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International validation of the Bullous Pemphigoid Disease Area Index severity score and calculation of cut-off values for defining mild, moderate and severe types of bullous pemphigoid*

W. Masmoudi[1] M. Vaillant,[2] S. Vassileva,[3] A. Patsatsi,[4] G. Quereux,[5] C. Moltrasio,[6] C. Abasq,[7] C. Prost-Squarcioni,[8] D. Kottler,[9] D. Kiritsi,[10] N. Litrowski,[11] P. Plantin,[12] L. Friedrichsen,[13] A. Zebrowska,[14] S. Duvert-Lehembre,[15] S. Hofmann,[16] V. Ferranti,[1] F. Jouen,[1,2] P. Joly,[1,2] V. Hebert[1,2] and the EADV Autoimmune Bullous Skin Disease Task Force

[1]Department of Dermatology, Centre de Référence des Maladies Bulleuses Autoimmunes and [2]Department of Immunology, INSERM U1234, Rouen University Hospital, Rouen, France
[3]Department of Dermatology, Medical University of Sofia, Sofia, Bulgaria
[4]2nd Department of Dermatology and Venerology, Papageorgiou General Hospital, Aristotle University School of Medicine, Thessaloniki, Greece
[5]Department of Dermatology, Nantes University Hospital, Nantes, France
[6]Università degli Studi di Milano, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[7]Department of Dermatology, Brest University Hospital, Brest, France
[8]Department of Dermatology, Avicenne Hospital, University Paris 13, Bobigny, France
[9]Department of Dermatology, Bichat Hospital, AP-HP, Paris, France
[10]Department of Dermatology, Medical Center, University of Freiburg, Freiburg, Germany
[11]Department of Dermatology, Monod General Hospital, Le Havre, France
[12]Department of Dermatology, Centre Hospitalier de Cornouaille, Quimper, France
[13]Department of Dermatology, University of Lubeck, Lubeck, Germany
[14]Department of Dermatology and Venerology, Medical University of Lodz, Lodz, Poland
[15]Department of Dermatology, Lille University Hospital, Lille, France
[16]Department of Dermatology, HELIOS University of Wuppertal, Wuppertal, Germany

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Summary

Background The Bullous Pemphigoid Disease Area Index (BPDAI) score has been proposed to provide an objective measure of bullous pemphigoid (BP) activity.
Objectives The objective of this study was to calculate BPDAI cut-off values defining mild, moderate and severe BP. We also aimed to assess the interrater reliability and correlation with the number of daily new blisters, and anti-BP180 and anti-BP230 antibodies.
Methods Severity scores were recorded by two blinded investigators. Anti-BP180 and anti-BP230 antibodies were measured using an enzyme-linked immunosorbent assay (ELISA). Cut-off values defining mild, moderate and severe subgroups were calculated based on the 25th and 75th percentiles of the BPDAI score.
Results In total, 285 patients with BP were enrolled from 50 dermatology departments in Europe. Median BPDAI activity was 37·5 points (range 0–164). Cut-off values corresponding to the first and third quartiles of the BPDAI score were 20 and 57, respectively; thus, these values were used to define mild (≤ 19), moderate (≥ 20 and ≤ 56) and severe (≥ 57) BP. The median BPDAI score for patients with ≤ 10 daily new blisters was 26 [interquartile range (IQR) 17–45], and for patients with > 10 daily new blisters the median score was 55 (IQR 39–82). The BPDAI intraclass correlation coefficient measured at baseline was 0·97 and remained higher than 0·90 up to month 6. The improvement in the BPDAI score was

Correspondence
W. Masmoudi.
Email: wafmasmoudi@gmail.com

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correlated with the absolute decrease in anti-BP180 ELISA value (Spearman's rank r = 0·34, P < 0·004), but not with anti-BP230 antibodies (r = 0·17, P = 0·15). *Conclusions* This study suggests cut-off values of 20–57 for BPDAI to distinguish mild, moderate and severe BP, and confirms that it is a robust tool to assess BP severity precisely.

What is already known about this topic?

