed in each individual data study (eMethods in the Supplement).

### Long-term Mortality and Causes of Deaths

Long-term mortality was assessed by the crude (unadjusted) annualized death rates by period (1-2 years, 2-3 years, and 3-5 years) after the inclusion (post hoc analysis) (eMethods in the Supplement). Causes of death were grouped (eg, pneumopathy into infectious diseases) and described by proportions (eMethods in the Supplement).

### Sensitivity Analyses and Analysis of Publication Bias

Because we noticed that 2 studies with passive follow-up had very low SMRs,[3,6] significantly below 1.00, we performed a post hoc sensitivity analysis excluding these 2 studies with the same model as the primary analysis. We assessed the publication bias

by a funnel plot by a graphical interpretation. No multiple testing procedures were used. All analyses were performed in R statistical software, version 3.6 (R Foundation for Statistical Computing). All tests were 2-sided Wald tests at the 5% significance level.

## Results

### Study Selection and Characteristics

The search strategy led to a total of 1488 unique citations eligible after title and abstract screening. After screening, 77 full-text articles were read, and 56 were included in the analysis (**Figure 1**). Among the 56 unique articles[2-12,17-25,27-29,34-66] (12 340 unique patients), individual patient data were available for 16 studies (n = 2122).[2,4,5,10,17-25,27-29] Characteristics of included studies, published from 1978 to April 2020, are summarized in **Table 1**.

The meta-analysis included 36 studies (**Figure 2**) performed in Europe (n = 10 132), including 14 in France (n = 1733),[2,10,18,27-29,37-44] 5 in the UK (n = 2922),[12,51-54] 3 in Sweden (n = 381),[47-49] and 1 in Denmark (n = 3281).[36] A total of 16 studies (n = 1903) were performed in Asia,[6,7,22-25,56-65] including Turkey, Iran, Kuwait, Israel, Taiwan, China, Hong Kong, Singapore, Japan, Thailand, and South Korea. Four studies were included from North and South America: 3 performed in the US (n = 260)[4,5,21] and 1 in Chile (n = 45).[66] The estimated mean (SD) ages, after pooling studies, were 75.6 (13.7) years in the US, 73.8 (13.6) years in Asia, and 78.1 (12.3) years in Europe. Women represented 55.9% and men represented 44.1% of the 12 340 patients (mean [SD] age, 77.3 [12.7] years).

### Estimation and Comparison of Pooled SMRs

The worldwide 1-year SMR (**Figure 3**) was estimated at 2.93 (95% CI, 2.59-3.28; $I^2$ = 85.6%; 56 studies). The τ value was estimated at 1.13, interpreted as the between-study SD of the true SMR. Therefore, the typical difference of SMR between 2 studies was estimated at 1.13, such as would be found for one study with an SMR at 2.00 and another with an SMR at 3.13. The coefficient of variation of the true SMR from study to study was estimated at 1.13/2.93 = 38.5%. The SMR was estimated at 2.77 (95% CI, 2.35-3.19; 36 studies) in Europe, 2.40 (95% CI, 0.89-3.90; 3 studies) in the US, 3.53 (95% CI, 2.85-4.20; 16 studies) in Asia, and 2.03 (95% CI, 0.33-3.74; 1 study) in Chile, with a pooled residual heterogeneity $I^2$ = 86.2%. After adjustment with the expected 1-year death rate in the study (multivariate meta-regression), the difference between SMR for the US compared with Europe was estimated at −0.48 (95% CI, −2.09 to 1.14; $P$ = .56); between Asia and Europe, 0.51 (95% CI, −0.56 to 1.58; $P$ = .35).

### Estimation and Comparison of Crude Death Rates

The crude 1-year death rate from the 56 studies (eFigure 1 in the Supplement) ranged from 0 to 52.4%.[2,3,6] The worldwide crude 1-year death rate (primary analysis) was estimated at 22.0% (95% CI, 19.4%-24.6%; $I^2$ = 89.5%; 56 studies). In Europe, the crude 1-year death rate was estimated at 23.1% (95% CI, 19.9%-26.4%; 36 studies); in the US, 17.7% (95% CI, 6.5%-28.9%; 3 studies); in Asia, 20.8% (95% CI, 16.0%-25.6%; 16 studies); and in Chile, 11.1% (95% CI, 1.8%-20.4%; 1 study). Pooled residual heterogeneity was $I^2$ = 89.2%. Other post hoc meta-regression models are described in the eResults in the Supplement.

### Individual Data Analysis

Sixteen studies[2,4,5,10,17-25,27-29] had individual data available that were analyzed. Of these studies, 9 were conducted in Europe (n = 1103),[2,10,17-20,27-29] 3 in the US (n = 260),[4,5,21] and 4 in Asia (n = 759).[22-25] Of the 9 studies in Europe, 6 (n = 702) were conducted in France.[2,10,18,27-29] The mean (SD) age of all individual data studies pooled together was 76.7 (12.7) (median, 78.7 [range, 18.9-104.3]) years, with a male-to-female sex ratio of 0.814. The precise age and sex distribution are shown in eFigure 2 in the Supplement. The worldwide 1-year random-effects SMR estimated from these 16 studies was 3.02 (95% CI, 2.37-3.75, $I^2$ = 86.0%). The SMRs in age subgroups are described in **Table 2**. The random-effects SMR was not significantly different ($P$ = .78) between men (SMR, 3.00; 95% CI, 2.35-3.73; $I^2$ = 70.2%; 16 studies) and women (SMR, 3.17; 95% CI, 2.34-4.12; $I^2$ = 82.7%; 16 studies). Directly standardized death rates are described in eFigure 3 and the eResults in the Supplement.

### Long-term Mortality

All-cause mortality beyond 1 year, assessed in large studies[25,36,46,53,57] (≥200 patients) with follow-up of at least 3 years and exhaustive mortality reporting, is reported in eTable 2 in the Supplement. The death rates were always higher in the first year (20% to 27%) than in subsequent years (9% to 16%).

### Causes of Death

A total of 690 deaths had their causes reported (eResults in the Supplement). The main causes of death (eTable 3 in the Supplement) were infectious diseases (44.4% at 1 year and 46.1% at any follow-up time) and cardiovascular diseases (33.2% at 1 year and 33.9% at any follow-up time).

### Sensitivity Analyses and Risk of Bias

After exclusion of the 2 studies[3,6] that had an SMR significantly less than 1.00, suggesting a high risk of underestimation of the true death rate, the worldwide 1-year SMR was estimated at 3.04 (95% CI, 2.75-3.34; $I^2$ = 78.1%; 54 studies). There was no evidence of publication bias according to the funnel plot (eFigure 4 in the Supplement). Risk of attrition bias was high (>10% censorship) in 16 studies (28.6%), low in 16 (28.6%) and unclear in 24 (42.9%). The risk of representativity was low in 4 studies (7.1%); risk of misclassification, 48 studies (85.7%); and risk of attrition bias, 16 studies (28.6%) (eFigure 5 and eResults in the Supplement).

