Cause-specific mortality in people with bullous pemphigoid and pemphigus vulgaris: a systematic review & meta-analysis

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Dear Editor,

Bullous pemphigoid (BP) and pemphigus vulgaris (PV) are autoimmune blistering skin disorders which are increasing in incidence and are associated with high mortality.[1,2] As people with BP and PV often have comorbidity and require treatment that has severe side-effects, they could die of various causes.[3,4,5] A systematic review on cause-specific mortality in has not previously been conducted. The aim of this study was to examine causes of death in patients with BP and PV.

The study protocol was registered with PROSPERO (CRD42020202620); PRISMA guidelines were followed. On 10th October 2020, a search was conducted in MEDLINE, Embase and Cochrane Central Register of Controlled Trials. Grey literature was identified using the EthOs library and OpenGrey. Randomised control trials (RCTS) and cohort studies were included due to follow-up being integrated within the study designs. To be included, studies had to report at least one measure of cause-specific mortality in people with BP or PV. All languages were included. Three authors performed independent study screening, data extraction and quality assessment, using the Joanna Briggs Institute tool for cohort studies.[6] Disparities were resolved by discussion. We defined high-quality studies as those with at least one-year of follow-up and a control group matched for age and gender as these criteria minimise bias and confounding.

For each study, the proportional mortality (PM) was calculated by dividing the number of deaths from a specific cause by the total number of deaths. The standardised mortality ratio (SMR) was calculated by observed deaths divided by expected deaths of the reference population. Meta-analyses were conducted using a Der Simonian-Lairds random-effects model, determining (i) the pooled PM and, (ii) the pooled SMR for causes of death where available.[7] Subgroup analysis was not carried out due to insufficient data. Heterogeneity was assessed using I^2 (>75% defined as considerable heterogeneity).

A total of 971 publications were identified. Of these, 88 full-text articles were assessed for eligibility and 28 studies were eligible for review. Of the 28 studies, 14 were for BP (11 cohort studies; 3 RCTs), 13 for PV (11 cohort studies; 2 RCTs), and one study included both (cohort study). Twenty-six were hospital-based studies and in two, the setting was missing. The majority were conducted in Europe (n=20).

For BP, the SMR was reported in two studies and calculated from data available in a third study, with only one cause of death being common in each. No study reported SMR in PV. No study measured follow-up with person-years. Odds ratios and relative risks were not available for the same causes of death so could not be pooled. One study was high-quality. Many were of poor quality due to a lack of a control group or follow-up of less than one year.

All studies were included in meta-analysis for PM. The highest recorded pooled PM for BP patients was due to respiratory disease 34% (95%CI 21%,47%), (I^2=80.82%) whereas cardiovascular disease predominated in PV 34% (95%CI 18%,50%), (I^2=76.77%; Figure 1). The pooled SMR for heart failure was 118.86 (95%Cl 35.84,394.19), (I^2=89%) in BP patients (Forest plots for BP are available on request from the corresponding author). Wide confidence intervals and low number of studies (n=3) suggest these results may not be reliable, therefore, caution must be applied when interpreting this data. Both pooled SMR and PM had considerable heterogeneity (I^2>75%).

Respiratory disease is the most common cause of death in BP patients whilst in PV, cardiovascular disease is the commonest. Observed deaths due to heart failure are 18.9% higher in people with BP than in the reference population however this result is not statistically significant. The reason for these results is uncertain but it is possible that treatment may contribute, particularly oral corticosteroids which are commonly used and have wide ranging metabolic and immunosuppressive actions.

A strength of this study was that we were able to pool PM. Methodological limitations of this study were the lack of high-quality studies and studies reporting SMR. Considering the small size and hospital-based nature of most studies, this review demonstrates poor generalisability of the current literature and the need for large, population-based cohort studies, which would also allow subgroup analysis based on treatments, comorbidities and disease characteristics. Future studies also require appropriate control groups, longer follow-up and a measure of person-years in order to calculate mortality rates. A recent systematic review on all-cause mortality in BP which included 56 studies

reported overall quality of follow-up was poor.[8] It is pertinent that researchers improve the reporting of mortality measures for these serious autoimmune blistering disorders.

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