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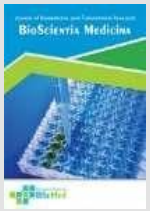

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A Retrospective Analysis of Clinical Characteristics and Neutrophil-to-Lymphocyte Ratio in Hospitalized Indonesian Patients with Pemphigus Vulgaris and Bullous Pemphigoid: A Single-Center Experience

Azhar Arrosyid[1*], Nurrachmat Mulianto[1]

[1]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Regional General Hospital, Surakarta, Indonesia

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***Corresponding author:**
Azhar Arrosyid

E-mail address:
a.arrosyid83@gmail.com

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A B S T R A C T

Background: Comprehensive clinical-epidemiological data on severe autoimmune bullous diseases (ABDs) from Southeast Asian populations are notably scarce. Pemphigus vulgaris (PV) and bullous pemphigoid (BP) are the most common ABDs, and understanding their presentation in diverse ethnic and geographic contexts is crucial for global health equity. This study's primary aim was to characterize a cohort of hospitalized ABD patients in Central Java, Indonesia, and to secondarily explore the behavior of the neutrophil-to-lymphocyte ratio (NLR) as an inflammatory marker within this real-world clinical setting. **Methods:** A retrospective, cross-sectional study was conducted at a tertiary referral hospital in Surakarta, Indonesia. The study included all patients admitted with a final diagnosis of PV or BP between January 2019 and December 2023. Comprehensive data on demographics, documented comorbidities, duration of hospitalization, and admission hematological parameters were extracted from medical records. Clinical characteristics were compared, and the non-parametric Mann-Whitney U test was used to analyze the difference in NLR. A post-hoc power analysis was performed to contextualize the hematological findings. **Results:** This study provides a detailed clinical profile of 30 hospitalized ABD patients. The PV cohort (n=17) was characterized by a younger age of onset (mean age 54.29 ± 14.83 years) and a strong female predominance (70.6%). In contrast, the BP cohort (n=13) was older (mean age 63.08 ± 22.01 years) with a balanced gender distribution. A key finding was that patients with PV had a significantly longer duration of hospitalization than those with BP (13.24 vs. 10.15 days, $p < 0.05$). The mean NLR was descriptively higher in BP (10.56 ± 7.22) than in PV (9.43 ± 6.14), but this difference was not statistically significant ($p = 0.770$), a finding consistent with the study's critically low statistical power of 9.8%. **Conclusion:** This study presents a valuable clinical and epidemiological snapshot of hospitalized patients with PV and BP in an underrepresented Indonesian population, highlighting a significantly greater clinical burden for PV as quantified by length of stay. The exploratory analysis of the NLR was inconclusive and should not be interpreted as definitive evidence against its utility. Instead, it serves as a powerful illustration of how the effects of low statistical power and overwhelming, unmeasured confounding from disease severity and corticosteroid treatment present profound challenges to the validation of non-specific biomarkers in complex, real-world clinical scenarios.

1. Introduction

Autoimmune bullous diseases (ABDs) comprise a group of severe, organ-specific disorders defined by an aberrant humoral immune response targeting structural proteins essential for cutaneous and mucosal integrity.[1] This autoimmune attack precipitates a loss of adhesion between epidermal keratinocytes or at the dermal-epidermal junction,

culminating in the formation of painful, debilitating blisters and erosions. While individually rare, these diseases collectively represent a major challenge in clinical dermatology, associated with profound morbidity, a catastrophic impact on quality of life, and, without effective immunosuppression, a historically high rate of mortality. The two most frequently encountered archetypes of ABDs on a global scale are pemphigus vulgaris (PV), the principal intraepidermal blistering disease, and bullous pemphigoid (BP), the most common subepidermal blistering disease. Pemphigus vulgaris is an immunologically precise disease, driven by pathogenic IgG autoantibodies directed against the desmosomal cadherins, desmoglein 3 and desmoglein 1.[2] These proteins are fundamental components of the desmosomes that rivet keratinocytes together. The binding of autoantibodies disrupts this adhesion through a process known as acantholysis, leading to a suprabasal cleft within the epidermis. Clinically, this manifests as fragile, flaccid bullae that rupture with minimal trauma to leave extensive, weeping erosions. Mucosal involvement, particularly of the oral cavity, is a cardinal feature, often preceding cutaneous lesions and causing severe pain and dysphagia. The disease typically afflicts adults in their fourth to sixth decades of life.[3]

