Original Investigation

Pemphigus Disease Activity Measurements
Pemphigus Disease Area Index, Autoimmune Bullous Skin Disorder Intensity Score, and Pemphigus Vulgaris Activity Score

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IMPORTANCE Recently, the clinical pemphigus disease activity indexes of Pemphigus Disease Area Index (PDAI), Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), and Pemphigus Vulgaris Activity Score (PVAS) were validated to correlate with physician global assessment. The antidesmoglein (anti-Dsg) autoantibodies are known to correlate mostly with pemphigus disease activity. The correlation between these indexes and anti-Dsg1 and anti-Dsg3 enzyme-linked immunosorbent assay values has not been previously evaluated.

OBJECTIVES To evaluate the PDAI, ABSIS, and PVAS in a large number of patients with pemphigus vulgaris and to compare the interrater reliability of these indexes and the convergent validity according to anti-Dsg values.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study was performed in 2012 in a referral university center for autoimmune bullous diseases. One hundred patients with confirmed diagnoses of pemphigus vulgaris and clinical pemphigus lesions (mean [SD] age, 43.3 [1.7] years; age range, 14-77 years; female-male ratio, 1:3) were studied. Three dermatologists familiar with immunobullous diseases and the indexes rated the patients.

INTERVENTIONS All 100 patients were evaluated with the PDAI, ABSIS, and PVAS. Three dermatologists independently rated all 3 indexes for each of the patients on the same day. Serum anti-Dsg1 and anti-Dsg3 enzyme-linked immunosorbent assay values were measured simultaneously.

MAIN OUTCOMES AND MEASURES Analyses of interrater reliabilities, convergent validities according to anti-Dsg titers, correlation between the distribution and types of lesions with disease activity, predictors of higher titers of antibody (multiple regression analysis), and cutoff values of measures for 2 titers of anti-Dsg with optimal area under the curve, sensitivity, and specificity were performed.

RESULTS The interrater reliabilities were highest for the PDAI, followed by the ABSIS and the PVAS (intraclass correlation coefficients of 0.98 [95% CI, 0.97-0.98], 0.97 [95% CI, 0.96-0.98], and 0.93 [95% CI, 0.90-0.95], respectively). The convergent validity was highest for the PDAI, followed by the PVAS and the ABSIS (Spearman ρ = 0.67, 0.52, and 0.33, respectively). Head, neck, and trunk involvement were predictors of higher titers of anti-Dsg1.

CONCLUSIONS AND RELEVANCE Among the 3 studied indexes, the PDAI had the highest validity and is recommended for use in multicenter studies for rare diseases, such as pemphigus vulgaris.

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Effective therapies have decreased the morbidity and mortality of pemphigus, but a recent Cochrane review[1] of randomized controlled trials in patients with pemphigus concluded that evidence was insufficient to determine the optimal therapy because of the lack of validated outcome measures. Disease activity indexes are pivotal in clinical studies to provide comparable, interpretable results and to facilitate evidence-based decision making for physicians.

The Pemphigus Disease Area Index (PDAI) and the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) are 2 independent disease severity assessments of pemphigus disease extent.[2] The PDAI was developed by the International Pemphigus Committee[2-4] and the ABSIS was developed by Pfütze et al[5] in 2007 and used in European studies.[6] The Pemphigus Vulgaris Activity Score (PVAS) was developed by Chams-Davatchi et al[7,8] and was validated and applied in a double-blind randomized controlled trial in Iran.

Elevated antidesmoglein (anti-Dsg) 1 and 3 antibody titers are used to diagnose pemphigus vulgaris (PV) and have been reported to correlate with disease activity in PV.[1,9-11] Recently, the PDAI, ABSIS, and PVAS were validated to correlate with the Physician Global Assessment (PGA) of pemphigus disease activity in a limited number of patients.[2,7] However, to our knowledge, the correlation between these measurements and anti-Dsg1 and anti-Dsg3 enzyme-linked immunosorbent assay (ELISA) values has not been previously evaluated. The high prevalence of PV in Iran provided the opportunity to evaluate disease activity indexes in a large number of patients with PV.[12]

The primary objectives of this study were to evaluate all 3 PV disease activity indexes in a large number of PV patients, to compare the interrater reliability of these indexes, and to assess the convergent validity with anti-Dsg values. The secondary objectives were to assess the correlation among different components of these indexes with anti-Dsg values, detect the predictors of higher anti-Dsg titers, and determine the disease severity cutoffs for 2 different antibody titers (20 and 100 U/mL of antibody).