## Discussion

This systematic review and meta-analysis is based on aggregate and individual patient data from 56 studies of patients with BP involving 12 340 patients from throughout the world,

Table 1. Characteristics of the Included Studies

| Source | Country | Period | Diagnostic method | Censorship at 1 y, % | Incident only | Follow-up | No. of patients (No. female) | Estimated age, mean (SD), y | Age distribution data |
|---|---|---|---|---|---|---|---|---|---|
| Bastos et al,[17] 2019 | 7[a] | 2015-2018 | Unknown | 8.0 | Yes | Passive | 187 (112) | 81.5 (8.6) | Individual data |
| Monshi et al,[34] 2020 | Austria | 2001-2012 | IF | 8.0 | Yes | Passive | 100 (56) | 79.7 (9.7) | Position, dispersion |
| Sticherling et al,[35] 2017 | Austria, Germany | 2001-2005 | IF | 18.5 | No | Active | 54 (39) | 77.0 (13.7) | Position, dispersion |
| Kibsgaard et al,[36] 2017 | Denmark | 1977-2015 | COD | 0.0 | Yes | Exhaustive | 3281 (1834) | 76.5 (12.6) | Histogram |
| Försti et al,[9] 2016 | Finland | 1985-2012 | IF | 0.0 | Yes | Exhaustive | 198 (102) | 77.5 (10.4) | Position, dispersion |
| Bernard et al,[37] 1986 | France | 1973-1982 | IF | Unknown | Yes | Passive | 57 (31) | 75.4 (10.7) | Position, range |
| De Rocco,[2] 1986 | France | 1975-1984 | IF | 5.8 | Yes | Active | 103 (57) | 75.5 (9.2) | Individual data |
| Devendeville et al,[28] 1990 | France | 1978-1988 | IF | 26.7 | No | Active | 30 (14) | 81.0 (6.5) | Individual data |
| Michel et al,[38] 1999 | France | 1981-1995 | IF | >19.4 | Yes | Passive | 62 (33) | 77.0 (10.0) | Position, range |
| Taïeb et al,[27] 1986 | France | 1982-1984 | IF | 0.0 | Yes | Active | 10 (4) | 74.1 (7.8) | Individual data |
| Roujeau et al,[39] 1998 | France | 1985-1992 | IF | 3.7 | Yes | Active | 217 (120) | 79.0 (11.0) | Position, dispersion |
| Depaire,[29] 1995 | France | 1993-1995 | IF | 20.0 | No | Active | 20 (14) | 80.5 (13.7) | Individual data |
| Joly et al,[18] 2002 | France | 1996-1998 | IF | 38.1 | Yes | Active | 341 (214) | 81.4 (9.6) | Individual data |
| Chevalier et al,[40] 2016 | France | 1997-2011 | IF | Unknown | Yes | Passive | 178 (122) | 79.5 (11.8) | Position, dispersion |
| Joly et al,[10] 2012 | France | 2001-2004 | IF | 35.9 | Yes | Passive | 198 (121) | 82.3 (9.7) | Individual data |
| Nespoulous et al,[41] 2018 | France | 2004-2017 | Unknown | Unknown | Yes | Unknown | 329 (187) | 83.3 (8.7) | Position |
| Cordel et al,[42] 2009 | France | 2006-2009 | IF | Unknown | Yes | Active | 26 (17) | 86.3 (8.5) | Position, dispersion |
| Cantegrit et al,[43] 2019 | France | 2010-2015 | IF | Unknown | Yes | Passive | 67 (46) | 82.0 (8.4) | Position, dispersion |
| Clapé et al,[44] 2020 | France | 2013-2017 | Unknown | 8.4 | Yes | Active | 95 (60) | 81.8 (9.4) | Position, dispersion |
| Rzany et al,[11] 2002 | Germany | 1987-1997 | IF | <8.1 | Yes | Active | 369 (199) | 77.8 (11.1) | Position, dispersion |
| Kyriakis et al,[3] 1999 | Greece | 1987-1988 | IF | Unknown | No | Unknown | 27 (13) | 74.8 (10.6) | Position, dispersion |
| Serwin et al,[45] 2014 | Poland | 1999-2012 | IF | <41.0 | Yes | Passive | 122 (70) | 74.2 (12.1) | Position, dispersion |
| Kalinska-Bienias et al,[46] 2017 | Poland | 2000-2013 | IF | 0.0 | Yes | Exhaustive | 205 (131) | 76.2 (11.8) | Histogram |
| Gual et al,[19] 2014 | Spain | 1989-2010 | IF | 10.9 | Yes | Passive | 101 (49) | 77.7 (11.5) | Individual data |
| Garcia-Doval et al,[8] 2005 | Spain | 1998-2003 | IF | 15.4 | Yes | Active | 26 | 76.5 (11.3) | Position, range |
| Heilborn et al,[47] 1999 | Sweden | 1996-1997 | IF | 0.0 | Yes | Active | 11 (7) | 80.3 (8.2) | Position, range |
| Kjellman et al,[48] 2008 | Sweden | 1999-2003 | IF | Unknown | Yes | Passive | 138 (79) | 81.0 (10.6) | Position, range |
| Fisch et al,[49] 2018 | Sweden | 2006-2015 | Unknown | Unknown | Yes | Unknown | 232 (122) | 84.6 (6.7) | Position, dispersion |
| Cortés et al,[50] 2012 | Switzerland | 1990-2003 | IF | Unknown | Yes | Active | 60 (34) | 79.5 (11.6) | Position, dispersion |
| Cortés et al,[20] 2011 | Switzerland | 2001-2002 | IF | 20.0 | Yes | Passive | 113 (66) | 78.1 (12.4) | Individual data |
| Burton et al,[51] 1978 | UK | 1973-1973 | IF | Unknown | Yes | Active | 25 (16) | 74.8 (14.0) | Position |
| Venning and Wojnarowska,[12] 1992 | UK | 1975-1988 | IF | 15.9 | Yes | Passive | 82 (44) | 73.9 (11.0) | Position, range |
| Gudi et al,[52] 2005 | UK | 1991-2001 | IF | Unknown | Yes | Passive | 83 (50) | 79.2 (12.8) | Histogram |
| Persson et al,[53] 2020 | UK | 1998-2017 | COD | 0.0 | Yes | Exhaustive | 2658 (1497) | 77.9 (13.9) | Histogram |
| Angit et al,[54] 2011 | UK | 2006-2007 | IF | 23.0 | Yes | Passive | 74 (39) | 79.7 (9.4) | Position, range |
| Chalmers et al,[55] 2017 | UK and Germany | 2009-2013 | IF | 23.3 | No | Active | 253 (120) | 77.7 (9.7) | Position, dispersion |
| Brick et al,[21] 2014 | US | 1963-2009 | IF | 4.9 | Yes | Passive | 82 (46) | 77.7 (12.0) | Individual data |
| Colbert et al,[5] 2004 | US | 1997-2002 | IF | 18.4 | Yes | Passive | 32 (15) | 77.0 (12.2) | Individual data |
| Parker et al,[4] 2008 | US | 1998-2003 | IF | 0.0 | Yes | Exhaustive | 146 (89) | 74.2 (14.6) | Individual data |
| Li et al,[22] 2013 | China | 1991-2011 | IF | Unknown | Yes | Active | 140 (58) | 64.7 (13.5) | Individual data |
| Zhang et al,[23] 2013 | China | 2005-2010 | IF | 23.4 | Yes | Passive | 94 (41) | 71.1 (12.7) | Individual data |
| Chang,[7] 2013 | Hong Kong | 2002-2011 | IF | Unknown | Yes | Unknown | 121 | 79.9 (9.9) | Position |
| Mokhtari et al,[56] 2019 | Iran | 2008-2016 | IF | 36.2 | Yes | Passive | 69 (41) | 69.6 (13.6) | Position, dispersion |
| Kridin et al,[57] 2019 | Israel | 2000-2015 | IF | 0.0 | Yes | Exhaustive | 287 (168) | 77.6 (12.1) | Position, dispersion |
| Rozenblat et al,[58] 2019 | Israel | 2009-2016 | IF | Unknown | Yes | Active | 87 (40) | 79.6 (9.1) | Histogram |
| Kanamori et al,[59] 2004 | Japan | 1988-2003 | Unknown | Unknown | Yes | Unknown | 26 (15) | 73.1 (14.3) | Position, range |