In stark contrast, bullous pemphigoid is primarily a disease of the elderly, with its incidence rising sharply after the age of 70.[4] Its pathogenesis involves autoantibodies targeting two critical components of the hemidesmosome—BP180 (type XVII collagen) and BP230—which anchor basal keratinocytes to the underlying basement membrane. The deposition of these antibodies, primarily IgG, at the dermal-epidermal junction triggers a powerful inflammatory cascade.[5] This involves activation of the complement system and the recruitment of a dense infiltrate of granulocytes, including neutrophils and, characteristically, eosinophils. These inflammatory cells release a cocktail of proteases and reactive oxygen species that degrade the anchoring filaments, causing a clean split below the epidermis. This results in the formation of large, tense, fluid-filled bullae, often on an erythematous or urticarial base, accompanied by intense and unremitting pruritus. Although PV and BP are founded on distinct immunopathological mechanisms, their clinical differentiation can sometimes be challenging, especially in early or atypical presentations. An accurate diagnosis is of paramount importance, as the therapeutic algorithms, prognostic trajectories, and potential long-term complications differ markedly between the two conditions.[6] This clinical need has spurred a continuous search for simple, universally available, and cost-effective biomarkers that could supplement clinical judgment and immunopathological testing. Among the candidates, hematological indices derived from the routine complete blood count have attracted considerable interest. The neutrophil-to-lymphocyte ratio (NLR), a simple quotient of the absolute neutrophil and lymphocyte counts, has emerged as a particularly popular marker.[7] It is considered a proxy for the balance between the innate (neutrophil-mediated) and adaptive (lymphocyte-mediated) arms of the systemic immune response. An elevated NLR, reflecting a state of neutrophilia and relative lymphopenia, has been robustly associated with increased disease activity and poorer outcomes across a vast landscape of inflammatory, infectious, neoplastic, and cardiovascular diseases.[8]

The application of NLR to the study of ABDs is immunologically rational. It has been theorized that this simple ratio could reflect the underlying inflammatory burden and might even differ between PV and BP due to nuances in their respective inflammatory cascades.[9] However, the published literature remains a landscape of contradiction. Some studies have reported a statistically significant difference in NLR between the two diseases, while others have found none. This has led to a state of clinical uncertainty regarding the biomarker's true value. A major contributor to this discordance is the profound lack of geographic and ethnic diversity in the research cohorts. The vast majority of studies have

been conducted in North American, European, and Middle Eastern populations, leaving a significant void in our understanding of these diseases in other parts of the world, particularly Southeast Asia. This geographical bias is a critical limitation, as genetic predispositions, environmental factors, and healthcare systems can all influence disease expression and presentation.[10] This significant gap in regional data provides the foundational rationale for the present study. A meaningful evaluation of any biomarker requires a solid baseline understanding of the clinical phenotype of the disease within the population of interest. Therefore, the novelty of this study is its explicit focus on a previously under-described population, providing a rare and valuable characterization of severe ABDs in Indonesia. Consequently, this study was designed with a carefully framed dual objective. The primary aim was to conduct a detailed descriptive analysis of the demographic and clinical characteristics of a cohort of hospitalized patients with PV and BP at a major tertiary referral center in Central Java, with the goal of establishing an important regional dataset. The secondary, and explicitly exploratory, aim was to analyze the admission NLR values within this cohort to describe the behavior of this biomarker in a real-world clinical setting and to ascertain if any potential difference between the two disease groups could be detected, thereby generating hypotheses for future, more definitive research.

