Scoring Criteria for Autoimmune Bullous Diseases: Utility, Merits, and Demerits

Abstract

Background: Scoring systems play a crucial role in dermatology by providing objective measurements of disease severity, treatment efficacy, and outcome comparisons. In autoimmune blistering diseases (AIBDs), standardized scoring systems are essential for accurate evaluations; however, there is currently a lack of consensus on scoring methods. **Objective:** This literature review explores scoring systems in AIBDs by tracing their development, addressing challenges, and highlighting their role in defining endpoints, regulatory considerations, and clinical trials. **Materials and Methods:** Existing scoring systems for AIBDs, such as the Pemphigus Disease Area Index, Autoimmune Bullous Skin Disorder Intensity Score, Pemphigus Oral Lesions Intensity Score, Oral Disease Severity Score, and Pemphigus Vulgaris Activity Score, are examined for their validity, reliability, and responsiveness. The Bullous Pemphigoid Disease Area Index for bullous pemphigoid is also discussed. The concept of minimal clinically important differences is explored to determine clinically significant improvements in disease severity. **Conclusion:** This review provides a comprehensive understanding of the central role of scoring systems in dermatology and their implications for research and clinical practice in AIBDs.

Keywords: *Autoimmune bullous diseases, COSMIN, dermatology MCID, pemphigus, quality of life, scoring systems, validation*

Henry Tseng[1,2], Corey Stone[1,2], Dédée F. Murrell[1,2]

[1]Department of Dermatology, St. George Hospital, Sydney, NSW, Australia, [2]Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

Introduction

Scoring systems are vital in dermatology for the objective measurement of disease severity, treatment efficacy, and outcome comparisons. With the diverse manifestations of dermatological conditions, standardized tools are crucial for accurate evaluations. However, the lack of consensus on measuring disease severity and treatment outcomes hampers accurate assessments and poses challenges in research and clinical practice. This literature review aims to explore the significance of scoring systems in autoimmune blistering diseases (AIBDs), tracing their development, addressing emerging challenges, and highlighting their role in defining endpoints, regulatory considerations, and clinical trials.

Background

AIBDs encompass a group of immune-mediated disorders characterized by the formation of blisters and erosions on the skin and mucous membranes due to autoantibodies targeting structural proteins. Examples of AIBDs include pemphigus vulgaris, bullous pemphigoid, and mucous membrane pemphigoid.[1,2]

Severity varies from localized skin lesions to life-threatening systemic disease, impacting patient's quality of life (QOL) with pain and impaired functioning and further highlighting the importance of accurate disease severity assessment and monitoring.[1,2]

Scoring systems have been developed to provide an objective assessment of disease severity by evaluating various disease parameters. Among these, body surface area assessment, visual analog scale (VAS), and physician global assessments are frequently utilized in dermatology. The utilization of disease severity scoring methods in dermatology has expanded significantly for several purposes such as prognostic assessment, treatment selection, medication effectiveness evaluation, and comparative analysis of treatment modalities in clinical research.[3] They provide a structured framework that enhances communication and facilitates meaningful discussions

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Address for correspondence:
Prof. Dédée F. Murrell, Department of Dermatology, St. George Hospital, Sydney, NSW, Australia.
E-mail: d.murrell@unsw.edu.au

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among healthcare professionals regarding disease severity and treatment outcomes.[4,5]

Utility, merits, and demerits

To address the problem of non-validated measurement tools, a collaborative effort known as the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) group conducted an international Delphi study from 2006 to 2007. Comprising 43 experts in health status measurement, the COSMIN group aimed to establish consensus on the essential measurement properties and their definitions for validating health-related patient-reported outcomes (HR-PROs). In addition, they developed standards and design requirements for evaluating these measurement properties.[4,6]

The study yielded three primary quality domains: reliability, validity, and responsiveness. Each domain encompassed specific measurement properties. While originally designed for HR-PROs such as QOL measures, the fundamental principles, quality domains, and definitions can be applied to validate tools for assessing disease severity.[6]

Reliability and validity

The *reliability* quality domain of a measurement instrument focuses on consistency and freedom from errors. It includes internal consistency (association between items), reliability (consistency between different observers and over time), and measurement error (reflecting changes not related to the intended construct).[6,7]

The *validity* quality domain includes content validity (the instrument's content representing the construct), construct validity (internal and external relationships), and criterion validity (alignment with a standard). These domains ensure that the instrument is reliable, consistent, and accurately measures the intended construct.[6,7]

Responsiveness

The responsiveness domain focuses on the instrument's ability to detect change over time. It evaluates the instrument's capability to capture true changes in the disease state, distinguishing them from measurement errors. This property, also referred to as sensitivity to change or discriminant validity, has significant implications for drawing conclusions about therapy efficacy in clinical studies.