Methods

This study was performed at the Autoimmune Bullous Diseases Research Center, Razi Hospital, Tehran, Iran. The study was approved in 2012 by the Ethics Review Board of Tehran University of Medical Sciences.

One hundred PV patients were enrolled from the Autoimmune Bullous Diseases Research Center during July 2012. The inclusion criteria were a confirmed PV diagnosis and the presence of clinical pemphigus lesions. The diagnosis of PV had been confirmed by histopathologic testing and direct immunofluorescent microscopy. All patients signed informed consent forms.

The clinical evaluation of each patient was performed in 1 day. Each patient was examined separately by 3 dermatologists (N.A., P.H., and Z.R.), and each dermatologist rated all 3 disease indexes (PDAI, ABSIS, and PVAS) for each patient. The evaluations were performed during weekly visits to the Autoimmune Bullous Diseases Research Center by dermatologists exclusively dedicated to this study. On each clinic day, approximately 20 patients were rated completely by all 3 raters, resulting in 100 patient assessments during a 5-week period. Nine distinct measurements were performed for each patient.

The raters were familiar with immunobullous diseases and the disease activity indexes and performed the assessment independently. We assumed that the first index rating would take longer than the subsequent index ratings because the rater was unfamiliar with the patient. Thus, we randomized the order of performance of the 3 indexes for each patient.

The following pemphigus disease indexes were used: PDAI, ABSIS, and PVAS. The PDAI has a potential range of 0 to 263 (120 points for skin activity, 10 points for scalp activity, 120 points for mucosal activity, and 13 points for postinflammatory hyperpigmentation [PIH], representing disease damage). It assigns scores to defined anatomical regions based on the number and size of the lesions (eFigure 1 in the Supplement).[2] The ABSIS has a potential range of 0 to 206 (150 points for skin involvement, 11 points for oral involvement, and 45 points for subjective oral discomfort). It takes into account body surface area weighted by the type of lesions to estimate skin activity. Discomfort during eating and drinking is also scored (eFigure 2 in the Supplement).[5] The PVAS has a potential range of 0 to 18 (11 points for skin activity and 7 points for mucosal activity). The number of lesions and the involvement of defined anatomical regions are weighted by the types of lesions. The Nikolsky sign is also incorporated in skin activity scoring (eFigure 3 in the Supplement).[7,8]

Serum samples were collected simultaneously and stored at −70°C. The autoantibody titers were performed at the end of the study by independent laboratory personnel not familiar with the clinical evaluation results using a commercially available Dsg1/Dsg3 ELISA kit (EUROIMMUN). Serum was diluted 1:100, according to the manufacturer's instructions. An ELISA value at or above 20 U/mL was considered positive for both Dsg1 and Dsg3 antibodies.[10,13] If both anti-Dsg1 and anti-Dsg3 titers were below 20 U/mL, they were considered in the low range, and if both titers were above 100 U/mL, they were considered in the high range.

Data computation and analysis were performed using SPSS statistical software, version 20 (SPSS Inc). Identical anatomical areas of skin and mucous membrane were recoded to compare the 3 measures (**Table 1**). Data were presented as mean (SD) for continuous variables. The scatterplot presented the statistical relationship among quantitative variables. To analyze the changes in the PDAI, ABSIS, and PVAS among the 3 physicians in the same patient, interrater reliability was assessed using the intraclass correlation coefficient (ICC). All ICCs were calculated using the 2-way random-effect analysis of variance model. The ICCs greater than 0.70 and 0.81 were considered acceptable and excellent, respectively. The Spearman ρ correlation coefficient between the mean PDAI, ABSIS, and PVAS and the anti-Dsg1 and anti-Dsg3 values estimated the convergent validity. In a subgroup analysis, the Kruskal-Wallis nonparametric analysis of variance test was performed to determine the differences in the anti-Dsg values based on the areas involved, type of lesions, and presence of a Nikolsky test. Post