(continued)

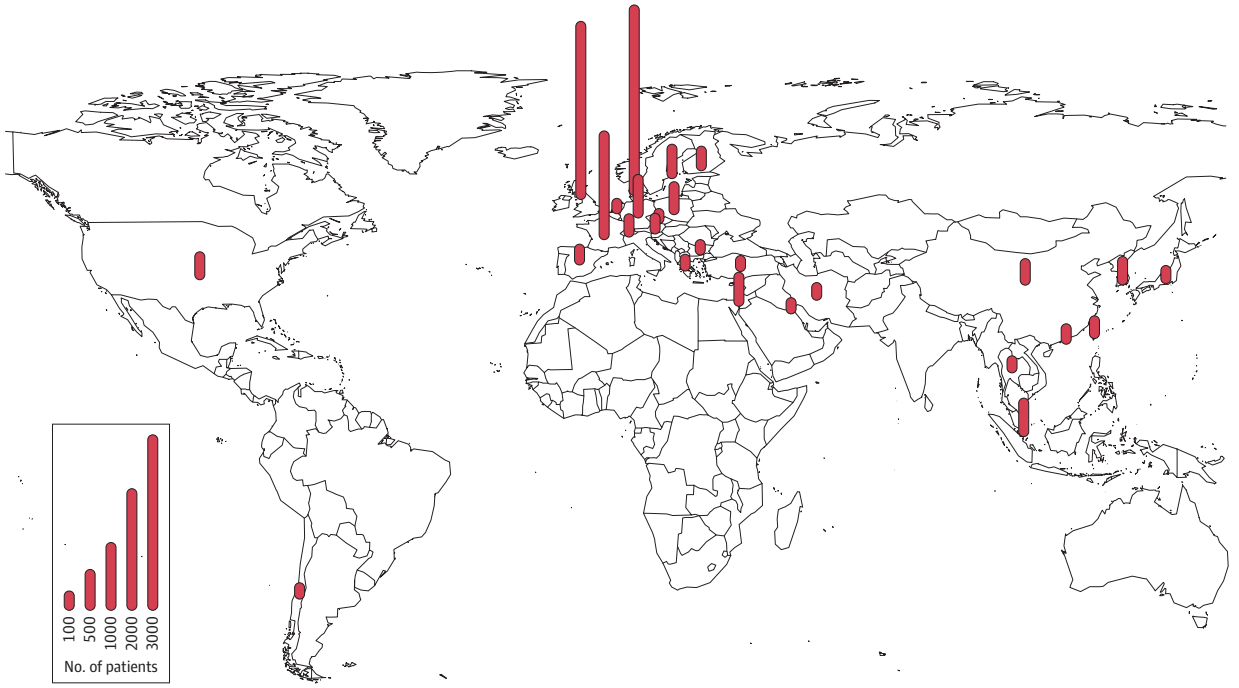
Table 1. Characteristics of the Included Studies (continued)

| Source | Country | Period | Diagnostic method | Censorship at 1 y, % | Incident only | Follow-up | No. of patients (No. female) | Estimated age, mean (SD), y | Age distribution data |
|---|---|---|---|---|---|---|---|---|---|
| Sasai et al,[60] 2015 | Japan | 2003-2012 | Unknown | Unknown | Yes | Passive | 52 (29) | 84.3 (6.3) | Position, range |
| Lee and Kim,[24] 2014 | South Korea | 1993-2013 | IF | Unknown | Yes | Passive | 166 (83) | 69.9 (14.3) | Individual data |
| Jeon et al,[61] 2018 | South Korea | 2006-2013 | IF | Unknown | Yes | Active | 103 (50) | 74.4 (10.6) | Histogram |
| Nanda et al,[62] 2006 | Kuwait | 1991-2005 | IF | 14.0 | Yes | Passive | 43 (36) | 65.2 (18.8) | Histogram |
| Phoon et al,[63] 2015 | Singapore | 2002-2011 | IF | Unknown | Yes | Passive | 97 (48) | 79.0 (11.0) | Position, dispersion |
| Cai et al,[25] 2014 | Singapore | 2004-2009 | IF | 0.0 | Yes | Exhaustive | 359 (187) | 75.7 (12.6) | Individual data |
| Wei,[64] 2018 | Taiwan | 2012-2017 | IF | Unknown | Yes | Unknown | 163 (78) | 70.0 (12.3) | Position, dispersion |
| Kulthanan et al,[65] 2011 | Thailand | 1991-2009 | IF | Unknown | Yes | Passive | 58 (42) | 69.3 (14.7) | Position, dispersion |
| Kızılyel et al,[6] 2015 | Turkey | 2003-2013 | IF | Unknown | Yes | Passive | 38 (23) | 62.4 (21.0) | Position, dispersion |
| Carvajal Aguilera et al,[66] 2020 | Chile | 2005-2017 | IF | Unknown | Yes | Passive | 45 (24) | 72.2 (16.6) | Position, dispersion |

Abbreviations: COD, code from a medical dictionary (eg, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*); IF, direct or indirect immunofluorescence plus standard histologic evaluation.