- The Bullous Pemphigoid Disease Area Index (BPDAI) is a new scoring system to measure bullous pemphigoid (BP) activity.
- The use of this score in clinical practice is limited by the absence of cut-off values.

What does this study add?

- Cut-off values of 20 and 57 were established to distinguish mild, moderate and severe BP using the BPDAI.
- These disease activity subgroups could help physicians in the management of patients with BP.

What are the clinical implications of this work?

- This study classified patients with BP into three subgroups (mild, moderate and severe) based on the BPDAI score.
- The BPDAI score is a robust tool to assess BP activity accurately, both at diagnosis and during the course of the disease, and could help physicians tailor treatment to disease activity, thereby providing better management of patients with BP.

Bullous pemphigoid (BP) is the most common autoimmune bullous disease.[1–5] It is characterized by the presence of autoantibodies against two proteins of the basement membrane zone (BMZ), BP180 (BPAG2) and BP230 (BPAG1).[6–10] BP mainly affects elderly patients and, in particular, those in poor general condition.[11] Treatment must be adapted to patient comorbidities and disease extent.[12]

Until recently, the severity of BP was determined based on the mean number of daily new blisters; moderate BP was defined as the occurrence of 10 daily new blisters or fewer, and extensive disease as the occurrence of more than 10 daily new blisters.[13,14] This classification, based only on the number of blisters, has limited relevance for assessing the severity of BP as it does not take into account urticarial, erythematous and/or eczematous lesions, which are frequently associated with blisters, but can also occur as isolated lesions without blisters in nonbullous types of BP.[15,16]

The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) was initially developed in 2007 by German dermatologists. This scoring system quantifies the extent of skin and mucosal erosions and includes a measure of patient discomfort.[17] It is not specific to a particular type of autoimmune blistering disease.[18]

More recently, an international consensus of experts proposed the Bullous Pemphigoid Disease Area Index (BPDAI) score, which is specific to BP, to provide an objective measure of BP activity.[19] The reliability of the BPDAI scoring system has been evaluated only once [the intraclass correlation coefficient (ICC) was 0·957 (0·901–0·982)] in a monocentric study that included 30 patients without comparison between the BPDAI score and the two previously used severity subgroups based on the number of daily new blisters (≤ 10 blisters per day vs. > 10 blisters per day).[20]

The aim of the present study was to prospectively assess the interrater reliability of the BPDAI score in a large population of 285 patients with newly diagnosed BP who were followed up for 6 months. We also aimed to calculate cut-off values in order to define three categories of BP activity (mild, moderate and severe) and their relationship with the two previous severity subgroups (≤ 10 blisters per day vs. > 10 blisters per day) based on the count of daily new blisters.

As a correlation has been reported between the level of serum anti-BP180 antibodies and BP severity,[21–24] we assessed the correlation between the BPDAI activity score and serum anti-BP180 and anti-BP230 antibodies using enzyme-linked immunosorbent assay (ELISA) values at baseline and during patient follow-up. As blood eosinophilia is frequently observed at the onset of BP and has been suggested to be a severity marker for BP,[25,26] we also assessed the correlation between the number of blood eosinophils and BPDAI severity score.

Patients and methods

Study population

A prospective European multicentre study was conducted in 50 dermatology departments in Bulgaria, the Czech Republic,

France, Germany, Greece, Italy and the Netherlands, corresponding to secondary and tertiary care centres.

Consecutive patients aged ≥ 18 years who had newly diagnosed BP between June 2015 and February 2019 were included. A diagnosis of BP was made according to previously reported clinical (absence of atrophic scars, absence of head and neck involvement, absence of mucosal involvement and age greater than 70 years) and histological criteria (subepidermal blister and positive direct immunofluorescence examination of a skin biopsy specimen showing linear IgG and/or C3 deposits along the BMZ).[27–29]

The present study was an ancillary study of a clinical trial where the objective was to assess the safety and efficacy of a 0·5 mg kg^{-1} per day dosage of prednisone as first-line treatment for BP, as proposed in the recent guidelines of the European Academy of Dermatology.[12]

As this clinical trial was an observational study, treatment was not controlled during the whole study period. All patients were initially treated with a daily dose of 0·5 mg kg^{-1} of prednisone. The treatment was then adapted by investigators depending on the evolution of lesions and treatment tolerance. This study was approved by the corresponding local ethics committees.