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Table 1. Distribution of Pemphigus Disease Activity Measurements in Defined Areas in 100 Patients With Pemphigus Vulgaris

	PDAI			ABSIS			PVAS[a]		
Disease Site	No. of Patients	Mean (SD)	Range/Score Range	No. of Patients	Mean (SD)	Range/Score Range	No. of Patients	Mean (SD)	Range/Score Range
Skin[b]	81	18.6 (17.5)	0-94.3/0-130	83	6.3 (7.7)	0-38.5/0-150	78	3.3 (2.3)	0-10.5/0-11
Head and neck	68	9.7 (7.5)	0-32.7/0-50	68	2.1 (2.0)	0-8.7/0-13.5	68	No. of lesions: 0, 25%; ≤20, 37%; >20, 38%	
Trunk	68	7.8 (5.5)	0-25/0-30	67	3.7 (4.2)	0-24.7/0-54	66	Type of lesions: none, 24%; crusted, 45%; erosion, 31%	
Limbs	54	5.3 (6.2)	0-31.7/0-40	42	2.5 (4.6)	0-27/0-81	49	Presence of Nikolsky sign: 0, 85%; around the lesion, 12%; on unaffected skin, 3%	
Genital	14	2.3 (2.5)	0-10/0-10	11	0.5 (0.3)	0-1/0-1.5	...	...	...
Mucosal[b]	81	12.4 (11.1)	0-54.3/0-120	82	4.3 (2.4)	0-10/0-11	82	2.2 (1.1)	0-6/0-7
Oral and pharynx	81	11.4 (10.4)	0-47/0-90	82	4.3 (2.4)	0-10/0-11	81	No. of lesions: 0, 20%; 1-2, 10%; >2, 70%	
Nasal and upper airways	34	1.1 (0.6)	0-3/0-10	...	...	...	47	Type of lesions: none, 22%; ulcer, 31%; erosion, 47%	
Anogenital	17	1.3 (1.7)	0-6.7/0-10	...	...	...	14		
Eye	11	1.1 (0.5)	0-2/0-10	...	...	...	12		
Damage or discomfort	75	3.3 (2.4)	0-10.3/0-13	57	20.4 (13.7)	0-45/0-45	...	...	...
Total	100	27.7 (21.1)	0-101.3/0-263	100	20.4 (18.7)	0-75.7/0- 206	100	4.5 (3.1)	0-14.8/0-18

Abbreviations: ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; PDAI, Pemphigus Disease Area Index; PVAS, Pemphigus Vulgaris Activity Score.

[a] The PVAS uses a complex formula and calculates total skin or mucosal membrane score as follows: Score of Type of Skin Lesions × (Score of Number of Lesions + Score of Distribution of Lesions + Presence of Nikolsky Sign) + Score of Type of Mucosal Lesions × (Score of Number of Lesions + Score of Distribution of Lesions). The discrete scores for defined anatomical areas cannot be independently measured.

[b] Variable numbers of patients reported by different measurements were due to differences in the corresponding scoring systems. The PDAI considers postinflammatory hyperpigmentation as a damage component that is not included in the skin activity score, the ABSIS includes postinflammatory hyperpigmentation in the score, and the PVAS gives a zero score to postinflammatory hyperpigmentation. In addition, the PDAI includes visible mucosal involvement according to regular physical examination, but the ABSIS and PVAS include subjective involvements of aerodigestive tract in addition to visible lesions.

hoc tests determined intergroup differences. Multiple regression analyses were used to calculate the predictive value of the PDAI, ABSIS, and PVAS components for the anti-Dsg antibody titers. A higher value of the standardized coefficient of β reflects the greater amount of change in the predicted response. Receiver operating characteristic (ROC) curves determined a cutoff value of the PDAI, ABSIS, and PVAS measures, with optimal sensitivity and specificity for positive anti-Dsg1 and anti-Dsg3 values and titers above 100 U/mL. Each point of the curve represented the relationship between sensitivity and 1 – specificity for a single cutoff value. The point with the highest sensitivity and specificity (ie, the upper left corner of the ROC graph) was considered the cutoff. Area-under-the-curve (AUC) values higher than 0.5 suggested better overall performance of a diagnostic test. $P < .05$ was considered statistically significant.