In addition to the COSMIN criteria, feasibility and cut-offs are additional considerations. Feasibility refers to the time required for completing the scoring process and the resources or costs associated with implementing the instrument. Feasibility considerations can significantly impact the practicality of the outcome measure. Disease severity cut-offs allow for categorizing disease status as mild, moderate, or severe, which has crucial implications in clinical practice for selecting appropriate therapies and in clinical studies for meaningful comparisons.[6]

MCID

While assessment tools are valuable in dermatology, it is essential to recognize that most of these tools are designed to detect only small differences in disease severity. However, such minimal differences may not have a noticeable impact on patients' QOL or the measurable burden of the disease. Hence, the concept of minimal clinically important differences (MCIDs) was developed to statistically determine the smallest difference in an outcome measure that reflects a clinically significant improvement or worsening in disease severity.[4]

MCIDs play a vital role in clinical studies and clinical practice. Values exceeding the MCID threshold provide evidence that a novel intervention or treatment is genuinely beneficial for patients. This information can guide clinical decision-making and help to direct management strategies in real-world settings. By considering MCIDs, clinicians and researchers can better understand the meaningfulness and significance of the observed changes in disease severity, leading to more accurate assessments and effective interventions.[8,9]

Current Scoring Systems for Pemphigus

PDAI

The Pemphigus Disease Area Index (PDAI) is a scoring system for pemphigus developed by the International Pemphigus Committee over a period of 3 years after 2006. It evaluates disease activity and damage, assigning a score for the skin, scalp, and mucous membranes. The activity score (0–20 for the skin and 0–120 for mucous membranes) assesses erosions, blisters, or erythema across 12 locations, while the damage score considers post-inflammatory hyperpigmentation or erythema on resolving lesions on the skin. Each instance of damage receives a score of 1, and the absence of these signs gets a score of 0.[10,11]

Three studies explored PDAI severity cut-offs, categorizing patients into mild, moderate, and severe groups. The Japanese study led by Shimizu *et al*. (2014)[12] relied on the physician's subjective impression, establishing cut-offs as mild (0–8), moderate (9–24), or severe (≥25). Conversely, the French study by Boulard *et al*. (2016)[13] used percentiles, resulting in higher cut-offs: mild (0–14), moderate (15–44), and severe (≥45). More recently, Krain *et al*. (2021)[14] recommended ≤8 for mild and ≥25 for severe, aligning with Shimizu *et al*.

While the PDAI has been widely adopted in the clinical setting, it is important to recognize some of its weaknesses. Mahmoudi *et al*.[15] pointed out several of its limitations,

including the fact that different lesions (such as the evolution of blisters to erosions and ulcers) have been assigned the same weight factor in the PDAI, despite indicating distinct disease activity levels.

ABSIS

The Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) is a scoring system initially developed for evaluating pemphigus, but has since gained widespread use in assessing all AIBDs. Introduced in Germany in 2007, the ABSIS provides a standardized tool for evaluating disease severity in these conditions. It assigns a score from 0 to 206 by taking into account factors, including the percentage of body surface area affected by pemphigus, the pattern and location of lesions on the skin and mucous membranes, and the degree of discomfort experienced by the patient during eating or drinking. Moreover, compared to the PDAI, the ABSIS integrates the damaged items into the overall score instead of treating them as separate items.[16] However, the ABSIS also has its limitations. For instance, the evaluation of lesion type as a weighting factor might introduce subjectivity to the assessment. These limitations should be considered when utilizing the ABSIS for disease evaluation.

Boulard *et al*. (2016)[13] established ABSIS cut-offs at 17 and 53, delineating moderate, significant, and extensive pemphigus forms. Mohebi *et al*. (2020)[17] identified 25th and 75th percentile cut-offs at 4 and 29.5, respectively, with model-based analysis yielding three groups (cut-points: 6.4 and 31.5) for ABSIS scores.