Assessment of bullous pemphigoid activity

The BP extent was evaluated with the BPDAI score at baseline and during follow-up visits at weeks 1 and 2, and months 1, 2, 3 and 6 by the same two blinded investigators via in-person contact, and was recorded using a standardized form. The BPDAI is a score ranging from 0 to 360 points. The BPDAI differentiates scores for the lesions of skin involvement (blisters/erosions vs. urticaria/erythema) and for the skin and/or mucosal activity; 120 points for blisters/erosions, 120 points for cutaneous urticarial and erythematous lesions and 120 points for mucosal blisters/erosions.[19] The complete description of the scoring system is available in Murrell *et al.*[19] Disease extent based on the number of daily new blisters was also recorded once at baseline by the same two investigators during a consultation. All investigators were dermatologists with extensive experience in the management of patients with BP.

Detection of serum anti-BMZ autoantibodies was performed using commercially available ELISA BP180 and ELISA BP230 assays (Neuroimmune, Lubeck, Germany) at baseline and at month 3 and month 6.

Statistical analysis

Three subgroups of severity, i.e. mild, moderate and severe, were defined based on the scores of the first and third quartiles (Q1 and Q3). Thus, mild, moderate and severe BP corresponded to patients with a score lower than the 25th percentile of the sample, greater than or equal to the 25th percentile and lower than the 75th percentile, and higher than or equal to the 75th percentile, respectively. From these defined categories, the median scores of the three severity subgroups (mild, moderate and severe) were compared separately for each score (i.e. median BPDAI activity scores were compared with the three severity subgroups from the BPDAI). The distribution of data from BPDAI scores was non-normal as revealed by the D'Agostino–Pearson normality test and the Shapiro–Wilk test of normality. Thus, all these comparisons relied on the nonparametric Kruskal–Wallis test or the Mann–Whitney U-test.

Interrater reliability was assessed by estimating the ICC overall and according to severity (mild, moderate and severe). It was evaluated at each study visit for the BPDAI score and for each severity subgroup (mild, moderate and severe).

Correlations between BPDAI score and other severity biomarkers, i.e. serum, were also assessed. Anti-BP180, anti-BP230 antibody ELISA values and blood eosinophilia were assessed using Spearman's rank correlation coefficient. Correlations were assessed for baseline values between BPDAI scores and severity biomarkers, and for their absolute changes between baseline and month-6 values. Quantitative variables were reported as mean, SD, median, range and interquartile range (IQR) and qualitative variables were reported as frequency and percentages. A P-value ≤ 0·05 was considered statistically significant. Statistical analyses were performed and graphs were created using GraphPad Prism version 6·0 (San Diego, CA, USA).

As the present study was an ancillary study, the target sample size (n = 280) was calculated to meet the main objective of the therapeutic trial, which assessed the efficacy of a 0·5 mg kg^{-1} per day dose of prednisone as an initial treatment for BP, and was not calculated specifically for this study. This sample size of 280 patients allowed us to assess the interrater reliability through estimation of the ICC with good precision, as measured by the width of the 95% ICC confidence interval (CI). Using this sample size (n = 280), the expected width was ± 0·094 for an ICC of 0·8. We hypothesized that an ICC ≥ 0·8 was required to conclude that the BPDAI score was a robust tool to assess BP activity accurately.

Results

Baseline characteristics of patients

In total, 285 patients with BP (166 women and 119 men) with a mean age of 81·75 ± 9·18 years were enrolled in the study.