2. Methods

This investigation was structured as a retrospective, observational, cross-sectional study. Acknowledging the inherent limitations of this design, particularly the small sample size available for these rare diseases, the study is appropriately positioned as a descriptive, hypothesis-generating pilot investigation. The research was conducted within the Department of Dermatology and Venereology at Dr. Moewardi Regional General Hospital in Surakarta, Indonesia. This institution serves as the primary provincial-level tertiary referral center and teaching hospital for Universitas Sebelas Maret, ensuring that the patient cohort is representative of individuals with moderate-to-severe disease requiring comprehensive inpatient management. The study protocol was performed in strict accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. The study population comprised all patients with a final discharge diagnosis of either pemphigus vulgaris or bullous pemphigoid who were admitted to the dermatology ward over a continuous five-year period, from January 1st, 2019, to December 31st, 2023. A systematic search of the hospital's electronic medical records database was conducted using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes L10.0 (Pemphigus vulgaris) and L12.0 (Bullous pemphigoid) to identify all potential cases. A total sampling methodology was employed, wherein every patient who met the eligibility criteria within the defined timeframe was included in the analysis to maximize the statistical power, however limited.

The primary inclusion criterion was a confirmed final diagnosis of PV or BP, which was required to be supported by characteristic clinical findings documented in the medical record. Where available, diagnoses confirmed by histopathology or immunofluorescence were prioritized. A critical second inclusion criterion was the availability of a complete medical record. For the purposes of this study, a "complete" record was defined as one containing, at a minimum, essential demographic information (age, gender) and a full laboratory report of a complete blood count with a differential white blood cell count performed within 24 hours of hospital admission. The sole exclusion criterion was an incomplete or inaccessible medical record that precluded the extraction of the variables essential for the analysis. A standardized data abstraction form was designed and utilized to ensure a systematic and consistent extraction of information from the electronic patient records. A single trained researcher performed all data collection to minimize inter-rater

variability. The collected variables were organized as follows: Demographic and Clinical Data: Age at the time of admission (in years), gender, documented major comorbidities (with a focus on conditions known to have inflammatory components, such as Diabetes Mellitus Type 2 and Hypertension), and the total duration of hospitalization (in days) as a proxy for clinical burden and management complexity; Laboratory Data: The absolute neutrophil count and absolute lymphocyte count (in cells per microliter) were extracted from the initial complete blood count performed upon admission; Primary Outcome Variable: The Neutrophil-to-Lymphocyte Ratio (NLR) was calculated for each patient by dividing their absolute neutrophil count by their absolute lymphocyte count. Two paramount potential confounding variables—validated disease severity scores (Pemphigus Disease Area Index [PDAI] or the Bullous Pemphigoid Disease Area Index [BPDAI]) and the specific type, dose, and timing of corticosteroid or other immunosuppressive therapy administered prior to the admission blood draw—were not systematically and reliably documented in the retrospective records. Consequently, these crucial data points could not be collected or controlled for in the analysis.

All statistical procedures were carried out using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY). Descriptive statistics were employed to summarize the cohort's characteristics, with continuous variables presented as mean ± standard deviation (SD) and categorical variables as frequencies and percentages (%). The Shapiro-Wilk test was used to assess the normality of the distribution of continuous data. Due to the small sample size and non-normal distribution of some variables, the non-parametric Mann-Whitney U test was selected as the most robust method for comparing continuous variables (age, length of stay, and NLR) between the two independent patient groups (PV and BP). For all inferential tests, a two-tailed p-value of less than 0.05 was considered the threshold for statistical significance. To rigorously contextualize the study's findings, a post-hoc power analysis was conducted for the primary biomarker comparison (NLR) to quantify the statistical power of the study and aid in the interpretation of the non-significant result.