Results

We evaluated 100 PV patients. The mean (SD) patient age was 43.3 (1.7) years (age range, 14-77 years), and the female-male ratio was 1:3. For disease activity measurement, only the skin and mucosal activity scores were used. The damage score was to remind the physicians not to score damage as part of activity. Because no significant differences were found among the raters' evaluations, the mean of their measurements were used to report the results. Table 1 gives the prevalence of skin, mucous membrane, and damage involvement in 100 patients and the distribution of measures according to the PDAI, ABSIS, and PVAS.

Reliability and Convergent Validity

The estimated interrater reliability revealed an ICC of 0.98 for the PDAI, 0.97 for the ABSIS, and 0.93 for the PVAS. **Table 2** gives the ICCs for skin, mucosal, and damage components of these indexes. The interrater reliability of the indexes at both ends of the spectrum of patients was also assessed. If anti-Dsg1 and anti-Dsg3 values were both negative, they were considered in the lower range (n = 10), and if anti-Dsg1 and anti-Dsg3 levels were greater than 100 U/mL, they were considered in the upper range (n = 35). The ICCs (95% CI) for those in the upper range were 0.96 (0.93-0.98), 0.97 (0.95-0.98), and 0.88 (0.80-0.94) for the PDAI, ABSIS, and PVAS, respectively, and

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Table 2. Interrater Reliability Values for Total, Skin, Mucosal, and Damage Components

Measure	Mean Intraclass Correlation Coefficients (95% CI)			
	Total	Skin	Mucous Membranes	Damage or Subjective Oral Discomfort
PDAI	0.98 (0.97-0.98)[a]	0.99 (0.98-0.99)[a]	0.95 (0.92-0.96)[a]	0.90 (0.85-0.93)[a]
ABSIS	0.97 (0.96-0.98)[a]	0.92 (0.89-0.94)[a]	0.95 (0.94-0.97)[a,b]	0.98 (0.97-0.99)[a]
PVAS	0.93 (0.90-0.95)[a]	0.94 (0.92-0.96)[a]	0.90 (0.86-0.93)[a]	...

Abbreviations: ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; PDAI, Pemphigus Disease Area Index; PVAS, Pemphigus Vulgaris Activity Score.

[a] Correlation is significant at the $P < .01$ level (2-tailed).

[b] The interrater reliability of the ABSIS oral involvement was increased to 0.98 (95% CI, 0.97-0.99) when subjective oral discomfort was also included.

Table 3. The PDAI Total Activity and Anti-Dsg1 and Anti-Dsg3 Values in Specific Anatomical Areas

Disease Site	No. of Patients	Mean (SD)	
		PDAI Activity	Anti-Dsg1 for Skin and Anti-Dsg3 for Mucosal Activity
Skin			
Head and neck	68	30.8 (21.0)	191.60 (148.18)
Trunk	68	31.3 (21.0)	181.69 (140.31)
Limbs	54	34.4 (21.1)	216.86 (137.85)
Lower limbs	36	39.5 (21.9)	243.65 (133.89)
Genital	14	47.6 (25.8)	243.06 (162.49)
Mucosal			
Oral and pharynx	81	27.4 (21.0)	233.31 (127.18)
Nasal, upper airways	34	36.37 (25.3)	280.62 (103.97)
Eye	11	40.0 (22.4)	247.70 (100.07)
Anogenital	17	42.4 (28.1)	289.40 (87.78)

Abbreviations: Dsg, desmoglein; PDAI, Pemphigus Disease Area Index.

the ICCs (95% CIs) for those in the lower range were 0.98 (0.94-0.99), 0.88 (0.64-0.97), and 0.88 (0.62-0.97). The ICCs revealed a statistically significant difference in the lower range of titers for the PDAI but not the ABSIS and PVAS because it showed higher values with no overlap within the 95% CIs. The correlation between the PDAI and the other indexes revealed a Spearman ρ coefficient of 0.82 for the PVAS and 0.66 for the ABSIS. See eTable 1 in the Supplement for the ICCs of the 3 different indexes measured for a single patient by each rater.