The median BPDAI activity score for included patients was 37·5 (0–164). From a total of 360 points on the BPDAI score, only 164 points, i.e. 45% of the scale, were used to assess BP activity in the whole population. Overall, 22 patients (7·7%) had a nonbullous type of BP, which included urticarial type (n = 9), eczematous type (n = 12) and dyshidrosiform type (n = 1). A total of 27 patients (9·5%) had mucosal involvement; the median BPDAI score of this subgroup was 51 points (IQR 20–84). The distribution of the BPDAI score among patients included in the study is shown in Figure 1.

According to the previous classification based on the number of daily new blisters, 165 patients (61·6%) had ≤ 10

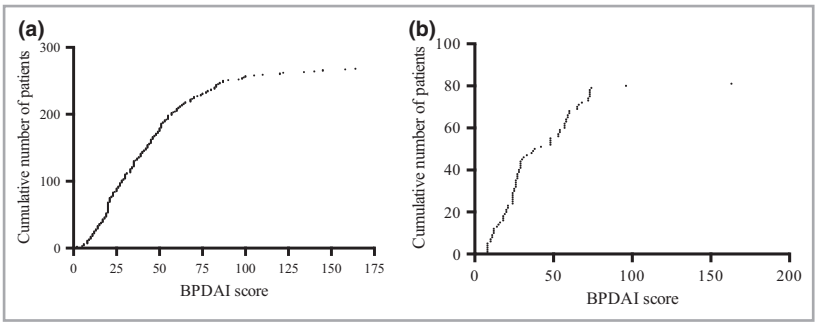

Figure 1 Distribution of the Bullous Pemphigoid Disease Area Index (BPDAI) scores in patients included in the study and among those who were excluded. The distribution of the scores was almost linear in both groups of patients. (a) Distribution of disease severity according to baseline BPDAI. (b) Distribution of disease severity among nonincluded patients according to BPDAI.

blisters per day (including the 22 patients with nonbullous type BP) and 103 patients (38·4%) had > 10 blisters per day. This information could not be recorded for 17 patients.

The median blood eosinophil count in the whole population was 0·85 g L^{-1} (IQR 0·32–1·64). Anti-BP180 and anti-BP230 antibodies were measured in 241 patients; 208 patients (86·3%) and 130 patients (53·9%) had positive baseline anti-BP180 and anti-BP230 antibodies, respectively. Median baseline ELISA values were 161 IU mL^{-1} (IQR 64–200) in patients with positive anti-BP180 antibodies and 87 IU mL^{-1} (IQR 20–178) in patients with anti-BP230 antibodies.

Evolution of Bullous Pemphigoid Disease Area Index score and anti-BP180 and anti-BP230 antibodies during patient follow-up

Prospective data up to the month-6 evaluation were available for 187 of 285 patients. The evolution of the mean BPDAI score and the mean anti-BP180 and anti-BP230 antibody ELISA values during the study is shown in Figure 2.

Calculation of cut-off values defining mild, moderate and severe subgroups of bullous pemphigoid activity according to the Bullous Pemphigoid Disease Area Index score

The cut-off values (first and third quartiles) for BPDAI scores were 20 points and 57 points, defining the three subgroups of severity. Thus, mild BP was defined as a BPDAI score ≤ 19, moderate BP was defined as a score ranging from 20 to 56, and severe BP was defined as a score ≥ 57.

Median BPDAI activity scores of the three severity subgroups were as follows: mild BP, 13 points (IQR 9–17); moderate BP, 35 points (IQR 25–45) and severe BP, 78 points (IQR 64–92). To ensure the absence of selection bias in the population included in the study, we then calculated the same