[a] Includes France, the Netherlands, Greece, Bulgaria, Poland, Germany, and Czech Republic.

Figure 2. Geographic Distribution of Patients With Bullous Pemphigoid at Inclusion in Studies Included in the Meta-analysis




including Europe, Asia, the US, and Chile. We found a 2.93-fold higher risk of all-cause death at 1 year in patients with BP compared with the general population in the same countries after adjusting for age and sex in a meta-analysis with a high heterogeneity ($I^2$ = 85.6%, τ = 1.13). There was no significant difference between continents.

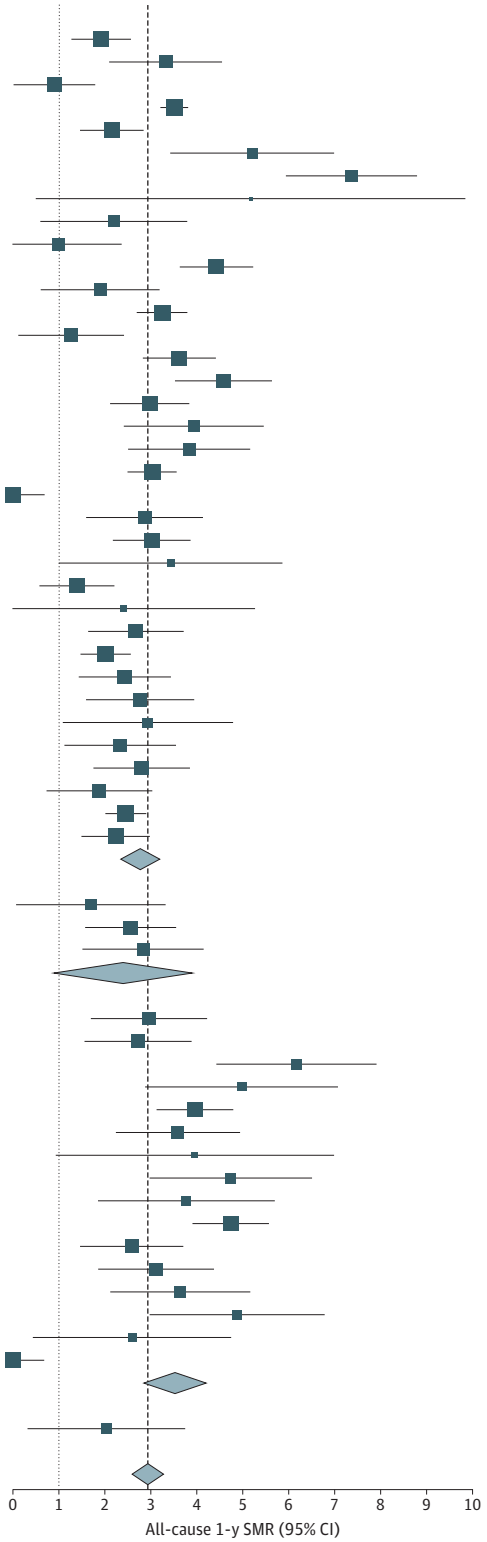
Kridin et al[57] performed a meta-analysis of death rates, finding a worldwide 1-year death rate similar to ours (23.5% vs 22.0%). With our combined aggregate-individual data, we could assess SMRs in all countries and compare SMRs between continents. Moreover, we analyzed all-cause mortality beyond 1 year on the most robust studies.

Roujeau et al[39] found a high death rate (41% at 1 year). We confirm the fact that this study has one of the highest death rates (eFigure 1 in the Supplement) we have seen. Korman[67] hypothesized that the study of Roujeau et al[39] may have a selection bias, favoring the inclusion of severe generalized forms. Korman also hypothesized that ethnic differences could be the cause of higher death rates in France; we did not confirm this latter hypothesis, because most other French studies found much lower death rates.[18,28,29,38,41-44]

We showed a higher all-cause mortality during the first year of follow-up than thereafter. This finding suggests that the first-year mortality may be due to BP itself and adverse effects of

Figure 3. Forest Plot of All-Cause 1-Year Standardized Mortality Ratio (SMR)