The convergent validity between anti-Dsg1 values and different measurements was 0.67 for the PDAI ($P < .001$), 0.33 for the ABSIS ($P = .002$), and 0.52 ($P < .001$) for the PVAS. However, the correlations between the measures and anti-Dsg3 titers were poor, with ICCs of 0.35 ($P = .001$), 0.38 ($P < .001$), and 0.35 ($P = .001$) for the PDAI, ABSIS, and PVAS, respectively.

Scoring Time

The time required to complete forms was recorded. The times for the PDAI, ABSIS, and PVAS ranged from 20 seconds to 5.8 minutes (mean [SD], 2.9 [1.3] minutes), 25 seconds to 5.6 minutes (mean [SD], 1.9 [1.1] minutes), and 15 seconds to 3.9 minutes (mean [SD], 1.1 [0.7] minutes), respectively.

Subgroup Analyses

Distribution of Lesions

Table 3 lists the total PDAI and anti-Dsg1 values by anatomical area. Total PDAI activity and anti-Dsg1 titers were higher in patients with genital and lower limb lesions compared with patients who had head and neck lesions. In addition, patients with anogenital mucosal lesions presented with higher PDAI activity and anti-Dsg3 titers compared with those with oral involvement.

Lesion Types

Patients with either active erosive or crusted lesions had higher PDAI and anti-Dsg1 values compared with those with only skin damage. Anti-Dsg1 titers did not reveal significant differences between crusted or erosive lesions (eTable 2 in the Supplement).

Nikolsky Sign

The presence of a Nikolsky sign was significantly associated with a higher titer of anti-Dsg1 antibodies, PDAI, and ABSIS compared with patients without a Nikolsky sign (anti-Dsg1: 313.16 vs 114.37; $P < .001$; anti-Dsg3: 254.28 vs 189.13, $P = .35$; PDAI: 50.2 vs 23.8, $P = .01$; and ABSIS: 34.8 vs 17.9, $P = .03$).

Mucosal Involvement

The correlations of PDAI mucosal activity with ABSIS oral involvement, PDAI mucosal activity with ABSIS subjective oral discomfort, and PDAI mucosal activity with PVAS mucosal involvement were acceptable (Spearman ρ = 0.96, 0.68, and 0.76, respectively). However, the scatterplot presented poor correlations between positive anti-Dsg3 titers and mucous membrane involvement (Spearman $\rho < .4$). In addition, the mean (SD) anti-Dsg3 titer was 127.73 (144.99) in 18 cutaneous dominant PV patients, although they had no clinical mucous membrane lesions.

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Table 4. Cutoff Values of Skin and Mucosal Activity on the PDAI, ABSIS, and PVAS That Predict 20- and 100-U/mL Titers of Anti-Dsg1 and Anti-Dsg3

	Anti-Dsg1,[a] U/mL		Anti-Dsg3,[a] U/mL	
Measure	20	100	20	100
PDAI				
Cutoff	4.8	9.8	2.8	4.8
AUC	0.84	0.89	0.84	0.78
Sensitivity	0.75	0.80	0.77	0.70
Specificity	0.87	0.87	0.83	0.72
ABSIS				
Cutoff	0.92	2.0	1.0	2.2
AUC	0.84	0.86	0.80	0.74
Sensitivity	0.70	0.84	0.76	0.70
Specificity	0.70	0.80	0.77	0.68
PVAS				
Cutoff	0.70	0.80	0.77	0.68
AUC	0.77	0.86	0.81	0.74
Sensitivity	0.76	0.75	0.75	0.75
Specificity	0.87	0.87	0.83	0.64

Abbreviations: AUC, area under the curve; Dsg, desmoglein; PDAI, Pemphigus Disease Area Index.

[a] Skin activity score had highest accuracy for anti-Dsg1 titer, and mucosal activity scores were better for anti-Dsg3 titer.

Predictors of Anti-Dsg Titers

The multiple linear regression models demonstrated that head and neck, trunk, and limb involvement and the type of lesions were associated with higher titers of anti-Dsg1. Oral and upper airway involvement was associated with higher titers of anti-Dsg3 (eTable 3 in the Supplement).