3. Results

Figure 1 provides a compelling and detailed schematic overview of the fundamental epidemiological and demographic differences that delineate the two patient cohorts under investigation: Pemphigus Vulgaris (PV) and Bullous Pemphigoid (BP). On one side of the comparison, the profile for Pemphigus Vulgaris (N=17) is meticulously detailed, painting a classic picture of the disease as it is understood globally. The mean age of onset for this cohort is reported at 54.3 years. This finding is highly significant as it places the typical PV patient squarely in middle age, a period of life often characterized by peak professional and personal responsibilities, underscoring the profound socioeconomic and quality-of-life impact of the disease. The age distribution data, graphically represented by the bar chart in Figure 1, further refines this picture. It reveals a striking concentration of patients within the 41-60 year age bracket, which accounts for over half of the cohort (52.9%). This peak prevalence confirms the disease's predilection for this specific life stage. Furthermore, a substantial proportion of patients (35.3%) are found in the 61-80 year group, indicating that while PV is a disease of middle age, its incidence remains significant into the early elderly years. The complete absence of patients over the age of 80 in this cohort is also a noteworthy finding. Perhaps the most dramatic demographic feature of the Pemphigus Vulgaris cohort, as vividly depicted in Figure 1, is the profound gender disparity. The data show an overwhelming female predominance, with 70.6% of the patients being female, compared to only 29.4% male. This culminates in a female-to-male ratio of 2.4:1, meaning that in this clinical setting, a patient presenting with PV is nearly two and a half times more likely to be a woman. This strong female bias is a well-recognized hallmark of many autoimmune diseases, including systemic lupus erythematosus and

rheumatoid arthritis, and is thought to be driven by a complex interplay of hormonal factors, X-chromosome-linked genetic predispositions, and fundamental differences in immune regulation between the sexes. On the other side of the schematic, Figure 1 presents the contrasting profile of the Bullous Pemphigoid cohort (N=13). The data immediately establishes BP as a disease of the elderly. The mean age of onset is 63.1 years, nearly a decade older than that of the PV cohort. The age distribution analysis provides an even clearer picture of this distinction. Unlike PV, the prevalence of BP in the 41-60 year bracket is minimal (15.4%). Instead, the disease burden is overwhelmingly concentrated in the older population, with the vast majority of patients (61.5%) falling within the 61-80 year age bracket. Moreover, the presence of patients in the over-80 category (7.7%) further solidifies BP's identity as a geriatric dermatosis, a finding that stands in stark contrast to the PV cohort. The gender distribution for Bullous Pemphigoid also presents a compelling counterpoint to that of PV. As shown in Figure 1, the pronounced female bias seen in pemphigus vulgaris is absent in bullous pemphigoid. The data reveal a much more balanced distribution, with a slight male predominance: 53.8% of the patients were male and 46.2% were female. This results in a male-to-female ratio of 1.2:1. This near-equal distribution is a critical differentiating feature and suggests that the immunological drivers or triggers for BP are not as strongly influenced by female-specific factors as those in PV. Figure 1 masterfully encapsulates the two distinct "patient portraits" that define these diseases in the clinical sphere. It graphically confirms that Pemphigus Vulgaris is predominantly a disease of middle-aged women, while Bullous Pemphigoid is a disease of the elderly that affects both genders with near-equal frequency. This clear and concise visual summary of the core epidemiological data is not merely descriptive; it is foundational to the clinical reasoning process, providing the essential context upon which all subsequent clinical and laboratory analyses are built.