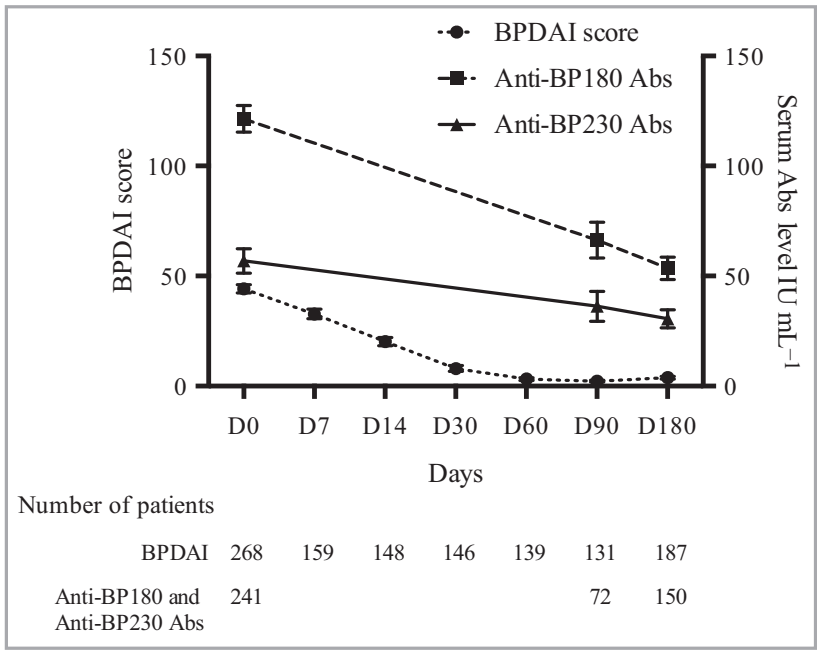

Figure 2 Evolution of mean Bullous Pemphigoid Disease Area Index (BPDAI) scores, and anti-BP180 and anti-BP230 antibody enzyme-linked immunosorbent assay values from baseline to month-6 evaluation. Vertical bars correspond to the SEM. Abs, antibodies.

thresholds (first and third quartiles) in the population of patients who were excluded from the clinical trial. Most of these patients were excluded because, according to investigator judgement, they had a contraindication to oral corticosteroids. The cut-off values were 20 and 57 points, which corresponded exactly to the 25th and 75th percentiles calculated in the sample of patients included in the study.

We then assessed the relationship between the three subgroups (mild, moderate, severe) defined by the two cut-off values with the two previously used subgroups based on the daily blister count (≤ 10 blisters per day vs. > 10 blisters per day). The median BPDAI score of the subgroup of patients with ≤ 10 daily new blisters was 26 points (IQR 17–45), which corresponded to an intermediate value between the median BPDAI score of patients with mild BP [13 points (IQR 9–17)] and that of patients with moderate BP [35 points (IQR 25–45)]. Similarly, the median BPDAI score of the subgroup of patients with more than 10 daily new blisters was 55 points (IQR 39–82), which corresponded to an intermediate value between the median BPDAI score of patients with moderate BP [35 points (IQR 25–45)] and severe BP [78 points (IQR 64–92)]. The median BPDAI score of patients with nonbullous BP (who were included in the subgroup of patients with ≤ 10 blisters per day) was 13 points (IQR 8·75–28·5).

Interrater reliability at baseline and during patient follow-up

At baseline, the interrater reliability was estimated for BPDAI score with an ICC of 0·97 (95% CI 0·96–0·98). Based on BP extent, the baseline ICCs for BPDAI were 0·94 (95% CI 0·86–0·97), 0·91 (95% CI 0·87–0·94) and 0·90 (95% CI 0·82–0·94) in patients with mild, moderate and severe BP, respectively.

The interrater reliability calculated for the whole population remained highly stable during patient follow-up, where ICC values remained higher than 0·90 during the follow-up from baseline to month 3 (Figure 3).

Correlation between the Bullous Pemphigoid Disease Area Index score, blood eosinophil count and serum anti-BP180 and anti-BP230 antibody enzyme-linked immunosorbent assay values

Baseline correlations

At baseline, we observed a moderate correlation between BPDAI score and blood eosinophil count ($r = 0·31$; $P < 0·001$) and anti-BP180 antibodies ($r = 0·3$; $P < 0·001$), whereas no correlation was demonstrated between the BPDAI score and anti-BP230 antibody ELISA values ($r = 0·08$; $P = 0·24$).

Interestingly, we observed a strong correlation between blood eosinophil count and the inflammatory BPDAI subscore in the subgroup of patients with a nonbullous type of BP ($r = 0·64$; $P < 0·031$).