Cutoff Values

On the basis of ROC curve analyses, we determined cutoff values of total PDAI, ABSIS, and PVAS activity for 2 titers of 20 and 100 U/mL of anti-Dsg1 and anti-Dsg3 (eFigure 4 in the Supplement). The point in the ROC curves with the highest sensitivity, at which an increase in sensitivity resulted in an abrupt decrease in specificity, was considered a cutoff. The AUC values above 0.5 revealed a better performance of each test with higher sensitivity and specificity. Comparing the AUCs of total activity, mucosal activity, and skin activity for anti-Dsg1 titer revealed the highest AUC value for skin activity. The same analysis performed for anti-Dsg3 titer revealed the highest AUC value for mucosal activity. We used skin activity measures to present cutoffs for anti-Dsg1 and mucosal activity measures for anti-Dsg3 cutoffs.

The estimated cutoff values of PDAI skin activity for 20- and 100-U/mL anti-Dsg1 titers were 5 and 10, respectively. The estimated cutoff values of PDAI mucosal activity for 20- and 100-U/mL anti-Dsg3 titers were 3 and 5, respectively. The ABSIS and PVAS cutoffs for 20- and 100-U/mL antibody titers are summarized in **Table 4**.

Discussion

This is the first study, to our knowledge, that evaluated the reliability and validity of the PDAI, ABSIS, and PVAS in a large number of PV patients and correlated these with anti-Dsg1 and anti-Dsg3 ELISA titers. We found the highest interrater reliability for skin activity and mucosal activity of the PDAI, followed by oral involvement of the ABSIS and skin activity of the PVAS (ICCs = 0.99, 0.95, 0.95, and 0.94, respectively). According to our convergent validity results, anti-Dsg1 ELISA values were closely correlated with the skin activity indexes, but anti-Dsg3 titers did not necessarily correlate with the mucosal activity indexes. The time to complete the disease activity form was minimal in PVAS compared with the other indexes. To date, few studies[2,5,7,14] have compared the pemphigus disease activity indexes.

Rosenbach et al[2] scored the PDAI and ABSIS in 15 patients with pemphigus by 10 assessors and estimated the reliability and the convergent validity relative to the PGA. The ICCs were 0.86 for the PDAI skin activity and 0.39 for the ABSIS skin involvement. Their results revealed that the PDAI correlated more closely with the PGA. The mean time to completion in minutes was 4.7 for the PDAI and 3.9 for the ABSIS.[2]

Pfütze et al[5] assessed the ABSIS in 13 PV patients for 6 months after initiation of immunosuppressive therapy and found that the decrease of the ABSIS skin score was accompanied by a gradual decrease of anti-Dsg1 and anti-Dsg3. The correlation coefficients between the scores and autoantibody titers were not presented.[5]

Chams-Davatchi et al[7] evaluated the PVAS in 50 PV patients relative to 5 experts and reported a convergent validity of 0.75 with the PGA. The reported mean time to completion was 3.1 minutes.

The findings for the interrater reliability, our primary objective, revealed that the PDAI skin activity measure provided the most reproducible results. This measure is sensitive to low numbers of lesions and incorporates sensitivity for the size of lesions in its scoring system within the defined anatomical areas, which results in increased interrater reliability. On the other hand, the ABSIS and PVAS use some items that make the measures less reproducible. The ABSIS uses the low-agreement rule of 9 to estimate the body surface area involve-

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ment. Although the raters were familiar with the rule, most of them reported difficulties in scoring, especially for limited disease activity. Both the ABSIS and PVAS require evaluation of lesion type and apply it as a weighting factor, which exaggerates the small differences between raters and causes lower interrater reliability. In addition, the assessment of the Nikolsky sign in PVAS varies among raters with different expertise. However, the intrarater correlation coefficient between the international consensus measure of the PDAI and the PVAS was higher than the correlation coefficient between the PDAI and the ABSIS (ICC = 0.82 vs 0.66). The ABSIS is believed to achieve much of its interrater reliability from the subjective component.[2] Our findings indicated that the interrater reliability was decreased when the patients' subjective information was not included (ICC = 0.98 when included vs 0.95 when not included) (Table 2). It seemed that asking the same questions about subjective oral discomfort several times in the same day, especially in a study setting, might result in falsely elevated reliability. Because the correlation coefficients between mucosal activity measured with the PDAI and ABSIS subjective oral discomfort revealed lower values than mucosal activity measured with the PDAI and ABSIS objective oral involvement (0.68 vs 0.96), the use of such a symptom scale in an objective ABSIS measure seems redundant.