| Source | Country | No. of patients | All-cause 1-y SMR (95% CI) | Weight, % |
|---|---|---|---|---|
| Europe | | | | |
| Bastos et al,[17] 2019 | 7[a] | 187 | 1.92 (1.28-2.56) | 2.20 |
| Monshi et al,[34] 2020 | Austria | 100 | 3.32 (2.10-4.54) | 1.83 |
| Sticherling et al,[35] 2017 | Austria and Germany | 54 | 0.90 (0.02-1.78) | 2.06 |
| Kibsgaard et al,[36] 2017 | Denmark | 3281 | 3.51 (3.22-3.80) | 2.34 |
| Försti et al,[9] 2016 | Finland | 198 | 2.15 (1.47-2.83) | 2.18 |
| Bernard et al,[37] 1986 | France | 57 | 5.20 (3.43-6.98) | 1.45 |
| De Rocco,[2] 1986 | France | 103 | 7.37 (5.95-8.78) | 1.69 |
| Taïeb et al,[27] 1986 | France | 10 | 5.17 (0.51-9.83) | 0.44 |
| Devendeville et al,[28] 1990 | France | 30 | 2.19 (0.61-3.78) | 1.57 |
| Depaire,[29] 1995 | France | 20 | 0.99 (0.00-2.35) | 1.73 |
| Roujeau et al,[39] 1998 | France | 217 | 4.43 (3.64-5.22) | 2.12 |
| Michel et al,[38] 1999 | France | 62 | 1.90 (0.62-3.18) | 1.78 |
| Joly et al,[18] 2002 | France | 341 | 3.24 (2.70-3.78) | 2.25 |
| Cordel et al,[42] 2009 | France | 26 | 1.27 (0.13-2.41) | 1.88 |
| Joly et al,[10] 2012 | France | 198 | 3.62 (2.84-4.41) | 2.12 |
| Chevalier et al,[40] 2016 | France | 178 | 4.58 (3.54-5.63) | 1.95 |
| Nespoulous et al,[41] 2018 | France | 329 | 2.98 (2.12-3.83) | 2.08 |
| Cantegrit et al,[43] 2019 | France | 67 | 3.93 (2.42-5.45) | 1.63 |
| Clapé et al,[44] 2020 | France | 95 | 3.83 (2.52-5.15) | 1.76 |
| Rzany et al,[11] 2002 | Germany | 369 | 3.03 (2.50-3.55) | 2.26 |
| Kyriakis et al,[3] 1999 | Greece | 27 | 0.00 (0.00-0.68) | 2.18 |
| Serwin et al,[45] 2014 | Poland | 122 | 2.86 (1.60-4.12) | 1.80 |
| Kalinska-Bienias et al,[46] 2017 | Poland | 205 | 3.02 (2.18-3.85) | 2.09 |
| Garcia-Doval et al,[8] 2005 | Spain | 26 | 3.43 (1.01-5.85) | 1.08 |
| Gual et al,[19] 2014 | Spain | 101 | 1.39 (0.59-2.20) | 2.10 |
| Heilborn et al,[47] 1999 | Sweden | 11 | 2.40 (0.00-5.26) | 0.89 |
| Kjellman et al,[48] 2008 | Sweden | 138 | 2.68 (1.65-3.70) | 1.96 |
| Fisch et al,[49] 2018 | Sweden | 232 | 2.02 (1.48-2.55) | 2.25 |
| Cortés et al,[20] 2011 | Switzerland | 113 | 2.44 (1.44-3.43) | 1.98 |
| Cortés et al,[50] 2012 | Switzerland | 60 | 2.77 (1.60-3.93) | 1.87 |
| Burton et al,[51] 1978 | UK | 25 | 2.94 (1.10-4.78) | 1.41 |
| Venning and Wojnarowska,[12] 1992 | UK | 82 | 2.33 (1.13-3.54) | 1.84 |
| Gudi et al,[52] 2005 | UK | 83 | 2.80 (1.76-3.84) | 1.95 |
| Angit et al,[54] 2011 | UK | 74 | 1.88 (0.74-3.02) | 1.88 |
| Persson et al,[53] 2020 | UK | 2658 | 2.46 (2.02-2.89) | 2.30 |
| Chalmers et al,[55] 2017 | UK and Germany | 253 | 2.23 (1.50-2.97) | 2.15 |
| Total Europe (random effects) | | 10 132 | 2.77 (2.35-3.19) | 67.1 |
| US | | | | |
| Colbert et al,[5] 2004 | US | 32 | 1.70 (0.08-3.31) | 1.55 |
| Parker et al,[4] 2008 | US | 146 | 2.56 (1.58-3.54) | 1.99 |
| Brick et al,[21] 2014 | US | 82 | 2.83 (1.52-4.14) | 1.77 |
| Total US (random effects) | | 260 | 2.40 (0.89-3.90) | 5.31 |
| Asia | | | | |
| Li et al,[22] 2013 | China | 140 | 2.96 (1.71-4.21) | 1.80 |
| Zhang et al,[23] 2013 | China | 94 | 2.72 (1.57-3.88) | 1.87 |
| Chang,[7] 2013 | Hong Kong | 121 | 6.17 (4.44-7.90) | 1.48 |
| Mokhtari et al,[56] 2019 | Iran | 69 | 4.97 (2.89-7.06) | 1.26 |
| Kridin et al,[57] 2019 | Israel | 287 | 3.96 (3.14-4.78) | 2.09 |
| Rozenblat et al,[58] 2019 | Israel | 87 | 3.59 (2.25-4.93) | 1.74 |
| Kanamori et al,[59] 2004 | Japan | 26 | 3.96 (0.94-6.98) | 0.83 |
| Sasai et al,[60] 2015 | Japan | 52 | 4.74 (2.98-6.50) | 1.46 |
| Nanda et al,[62] 2006 | Kuwait | 43 | 3.77 (1.86-5.69) | 1.36 |
| Cai et al,[25] 2014 | Singapore | 359 | 4.74 (3.92-5.56) | 2.10 |
| Phoon et al,[63] 2015 | Singapore | 97 | 2.58 (1.47-3.70) | 1.90 |
| Lee and Kim,[24] 2014 | South Korea | 166 | 3.11 (1.87-4.36) | 1.81 |
| Jeon et al,[61] 2018 | South Korea | 103 | 3.64 (2.13-5.15) | 1.62 |
| Wei,[64] 2018 | Taiwan | 163 | 4.88 (2.99-6.77) | 1.38 |
| Kulthanan et al,[65] 2011 | Thailand | 58 | 2.59 (0.44-4.74) | 1.23 |
| Kızılyel et al,[6] 2015 | Turkey | 38 | 0.00 (0.00-0.67) | 2.18 |
| Total Asia (random effects) | | 1903 | 3.53 (2.85-4.20) | 26.1 |
| South America | | | | |
| Carvajal Aguilera et al,[66] 2020 | Chile | 45 | 2.03 (0.33-3.74) | 1.50 |
| Worldwide (random effects) | | 12 340 | 2.93 (2.59-3.28) | 100 |
| Heterogeneity: $\chi^2_{55}$ = 382 ($P$ <.001); $I^2$ = 85.6% | | | | |




Different sizes of markers indicate different weights. Wide points of diamonds indicate SMR; ends of diamonds, 95% CI.

[a] Includes France, the Netherlands, Greece, Bulgaria, Poland, Germany, and Czech Republic.

Table 2. All-Cause 1-Year SMR and Absolute Risk Differences of Bullous Pemphigoid by Age[a]

| Variable | Age group, y | | | | |
|---|---|---|---|---|---|
| | <60 (n = 210) | 60-69 (n = 297) | 70-79 (n = 631) | 80-89 (n = 758) | >90 (n = 226)[b] |
| 1-y death rate, No. (%) | | | | | |
| Expected | 0.9 (0.42) | 5.1 (1.7) | 24.8 (3.93) | 72.5 (9.55) | 45.7 (20.22) |
| Observed | 15 (7.14) | 40 (13.47) | 121 (19.18) | 224 (29.55) | 88 (38.94) |
| Absolute risk difference estimate (95% CI), % | | | | | |
| Fixed effects | 6.7 (3.2-10.2) | 11.8 (7.9-15.7) | 15.2 (12.2-18.3) | 20.0 (16.7-23.2) | 18.7 (12.4-25.0) |
| Random effects | 10.2 (6.1-15.2) | 13.5 (9.7-17.8) | 14.1 (9.0-20.1) | 21.8 (13.4-31.4) | 18.8 (8.6-30.6) |
| SMR (95% CI), % | | | | | |
| Fixed effects | 17.4 (9.1-25.8) | 8.0 (5.7-10.3) | 4.9 (4.1-5.7) | 3.1 (2.8-3.4) | 1.9 (1.6-2.2) |
| Random effects | 25.4 (15.2-38.1) | 8.9 (6.1-12.1) | 4.6 (3.2-6.1) | 3.1 (2.4-4.0) | 1.9 (1.4-2.4) |

Abbreviation: SMR standardized mortality ratio.