PVAS

The Pemphigus Vulgaris Activity Score (PVAS) is a scoring system for pemphigus vulgaris, developed in Iran. It evaluates disease activity based on antigen expression, healing process, mucocutaneous involvement, lesion type, and Nikolsky's sign. The scale ranges from 0 to 18 (skin activity: 11 points; mucosal activity: 7 points), with specific scores assigned for each component, including total lesions, anatomical regions, the presence of Nikolsky's sign, and lesion types, considering the overall score's weight. In addition, the type of lesion is taken into consideration to weigh the overall score.[18]

Validity and reliability – PDAI, ABSIS, and PVAS

In two multicenter studies conducted in 2009 and 2012, the reliability and convergent validity of the PDAI and ABSIS were assessed in patients with pemphigus. In the 2009 study involving 15 patients, the PDAI demonstrated higher inter- and intra-rater reliability (ICC = 0.76 and ICC = 0.98, respectively) compared to the ABSIS (ICC = 0.77 and ICC = 0.80, respectively). The PDAI also correlated more strongly with the physician's assessment of disease extent, particularly in cases of mild-to-moderate disease activity.[19] Similarly, in the 2012 study in Iran on 100 pemphigus vulgaris patients, the PDAI showed the highest interrater reliability (ICC = 0.98) among the scoring systems, followed by ABSIS (ICC = 0.97) and PVAS (ICC = 0.93). Moreover, the PDAI exhibited the strongest correlation with anti-desmoglein (DSG) titers, indicating a closer association between PDAI scores and antibody levels. These findings collectively suggest that the PDAI is a more reliable tool for assessing pemphigus severity, particularly in cases involving variability in cutaneous disease.[18,19]

In a more recent 24-month multicenter international study in 2019 involving 116 newly diagnosed pemphigus patients, the PDAI and ABSIS demonstrated high ICC values at baseline, indicating strong agreement between raters. The PDAI had higher ICCs in moderate and extensive cases, while ABSIS had higher ICCs in intermediate and extensive cases. The skin sub-scores of both scoring systems moderately correlated with anti-desmoglein antibody values, while mucosal sub-scores showed weaker correlations.[20] These findings not only underscore the validity and reliability of the PDAI and ABSIS but also emphasize the utility of specific cut-off values for the PDAI and ABSIS (PDAI: 15 and 45; ABSIS: 17 and 53), as reported by a multicenter study.[13] These cut-off values effectively distinguish between moderate, significant, and extensive forms of pemphigus, thereby providing a valuable tool for assessing disease severity. Besides these scoring systems for pemphigus, it is important to acknowledge the existence of other scoring systems for pemphigus. Among these is the Pemphigus Area and Activity Score (PAAS), an early entrant in the field.[21] Although it considers body surface area (BSA) and lesion count, it relies on subjective severity descriptions and lacks lesion size quantification, rendering it less precise for assessing disease activity.[22]

Moreover, it is important to note the apparent lack of patient assessment in evaluating pemphigus. While a validated VAS for pemphigus is currently unavailable, its potential utility in the future remains an important consideration.

Responsiveness

To date, no study has been conducted to specifically examine the responsiveness of the PDAI, ABSIS, and PVAS scoring systems.

BPDAI

The Bullous Pemphigoid Disease Area Index (BPDAI) is a scoring system specifically developed by the International Bullous Diseases Group (IBDG) in 2007 to assess bullous pemphigoid. The scoring system ranges from 0 to 360 points based on four main components: body surface area percentage affected, peak pruritus numerical rating scale (NRS) score, disease extent index, and area index. Notably, the pruritus component is evaluated separately as it represents a subjective aspect of the BPDAI. The BPDAI was designed to provide a comprehensive

evaluation of disease severity and the impact of symptoms on the patient's QOL. Its development involved careful consideration of the key features and manifestations of bullous pemphigoid, aiming to capture both objective and subjective aspects of the condition.[23]

Validity and reliability – BPDAI

In a 2017 Australian study by Wijayanti *et al*.,[23] data revealed that the Bullous Pemphigoid Disease Area Index (BPDAI) demonstrated strong interrater reliability (ICC = 0.976) and even higher intrarater reliability (ICC = 0.996). These results indicate consistent and reliable BPDAI scores when assessed by different raters and on different occasions. In relation to the ABSIS, which is also utilized for scoring bullous pemphigoid, Wijayanti *et al*.[23] in their same study observed slightly lower reliability, validity, and responsiveness with the ABSIS compared to the BPDAI. Despite this, the authors deemed its performance to be moderate to good.

Similarly, in a more recent multicenter study conducted in Europe in 2021, the BPDAI score was evaluated to establish cut-off values for categorizing mild, moderate, and severe cases of bullous pemphigoid. The study involved 285 BP patients from 50 dermatology departments. The calculated cut-off values were 20, 57, and above 57, respectively, based on BPDAI score percentiles. The study further demonstrated a high baseline intraclass correlation coefficient (ICC = 0.97), which remained stable up to month 6. In addition, the BPDAI improvement correlated with decreased anti-BP180 antibodies but not with anti-BP230 antibodies. These findings confirm the BPDAI's reliability and precision in assessing BP severity and provide valuable clinical classification cut-off values.[24]

Responsiveness

In Wijayanti *et al*.'s (2017)[23] study, researchers categorized the 32 patients as improved, stable, or deteriorated and conducted a paired *t*-test using BPDAI scores. Statistically significant differences were expected between the improved and deteriorated groups, indicating treatment response or disease progression. No significant differences were anticipated for the stable group. This approach aimed to assess the BPDAI's ability to capture changes in patient conditions based on physician subjective assessments.