The convergent validity with ELISA titers confirms the previously suggested close correlation between anti-Dsg1 ELISA values and the course of disease.[9,12] Our study revealed a close correlation between anti-Dsg1 and skin activity measures of the PDAI, PVAS, and ABSIS. The higher convergent validity with anti-Dsg1 of 0.67 for the PDAI but only 0.33 for the ABSIS suggests that ABSIS is likely not a good measure to use for pemphigus foliaceus. In addition, healing of the eroded and crusted lesions, with resultant PIH, was associated with decreased titers of anti-Dsg1 (eTable 2 in the Supplement). Some studies[9,15,16] have found that anti-Dsg3 titers did not necessarily parallel the course of mucosal lesions in PV patients. Our study revealed low correlation coefficients between anti-Dsg3 titers and the disease activity indexes. In addition, anti-Dsg3 antibody titers greater than 130 U/mL were detected in 8 patients, although these patients had no clinical mucous membrane lesions. To determine the predictors of anti-Dsg3 values, scatterplots revealed that other unknown independent variables are involved in high titers of anti-Dsg 3, possibly nonpathogenic antibodies that do not contribute to disease activity.

According to the current study based on interrater and intrarater studies, the PDAI would be the measurement of choice. The use of a single disease severity tool would help direct comparison among studies. In addition, the optimal quality-of-life tool will need to be determined and should be used in combination with the physician-derived disease severity.

We did not assess the convergent validity of these measures according to the PGA, which was a limitation of our study. A poor interrater reliability for PGA (ICC = 0.44) was detected by Rosenbach et al,[2,15] and such a low reliability measure would make PGA assessments less consistent.[14]

Our results revealed that the measures seemed weighted toward lower scales, as noted in the study by Rosenbach et al.[2] Although patients with severe pemphigus disease were also included in our study, the PDAI, ABSIS, and PVAS did not reach their potentially maximum scores. Even in the previous study of our authors[8] that included exclusively new PV patients, the initial mean (SD) PVAS was 6.08 (3.3) of a maximum score of 18 (approximate PDAI of 53.22 of a maximum score of 263). Although our patients were enrolled from a follow-up clinic, they were more severely diseased than patients in the study by Rosenbach et al (mean [SD] PDAI, 27.82 [21.17] vs 13.1 [9.03]).[2] It is likely that the potential maximum scores might not be observed in real patients. The loss of intact skin increases the risk of infections, massive transepidermal fluid loss, and electrolyte imbalance.[17] Higher scores may have similar high mortality rates, such as with severe burns or toxic epidermal necrolysis.

The time to complete the PDAI, ABSIS, and PVAS measures was longer in previous studies[2,7] in which these measures were performed for the first time in a small population of patients. In addition, in our study, completion times usually started off higher in the beginning and became lower as the study progressed, suggesting a learning curve.

We found that the upper body involvement was detected in most patients and was associated with less severe pemphigus disease according to the PDAI and anti-Dsg1 and anti-Dsg3 values. In addition, the regression model presented head and neck involvement and oral involvement as independent predictors of anti-Dsg. These findings reflect the variable expression of PV antigens, with the highest PV antigens in the head and neck and decreased densities in the lower back and groin.[18] Therefore, the involvement of the areas with low expression of PV antigens is a sign of more severe pemphigus disease. This finding correlates with our observation of higher PDAI and anti-Dsg1 and anti-Dsg3 values when there is genital and lower-body involvement.

We also presented measurement cutoffs based on different levels of anti-Dsg1 and anti-Dsg3 with previous evidence of their clinical significance. Two previous suggestions of 20-U/mL anti-Dsg1 and anti-Dsg3 titer as positive serum[13] and 130-U/mL titer to predict recurrence of PV[15] were considered, and the ROC analyses and estimations of the optimal PDAI disease activity, ABSIS, and PVAS cutoffs corresponding to 2 titers of 20 and 100 U/mL were performed. In terms of practical use of these measurements, patients with a PDAI greater than 10 likely have a high titer of anti-Dsg1 above 100 U/mL. Although these cutoffs were both in the lower range of measurements, they would potentially provide estimates for staging disease severity.