Correlations during disease course

The evolution of the BPDAI score and anti-BP180 and anti-BP230 antibodies is shown in Figure 3. The absolute improvement of the BPDAI score from baseline to month 6 was correlated with the absolute decrease in anti-BP180 ELISA value ($r = 0·34$; $P < 0·004$), but not with anti-BP230 antibodies ($r = 0·17$; $P = 0·15$).

Discussion

This study suggests that a BPDAI activity value of 20 points allows differentiation between mild and moderate BP, whereas a BPDAI activity value of 57 points allows differentiation between moderate and severe BP. Indeed, a precise assessment of disease activity is important so that treatment can be adapted for patients with BP, who are often old and fragile.

In this study, the BPDAI score was chosen rather than the ABSIS score because the BPDAI score is established by a consensus of international experts, and also because it takes into account items specific to BP.

Although somewhat arbitrary, the main rationale for using the classical 25th and 75th percentiles of the BPDAI score was to categorize two limited populations of patients with limited extent (< 25th percentile) and another population with severe extent (> 75th percentile), and a larger population of patients with moderate activity (25th–75th percentile) that could benefit from different options.

The choice of these thresholds was supported by the almost linear distribution of BPDAI values among patients in this study, which did not allow for the identification of other particular subsets of patients or provide any rationale for selecting thresholds other than the 25th and 75th percentiles. Importantly, the calculation of cut-off values corresponding to the first and third quartiles of the BPDAI score in the population of patients who were excluded from the study corresponded exactly to the 25th and 75th percentile that we determined in the sample of patients included in the study (20 points and 57 points).

The clinical relevance of these subgroups of BP activity is illustrated by the results of the clinical trial, which was conducted in parallel to the present study and assessed the efficacy of a 0·5 mg kg^{-1} per day dosage of prednisone in patients with BP. Indeed, the proportion of patients who achieved control of disease activity was 75% among patients with mild BP extent, 69·4% in those with moderate extent, but only 44·2% among those with severe BP activity. This validated the usefulness of defining subgroups of patients with BP based on disease activity, as less than half the patients with extensive BP could be controlled with a medium dose of oral prednisone. While both subgroups of patients with mild and moderate BP were adequately controlled with a 0·5 mg kg^{-1} dose of prednisone, one could hypothesize that many patients with mild BP could have been controlled with a lower dose of prednisone. This is also in accordance with the results of our randomized clinical trial that tested two regimens of topical

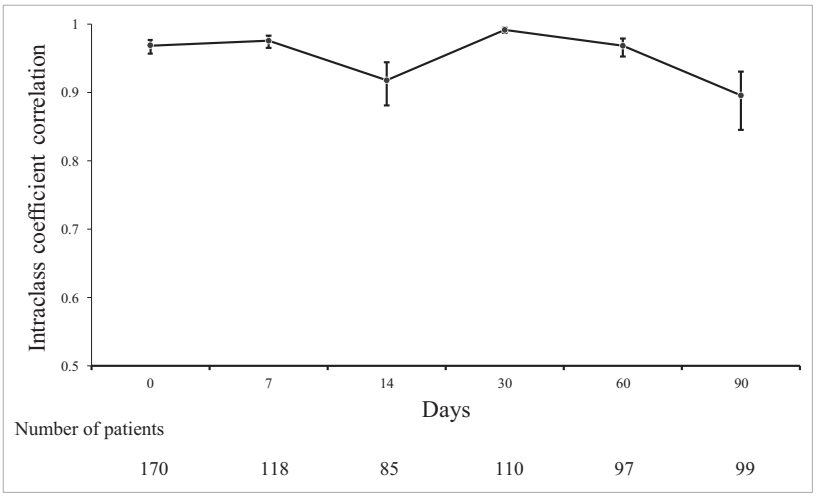

Figure 3 Evolution of mean intraclass coefficients correlation of Bullous Pemphigoid Disease Area Index scores during patient follow-up from day 0 to day 90. Vertical bars correspond to the 95% confidence intervals.