An additional noteworthy scoring system for pemphigoid is the partially validated Mucous Membrane Pemphigoid Disease Area Index (MMPDAI). Although proposed with content validation, its reliability is yet to be tested. Like the PDAI and BPDAI, the MMPDAI evaluates separate activity scores for the skin, scalp, and mucous membranes.[25]

POLIS

Other scoring systems address the need for particular emphasis on oral lesions in patients with pemphigus vulgaris given their clinical significance, which almost parallels that of other mucocutaneous involvement. An illustrative example is the recently introduced Pemphigus Oral Lesions Intensity Score (POLIS), introduced in 2020. The POLIS considers 16 factors, including the number of relapses, disease duration, and the persistence of oral lesions after the subsidence of cutaneous lesions. It also considers aspects such as changes in the size of oral lesions, the development of new oral lesions, and difficulties in activities such as speaking, brushing teeth, and swallowing over the past week. In addition, it assesses the overall size and depth of erosions.[26]

In terms of strengths, POLIS offers a relatively sensitive measurement and exhibits good agreement with the clinical severity of oral lesions in pemphigus. Moreover, it is convenient for bedside assessment. However, it is crucial to note certain limitations. As a new scoring system, there is limited knowledge about its nuances. Furthermore, POLIS relies somewhat on patient history, making it susceptible to recall errors on the part of patients.[27]

ODSS

Another recently introduced scoring system designed to specifically address oral lesions in pemphigus vulgaris is the Oral Disease Severity Score (ODSS), introduced in 2018. Developed by the Oral Medicine group at Guy's Hospital, ODSS originated from a scoring system designed for multisite mucous membrane pemphigoid (MMP). The ODSS assesses the presence and activity level of lesions across multiple oral sites. It also incorporates a subjective evaluation of the patient's oral pain over the preceding week.[28]

The strengths of ODSS lie in its validation for assessing oral pemphigus vulgaris, demonstrating superior inter- and intra-observer reliability (0.83) compared to PDAI, ABSIS, and PGA.[28] Notably, ODSS exhibits efficiency, providing a quick evaluation. In addition, previous studies have confirmed its reliability in assessing conditions such as lichen planus (LP) and MMP.[29,30] Moreover, ODSS has proven valuable in evaluating therapeutic responses over time, particularly in severe cases of mucosal LP and pemphigus vulgaris.[31,32]

Additional scoring systems, though briefly mentioned for completeness, include the Pemphigus Area and Activity Score (PAAS), Saraswat's oral pemphigus scoring, Pemphigus vulgaris lesion severity score, Harman *et al*.'s pemphigus grading, Kumar's scoring system, and Mahajan's scoring system.[21,33-37]

FDA desire for IGA

The U.S. Food and Drug Administration (FDA) favors the Investigator Global Assessment (IGA) scores for skin disease assessment for several reasons. These offer a quick and straightforward global assessment on a five-point scale (ranging from 0 to 4), ensuring standardized and consistent evaluation of disease severity and treatment

response in clinical trials.[38] The use of IGA scores promotes effective communication among investigators, sponsors, and regulatory authorities. However, the IGA might not fully capture the complexity of skin diseases such as atopic dermatitis (AD) as it excludes key information such as body surface area, symptoms, and QOL as primary endpoints. In addition, the FDA's use of IGA score ≤1 as the primary endpoint may favor treatment success in mild patients over severe ones, sparking controversy.[38] There is a debate about whether the FDA should continue with IGA or develop a new, all-encompassing tool for disease severity assessment.[39] IGA scores for pemphigus and bullous pemphigoid are currently under testing by the IBDG.

Subjective Scores in Dermatology

In dermatology, disease severity assessment requires a balance between objective and subjective measures. Objective assessments ensure accuracy and consistency, while subjective scoring offers insights into the patient's personal experience and its impact on their well-being. While reliability and validity studies establish the scientific rigor of objective measures, integrating subjective reports provide a holistic understanding of the patient's experience. This comprehensive approach allows healthcare professionals to tailor personalized care that addresses both physical and psychosocial aspects of the disease.