Conclusions

The PDAI is a highly reliable measurement, especially for skin activity, because it simply calculates the visible lesions in a systematic order. It does not require assessment of the Nikolsky sign, types of lesions, or use of the rule of nines that would be sources of variability. Although it takes slightly more time than other measures and seems more difficult in the beginning, it is reasonable to use this measure in future multicenter studies on pemphigus.

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REFERENCES

1. Martin LK, Werth VP, Villaneuva EV, Murrell DF. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. *J Am Acad Dermatol*. 2011;64(5):903-908.

2. Rosenbach M, Murrell DF, Bystryn JC, et al. Reliability and convergent validity of two outcome instruments for pemphigus. *J Invest Dermatol*. 2009;129(10):2404-2410.

3. Murrell DF, Dick S, Ahmed AR, et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol*. 2008;58(6):1043-1046.

4. Daniel BS, Hertl M, Werth VP, Eming R, Murrell DF. Severity score indexes for blistering diseases. *Clin Dermatol*. 2012;30(1):108-113.

5. Pfütze M, Niedermeier A, Hertl M, Eming R. Introducing a novel Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) in pemphigus. *Eur J Dermatol*. 2007;17(1):4-11.

6. Behzad M, Möbs C, Kneisel A, et al. Combined treatment with immunoadsorption and rituximab leads to fast and prolonged clinical remission in difficult-to-treat pemphigus vulgaris. *Br J Dermatol*. 2012;166(4):844-852.

7. Chams-Davatchi C, Rahbar Z, Daneshpazhooh M, et al. Pemphigus vulgaris activity score and assessment of convergent validity. *Acta Med Iran*. 2013;51(4):224-230.

8. Chams-Davatchi C, Mortazavizadeh A, Daneshpazhooh M, et al. Randomized double blind trial of prednisolone and azathioprine, vs prednisolone and placebo, in the treatment of pemphigus vulgaris. *J Eur Acad Dermatol Venereol*. 2012;27(10):1285-1292.

9. Harman KE, Seed PT, Gratian MJ, Bhogal BS, Challacombe SJ, Black MM. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol*. 2001;144(4):775-780.

10. Amagai M, Tsunoda K, Zillikens D, Nagai T, Nishikawa T. The clinical phenotype of pemphigus is defined by the anti-desmoglein autoantibody profile. *J Am Acad Dermatol*. 1999;40(2, pt 1):167-170.

11. Cheng SW, Kobayashi M, Kinoshita-Kuroda K, Tanikawa A, Amagai M, Nishikawa T. Monitoring disease activity in pemphigus with enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3. *Br J Dermatol*. 2002;147(2):261-265.

12. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, et al. Pemphigus: analysis of 1209 cases. *Int J Dermatol*. 2005;44(6):470-476.

13. Amagai M, Komai A, Hashimoto T, et al. Usefulness of enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus. *Br J Dermatol*. 1999;140(2):351-357.

14. Bastuji-Garin S, Sbidian E. How to validate outcome instruments for pemphigus. *J Invest Dermatol*. 2009;129(10):2328-2330.

15. Abasq C, Mouquet H, Gilbert D, et al. ELISA testing of anti-desmoglein 1 and 3 antibodies in the management of pemphigus. *Arch Dermatol*. 2009;145(5):529-535.

16. Kwon EJ, Yamagami J, Nishikawa T, Amagai M. Anti-desmoglein IgG autoantibodies in patients with pemphigus in remission. *J Eur Acad Dermatol Venereol*. 2008;22(9):1070-1075.

17. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis, part II: the higher scores may have a similar scenario of prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol*. 2013;69(2):187.e1-16.

18. Sison-Fonacier L, Bystryn JC. Regional variations in antigenic properties of skin: a possible cause for disease-specific distribution of skin lesions. *J Exp Med*. 1986;164(6):2125-2130.

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