[a] Includes the 16 studies where individual data are available. Data are estimated in random effects (planned analysis) and fixed effects (sensitivity analysis) models.

[b] Includes 6 patients aged 100 years or older.

treatment, whereas some part of the excess mortality beyond the first year of follow-up may be additionally due to associated chronic disorders, which are particularly frequent in patients with BP.[7,13,40,46] As expected, infections and cardiovascular disorders, which are favored by the older age of patients with BP and the use of corticosteroids and immunosuppressive drugs, were the main cause of death observed in this meta-analysis.

As shown in Table 2, the 1-year SMR decreases greatly with age, although the absolute risk difference at 1 year increases with age. The very high SMR (>15.00) in younger patients (<60 years) with fewer associated disorders confirms the fact that BP or its treatment can be deadly. Older patients may either die of their BP (as demonstrated by the high absolute risk difference) or of associated disorders, as demonstrated by the high expected risk of death without BP and lower SMR. Because SMRs depend on age, they cannot be used to reliably compare the prognosis of BP in different populations with very different average ages. Instead, direct standardization should be performed.

### Strengths and Limitations

An important strength of our study was the combination of individual and aggregate data, allowing inclusion of all studies reporting basic age statistics and 1-year crude death rate (56 studies), including the ones obtained by graphical extraction. However, our data were limited because there were few US studies, only 1 South American study, and no African studies. Many studies had a poor quality of follow-up, with 1-year loss to follow-up as high as 38%, and 2 studies had SMRs significantly less than 1.00, probably because patients who died were lost to follow-up.[3,6] Beyond 1 year, mortality data were too scarce to be reliably included in the meta-analysis. The poor quality of follow-up may explain another part of the high heterogeneity we found ($I^2$ = 85.6%). Because many patients were recruited at the hospital, with variable indications of hospitalizations, a differential selection bias may explain part of the heterogeneity. Although most studies recruited older patients, some of them recruited younger patients[6,22,62] who have a different prognosis (lower death rate but higher SMR). Inclusion of inpatients could lead to a selection bias with an overestimation of the death rate, such as suggested by Chang.[7] There was a high risk of misclassification bias in the 2 studies using registry linking by code from medical dictionaries.[36,53] Moreover, the exact clinical, histological, and immunological diagnostic criteria varied from study to study and were often poorly reported, with a possible evolution with time (from 1963 to 2018).

Causes of death were recorded and reported from medical records without standardized methods in all articles except that of Cai et al,[25] who used a national death registry. Even in the study by Cai et al,[25] the death registry may include possible conventions and practices that differ from those of other countries. Moreover, causes of deaths were sometimes grouped without standardization. One article may include pneumopathy in respiratory causes, whereas another would include it in infectious diseases. When multiple causes of deaths were identified, only one of them was reported by authors; the selection method was never reported. Many causes of deaths (157 of 690 [22.8%]) were unknown in articles reporting causes of death, with probable selection bias (eg, fewer missing data in hospital deaths).

## Conclusions

This meta-analysis found that patients with BP had a major increase in the risk of all-cause death in all continents, with a nonsignificant difference between continents. However, the low number of US studies cannot allow us to conclude that there is no difference.

ARTICLE INFORMATION

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## REFERENCES

1. Bastuji-Garin S, Joly P, Lemordant P, et al; French Study Group for Bullous Diseases. Risk factors for bullous pemphigoid in the elderly: a prospective case-control study. *J Invest Dermatol*. 2011;131(3):637-643. doi:10.1038/jid.2010.301

2. De Rocco F. Pemphigoide bulleuse: devenir, facteurs pronostiques, traitement: a propos de 130 observations. Master's thesis. Université Lille-II; 1986.

3. Kyriakis KP, Paparizos VA, Panteleos DN, Tosca AD. Re-evaluation of the natural course of bullous pemphigoid: a prospective study. *Int J Dermatol*. 1999;38(12):909-913. doi:10.1046/j.1365-4362.1999.00754.x

4. Parker SRS, Dyson S, Brisman S, et al. Mortality of bullous pemphigoid: an evaluation of 223 patients and comparison with the mortality in the general population in the United States. *J Am Acad Dermatol*. 2008;59(4):582-588. doi:10.1016/j.jaad.2008.07.022

5. Colbert RL, Allen DM, Eastwood D, Fairley JA. Mortality rate of bullous pemphigoid in a US medical center. *J Invest Dermatol*. 2004;122(5):1091-1095. doi:10.1111/j.0022-202X.2004.22504.x

6. Kızılyel O, Elmas ÖF, Bilen H, et al. Bullous pemphigoid in Erzurum: a 10 year retrospective study. *Turkderm*. 2015; 49(1):66-69. doi:10.4274/turkderm.12144

7. Chang M. Bullous pemphigoid: a review of patients managed in hospital and its risk factors for poor prognosis and early mortality. Abstract presented at: Hong Kong Society of Dermatology and Venereology Annual Scientific Meeting; May 26, 2013; Hong Kong.

8. Garcia-Doval I, Conde Taboada A, Cruces Prado MJ. Sepsis associated with dermatologic hospitalization is not the cause of high mortality of bullous pemphigoid in Europe. *J Invest Dermatol*. 2005;124(3):666-667. doi:10.1111/j.0022-202X.2005.23628.x

9. Försti A-K, Jokelainen J, Timonen M, Tasanen K. Risk of death in bullous pemphigoid: a retrospective database study in Finland. *Acta Derm Venereol*. 2016;96(6):758-761.