ABQOL

In 2012, Murrell *et al*. introduced the Autoimmune Bullous Disease Quality of Life (ABQOL) questionnaire, the first disease-specific tool to assess QOL in blistering diseases. The ABQOL showed moderate correlations with the Dermatology Life Quality Index (DLQI) and Short Form 36, indicating convergent validity and higher sensitivity in discriminant validity. Reliability and convergent validity were confirmed in various populations, including Australian, North American, Persian, Greek, Turkish, French, Polish, Chinese, and Arabic-speaking cohorts.[40-46] The ABQOL's value was demonstrated in clinical trials with pemphigus vulgaris patients and mucosal involvement.

DLQI

The DLQI is a validated questionnaire widely used to assess the impact of dermatological diseases on health-related quality of life (HRQOL). Developed in 1994 by Finlay and Khan, it has been translated into over 90 languages and used in 40 dermatoses studies. It comprises ten items grouped into six categories, reflecting symptoms, daily activities, leisure, work/study, relationships, and treatment. Patients rate the disease's impact over the past week on a scale from "not at all" to "very much." Scores range from 0 to 30, with higher scores indicating more significant HRQOL impairment. The DLQI has shown good psychometric properties and has been well-received in diverse cultural contexts.[47]

Validity and reliability – ABQOL and DLQI

Before the ABQOL questionnaire, generic and dermatology-specific instruments such as the DLQI were used to assess disease activity and evaluate care effectiveness in patients with AIBDs. Studies have revealed that AIBD patients, especially those with pemphigus, experience significantly reduced QOL and have a high prevalence of psychiatric comorbidity. While the DLQI and General Health Questionnaires have been used, the ABQOL has shown better responsiveness in assessing disease activity.[46]

Multiple studies have shown a strong correlation between ABQOL scores and pemphigus-specific severity indices such as PDAI. Krain *et al*.[48] found a close link between ABQOL, Skindex-29, SF-36, and PDAI scores, particularly in mucosal involvement patients, indicating ABQOL's sensitivity for symptom changes and longitudinal monitoring. A further study by Bax *et al*. emphasized that even minimal disease activity in pemphigus patients can significantly impact their QOL, highlighting the importance of considering QOL outcomes in treatment evaluation.[49]

Other QOL measurement tools

Other significant QOL measurement tools in dermatology are the Treatment Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaire and the EQ-5D. The EQ-5D is a generic measure of health-related quality, evaluating mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; it uses a visual analog scale (EQ-VAS) from 0 to 100.[50]

GTI

The Glucocorticoid Toxicity Index (GTI) is a reliable measure of glucocorticoid (GC) toxicity in inflammatory diseases, addressing the need for assessing and mitigating GC-related adverse effects to improve patient care. It focuses on GC therapy-associated toxicities, categorized into domains such as glucose metabolism, infection, and neuropsychiatric effects.[51]

Liang *et al*.[52] found a significant linear correlation between GTI scores and prednisone doses in AIBD patients, demonstrating the GTI's ability to effectively capture glucocorticoid toxicity changes over time. This establishes its feasibility as a valuable tool for future clinical trials.

In addition, the GTI has been validated in various studies for pathologies such as ANCA-associated vasculitis, asthma, and systemic lupus erythematosus. It has been utilized in over 45 studies, including 12 phase-3 clinical trials, making it a valuable tool for assessing the impact of GC-induced toxicity across multiple medical conditions.[51,53]

Importance of Endpoints in Clinical Trials

Endpoints are critical in clinical trials to evaluate treatment efficacy and its impact on disease characteristics. Assessing multiple endpoints is common to comprehensively measure

drug efficacy, as relying on one aspect may be insufficient. Failing to account for multiplicity when analyzing multiple endpoints can lead to inaccurate conclusions.[54]

In dermatology, the International Pemphigus Committee has put forth the consensus regarding late endpoints of disease activity of pemphigus, which includes two main categories: complete remission off therapy and complete remission on therapy. Complete remission off therapy means no new or existing lesions without systemic treatment for at least 2 months, whereas complete remission on therapy involves minimal therapy with no new or existing lesions for at least 2 months. Minimal therapy is defined as a prednisone dose of 10 mg/day or less (or an equivalent medication) and/or minimal adjuvant therapy for at least 2 months.[55]

Conclusion

Significant advances have been made in the assessment of AIBDs since 2006 with the utilization of standardized scoring systems such as the PDAI, ABSIS, PVAS, BPDAI, ABQOL, and DLQI to assess disease severity and treatment efficacy. Further research should focus on responsiveness and MCIDs to enhance assessments. The validity of IGA scores being tested for disease severity remains to be seen.

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Conflicts of interest

There are no conflicts of interest.

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