corticosteroids, in which patients with BP received a daily dose of 10–40 g of clobetasol propionate based on patient weight and disease extent. Indeed, most patients with mild BP were adequately controlled with a daily dose of 10 g of clobetasol propionate, while those with moderate BP usually needed 20–30 g per day, and those with extensive BP needed 30–40 g for disease activity to be controlled.[14]

The validity of a disease activity score primarily relies on its interrater reliability. The present study showed a high interrater reliability for the BPDAI score (ICC > 0·90), which was tested on a large sample of patients from various countries, both at baseline and during patient follow-up. Our results are also in accordance with the 0·95 ICC (0·901–0·982), previously reported in a monocentric study that included 32 patients who were recruited over 4·5 years and rated by a number of Dermatology fellows.[20] Additionally, this high interrater reliability of the BPDAI score was observed in all severity subgroups in our study (mild, moderate and severe), whereas we previously showed that the interrater reliability of the pemphigus severity score on the Pemphigus Disease Area Index was lower in patients with moderate pemphigus activity than in those with mild or severe activity.[30]

Despite the fact that there is no unanimously accepted gold standard biomarker of BP activity, we then studied the correlations between the BPDAI score and blood eosinophilia, and anti-BP180 antibody ELISA values, which have both been suggested to correspond to severity markers for BP.[21–24,26]

In accordance with studies that reported a correlation between the extent of BP lesions and anti-BP180 antibody levels, we observed a moderate correlation between the BPDAI score with serum anti-BP180 antibodies both at baseline ($r = 0·3$; $P < 0·001$) and during patient follow-up, but not with anti-BP230 antibodies ($r = 0·08$; $P = 0·24$).[20–24] While we previously showed that high titres of anti-BP180 antibodies was an independent predictive factor of relapse for patients with BP after cessation of therapy,[31] the moderate correlation between the evolution of the BPDAI score and that of serum anti-BP180 antibodies suggests that in clinical practice the improvement of BP lesions is more precisely reflected by the evolution of the BPDAI score than by the evolution of anti-BP180 antibodies. It has recently been reported that BP activity was also correlated with serum anti-BP180 NC16A IgE levels.[32]

Interestingly, we found a high correlation between the BPDAI score and blood eosinophil count, particularly in patients with nonbullous BP ($r = 0·64$). This exemplifies one of the main features of the BPDAI score, which takes into account inflammatory lesions in addition to blistering lesions, not only in patients with extensive lesions, but also in those with the prebullous or nonbullous form of the disease.

This study has several limitations. A selection bias is unlikely in this large multicentre international study of newly diagnosed and still untreated patients with BP who had varying degrees of disease activity. Importantly, the distribution of the BPDAI scores among excluded patients did not appreciably differ from the distribution among patients in the study. Moreover, the calculation of cut-off values corresponding to the first and third quartiles of the BPDAI score was exactly the same in both patient populations. This was mainly related to the fact that most patients who were excluded from the therapeutic trial, which was conducted in parallel to the present study, had associated disorders that contraindicated the use of a 0·5 mg kg^{-1} per day dosage of prednisone, but were not excluded based on criteria relating to disease extent.

Additionally, despite the recruitment of patients in secondary and tertiary care centres, a selection bias is unlikely as most of the patients with BP (who were elderly and/or in poor general condition) were recruited locally, and very few were referred to a reference centre from primary care centres. A total of 98 patients died or were lost to follow-up during the study. However, it is unlikely that this could have significantly biased our results because the r correlations observed at baseline, month 3 and month 6 were very close.

Overall, this study calculated cut-off values based on BPDAI score to classify patients with BP into three subgroups, i.e. mild, moderate and severe. Additionally, it showed a high interrater reliability of BPDAI score and its correlation with other biomarkers related to disease activity such as anti-BP180 antibodies. Our results provide strong evidence that the BPDAI score is a robust tool to assess BP activity accurately, both at the time of diagnosis and during disease course, which might help clinicians to adapt treatment to disease activity and drive controlled therapeutic trials.

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