10. Joly P, Baricault S, Sparsa A, et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol*. 2012;132(8):1998-2004. doi:10.1038/jid.2012.35

11. Rzany B, Partscht K, Jung M, et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol*. 2002;138(7):903-908. doi:10.1001/archderm.138.7.903

12. Venning VA, Wojnarowska F. Lack of predictive factors for the clinical course of bullous pemphigoid. *J Am Acad Dermatol*. 1992;26(4):585-589. doi:10.1016/0190-9622(92)70085-T

13. Joly P, Benichou J, Lok C, et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol*. 2005;141(6):691-698. doi:10.1001/archderm.141.6.691

14. National Institute for Health Research. Mortality in bullous pemphigoid: a systematic review and meta-analysis combining individual patient data and aggregate data. CRD42020164085. Accessed November 29, 2020. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=164085

15. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008

16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535

17. Bastos S, Hebert V, Vassileva S, et al. Efficacy and tolerance of prednisone at 0.5mg/kg/day in initial treatment of bullous pemphigoid [in French]. *Ann Dermatol Vénéréol*. 2019;146(12, suppl):A61-A62. doi:10.1016/j.annder.2019.09.038

18. Joly P, Roujeau J-C, Benichou J, et al; Bullous Diseases French Study Group. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med*. 2002;346(5):321-327. doi:10.1056/NEJMoa011592

19. Gual A, Mascaró JM Jr, Rojas-Farreras S, Guilabert A, Julià M, Iranzo P. Mortality of bullous pemphigoid in the first year after diagnosis: a retrospective study in a Spanish medical centre. *J Eur Acad Dermatol Venereol*. 2014;28(4):500-506. doi:10.1111/jdv.12065

20. Cortés B, Marazza G, Naldi L, Combescure C, Borradori L; Autoimmune Bullous Disease Swiss Study Group. Mortality of bullous pemphigoid in Switzerland: a prospective study. *Br J Dermatol*. 2011;165(2):368-374. doi:10.1111/j.1365-2133.2011.10413.x

21. Brick KE, Weaver CH, Lohse CM, et al. Incidence of bullous pemphigoid and mortality of patients with bullous pemphigoid in Olmsted County, Minnesota, 1960 through 2009. *J Am Acad Dermatol*. 2014;71(1):92-99. doi:10.1016/j.jaad.2014.02.030

22. Li J, Zuo Y-G, Zheng H-Y. Mortality of bullous pemphigoid in China. *JAMA Dermatol*. 2013;149(1):106-108. doi:10.1001/archdermatol.2012.2994

23. Zhang L-M, Wu J, Xiao T, et al. Treatment and mortality rate of bullous pemphigoid in China: a hospital-based study. *Eur J Dermatol*. 2013;23(1):94-98. doi:10.1684/ejd.2012.1906

24. Lee JH, Kim S-C. Mortality of patients with bullous pemphigoid in Korea. *J Am Acad Dermatol*. 2014;71(4):676-683. doi:10.1016/j.jaad.2014.05.006

25. Cai SCS, Allen JC, Lim YL, Chua SH, Tan SH, Tang MBY. Mortality of bullous pemphigoid in Singapore: risk factors and causes of death in 359 patients seen at the National Skin Centre. *Br J Dermatol*. 2014;170(6):1319-1326. doi:10.1111/bjd.12806

26. Tedbirt B, Andrieu E, Ezzedine K, et al. Mortality in bullous pemphigoid: individual patient data meta-analysis on 12 international studies [in French]. *Ann Dermatol Vénéréol*. 2019;146(12, suppl):A96. doi:10.1016/j.annder.2019.09.098

27. Taïeb A, Klene C, Maleville J. Immediate treatment of bullous pemphigus with a corticosteroid-cyclophosphamide combination [in French]. *Ann Dermatol Venereol*. 1986;113(12):1223-1229.

28. Devendeville A, Lok C, Buleux E, Denoeux JP, Lienard J. Bullous pemphigoid and its prognostic: retrospective study of 33 patients [in French]. *Rev Gériatr*. 1991;16(6):249-254.

29. Depaire F. Traitement des pemphigoides bulleuses par tétracyclines. Master's thesis. Université Montpellier I; 1995.

30. Wells GA, Shea B, O'Connell D, et al; Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Published 1999. Accessed November 29, 2020. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

31. World Population Prospects, Population Division, United Nations. Standard projections (estimates and projection variants). Published August 2019. Accessed October 29, 2019. https://population.un.org/wpp/Download/Standard/Mortality/

**32**. Pflaumer P. *Life Table Forecasting with the Gompertz Distribution*. American Statistical Association; 2007. doi:10.17877/DE290R-8212

**33**. Trikalinos TA, Trow P, Schmid CH. Simulation-based comparison of methods for meta-analysis of proportions and rates. Agency for Healthcare Research and Quality; 2013. Accessed November 29, 2020. https://www.ncbi.nlm.nih.gov/books/NBK179162/

**34**. Monshi B, Gulz L, Piringer B, et al. Anti-BP180 autoantibody levels at diagnosis correlate with 1-year mortality rates in patients with bullous pemphigoid. *J Eur Acad Dermatol Venereol*. 2020; 34(7):1583-1589. doi:10.1111/jdv.16363

**35**. Sticherling M, Franke A, Aberer E, et al. An open, multicentre, randomized clinical study in patients with bullous pemphigoid comparing methylprednisolone and azathioprine with methylprednisolone and dapsone. *Br J Dermatol*. 2017;177(5):1299-1305. doi:10.1111/bjd.15649

**36**. Kibsgaard L, Rasmussen M, Lamberg A, Deleuran M, Olesen AB, Vestergaard C. Increased frequency of multiple sclerosis among patients with bullous pemphigoid: a population-based cohort study on comorbidities anchored around the diagnosis of bullous pemphigoid. *Br J Dermatol*. 2017;176(6):1486-1491. doi:10.1111/bjd.15405

**37**. Bernard P, Venot J, Rommel A, Bonnetblanc JM, Texier L. Bullous pemphigoid: a prognostic study: review of fifty-seven observations [in French]. *Sem Hôp Paris*. 1986; 62(18):1229-1232.

**38**. Michel JL, Bourdet JF, Perrot JL, et al. Corticosteroid treatment, risk factor of pemphigoid: retrospective analysis of 62 cases [in French]. *Nouv Dermatol*. 1999;18:331-335.

**39**. Roujeau JC, Lok C, Bastuji-Garin S, Mhalla S, Enginger V, Bernard P. High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol*. 1998;134(4):465-469. doi:10.1001/archderm.134.4.465

**40**. Chevalier V, Barbe C, Reguiai Z, Plée J, Grange F, Bernard P. Impact of neurological diseases on the prognosis of bullous pemphigoid: a retrospective study of 178 patients [in French]. *Ann Dermatol Venereol*. 2016;143(3):179-186. doi:10.1016/j.annder.2015.12.016

**41**. Nespoulous L, Dalmay F, Bedane C, Assikar S. Prognostic factors of bullous pemphigoid in 329 patients [in French]. *Ann Dermatol Vénéréol*. 2018; 145(12, suppl):S164-S165. doi:10.1016/j.annder.2018.09.219

**42**. Cordel N, Renier M, Samyn A, Fauvel C, Hope-Rapp E, Gilbert D; la Société de dermatologie de la Guadeloupe. Epidemiology of bullous pemphigoid in Guadeloupe (French West Indies) [in French]. *Ann Dermatol Venereol*. 2009;136(12): 907-909. doi:10.1016/j.annder.2009.10.182

**43**. Cantegrit T, Merklen C, Birckel E, et al. One- and three-year mortality in patients with bullous pemphigoid treated as first-line with intensive local corticosteroid therapy [in French]. *Ann Dermatol Vénéréol*. 2019;146(12, suppl):A161. doi:10.1016/j.annder.2019.09.215

**44**. Clapé A, Muller C, Plée J, Viguier M, Vanhaecke C, Bernard P. Feasibility and healthcare costs of superpotent topical corticosteroid therapy in bullous pemphigoid: a prospective, observational study in an academic centre in France. *Br J Dermatol*. 2020;183(4):775-776. doi:10.1111/bjd.19151

**45**. Serwin AB, Musialkowska E, Piascik M. Incidence and mortality of bullous pemphigoid in north-east Poland (Podlaskie Province), 1999-2012: a retrospective bicentric cohort study. *Int J Dermatol*. 2014;53(10):e432-e437. doi:10.1111/ijd.12492

**46**. Kalinska-Bienias A, Lukowska-Smorawska K, Jagielski P, Kowalewski C, Wozniak K. Mortality in bullous pemphigoid and prognostic factors in 1st and 3rd year of follow-up in specialized centre in Poland. *Arch Dermatol Res*. 2017;309(9):709-719. doi:10.1007/s00403-017-1772-x

**47**. Heilborn JD, Ståhle-Bäckdahl M, Albertioni F, Vassilaki I, Peterson C, Stephansson E. Low-dose oral pulse methotrexate as monotherapy in elderly patients with bullous pemphigoid. *J Am Acad Dermatol*. 1999;40(5, pt 1):741-749. doi:10.1016/S0190-9622(99)70156-8

**48**. Kjellman P, Eriksson H, Berg P. A retrospective analysis of patients with bullous pemphigoid treated with methotrexate. *Arch Dermatol*. 2008; 144(5):612-616. doi:10.1001/archderm.144.5.612

**49**. Fisch A, Morin L, Talme T, Gallais Sérézal I. Bullous pemphigoid treated with methotrexate: safety profile based on renal function at diagnosis [in French]. *Ann Dermatol Vénéréol*. 2018;145(12, suppl):S48. doi:10.1016/j.annder.2018.09.006

**50**. Cortés B, Khelifa E, Clivaz L, et al. Mortality rate in bullous pemphigoid: a retrospective monocentric cohort study. *Dermatology*. 2012;225(4):320-325. doi:10.1159/000345625

**51**. Burton JL, Harman RR, Peachey RD, Warin RP. Azathioprine plus prednisone in treatment of pemphigoid. *BMJ*. 1978;2(6146):1190-1191. doi:10.1136/bmj.2.6146.1190

**52**. 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(2):424-427. doi:10.1111/j.1365-2133.2005.06662.x

**53**. Persson MSM, Harman KE, Vinogradova Y, et al. Incidence, prevalence and mortality of bullous pemphigoid in England 1998-2017: a population-based cohort study. *Br J Dermatol*. 2020. doi:10.1111/bjd.19022

**54**. Angit C, King C, Lister KR. Regional audit of bullous pemphigoid. *J Am Acad Dermatol*. 2011;64 (2 suppl 1):AB94.

**55**. Chalmers JR, Wojnarowska F, Kirtschig G, et al. A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid: the Bullous Pemphigoid Steroids and Tetracyclines (BLISTER) trial. *Health Technol Assess*. 2017;21(10):1-90. doi:10.3310/hta21100

**56**. Mokhtari F, Fariba I, Radfar S, Asilian Mahabadi A, Faghihi G, Hosseini SM. Epidemiological survey of the patients with bullous pemphigoid hospitalized in Alzahra Hospital, Isfahan, Iran, during the years 2006-2015. *J Isfahan Med School*. 2019;36(507): 1491-1497. doi:10.22122/jims.v36i507.10647

**57**. Kridin K, Shihade W, Bergman R. Mortality in patients with bullous pemphigoid: a retrospective cohort study, systematic review and meta-analysis. *Acta Derm Venereol*. 2019;99(1):72-77.

**58**. Rozenblat M, Halaj A, Rozenblat T, et al. Mortality and risk factors among Israeli bullous pemphigoid patients. *Arch Dermatol Res*. 2019;311 (1):19-27. doi:10.1007/s00403-018-1875-z

**59**. Kanamori S, Nagata T, Uezato H, Nonaka S. Statistical observation of bullous pemphigoid patients reported at the Dermatology Clinic, Ryukyus University Hospital [in Japanese]. *Nishi Nihon Hifuka*. 2004;66:183-187. doi:10.2336/nishinihonhifu.66.183

**60**. Sasai S, Asano M, Numata Y, et al A retrospective statistical analysis of prognostic factors for a lethal outcome in 52 elderly Japanese patients with bullous pemphigoid [in Japanese]. *Jap J Dermatol*. 2015;125(2):235-241. doi:10.14924/dermatol.125.235

**61**. Jeon HW, Yun SJ, Lee S-C, Won YH, Lee J-B. Mortality and comorbidity profiles of patients with bullous pemphigoid in Korea. *Ann Dermatol*. 2018;30(1):13-19. doi:10.5021/ad.2018.30.1.13

**62**. 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;31(3):339-342. doi:10.1111/j.1365-2230.2005.02040.x

**63**. Phoon YW, Fook-Chong SM, Koh HY, Thirumoorthy T, Pang SM, Lee HY. Infectious complications in bullous pemphigoid: an analysis of risk factors. *J Am Acad Dermatol*. 2015;72(5): 834-839. doi:10.1016/j.jaad.2015.01.029

**64**. Wei L. *Clinical analysis of 163 cases of bullous pemphigoid*. Master's thesis. China Medical University; 2018.

**65**. Kulthanan K, Chularojanamontri L, Tuchinda P, Sirikudta W, Pinkaew S. Prevalence and clinical features of Thai patients with bullous pemphigoid. *Asian Pac J Allergy Immunol*. 2011;29(1):66-72.

**66**. Carvajal Aguilera D, Fernández Moraga J, Valenzuela Ahumada F, Morales Huber C, Fernández Moraga A. Autoimmune blistering diseases: clinical characterization, therapeutic response and mortality in a university center in Chile [in Spanish]. *Piel*. 2020;35(1):10-15. doi:10.1016/j.piel.2019.03.002

**67**. Korman NJ. Bullous pemphigoid: the latest in diagnosis, prognosis, and therapy. *Arch Dermatol*. 1998;134(9):1137-1141.