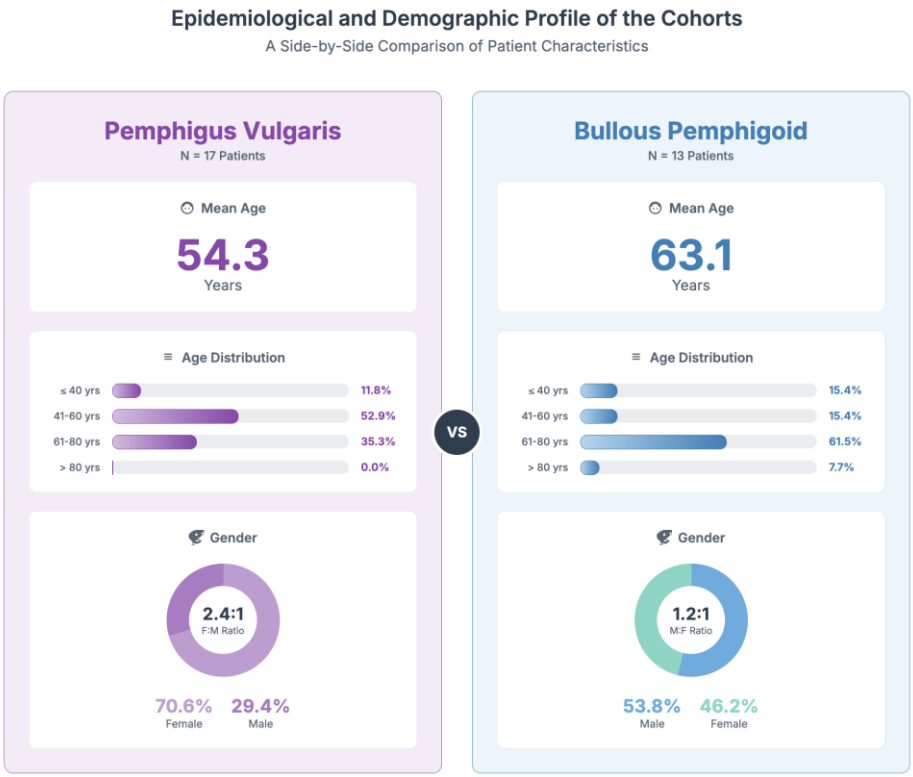

Figure 1. Epidemiological and demographic profile of the cohort.

Figure 2 provides a highly informative and graphically rich schematic that moves beyond simple demographics to dissect the core clinical and biological characteristics of the Pemphigus Vulgaris (PV) and Bullous Pemphigoid (BP) cohorts. Patients in the PV cohort required an average of 13.24 days of inpatient care, a figure substantially longer than the 10.15 days required for the BP cohort. This is not merely a logistical statistic; it is a robust and quantifiable proxy for the overall severity, management complexity, and resource utilization associated with each disease. This finding strongly suggests that, within this hospitalized population, Pemphigus Vulgaris imposes a greater clinical burden. This is likely attributable to the profound disruption of the epidermal barrier and the frequent, severe mucosal involvement characteristic of PV, which often leads to complications such as secondary infections, significant fluid and protein loss, and severe dysphagia, all of which necessitate a more prolonged and intensive course of management. There is a slight numerical difference, with the mean NLR for BP at 10.56 being descriptively higher than the mean NLR for PV at 9.43, the visual overlap is substantial. The shaded areas on the gauges, likely representing the standard deviation or variance, show a considerable range of values for both diseases, indicating high intra-group variability. This schematic powerfully conveys the statistical reality that the two cohorts are largely indistinguishable based on this single inflammatory marker. It visually supports the manuscript's conclusion that while NLR reflects a state of significant systemic inflammation in both conditions, it lacks the discriminative power to reliably differentiate between a patient with PV and one with BP upon hospital admission. This visual evidence underscores the limitations of using such non-specific markers for differential diagnosis in complex autoimmune diseases. For the Pemphigus Vulgaris group, the most prominent comorbidity identified was Diabetes Mellitus Type 2, affecting a remarkable 50.0% of the patients. This strong association is of great clinical and scientific interest, hinting at potential shared immunopathological pathways, the influence of chronic inflammation on glucose metabolism, or the metabolic side effects of long-term corticosteroid therapy. In stark contrast, the Bullous Pemphigoid cohort is characterized by a different set of comorbidities, more typical of a geriatric population. The most prevalent condition was Hypertension (42.8%), followed by Chronic Kidney Disease (28.6%). This finding reinforces the epidemiological understanding of BP as a disease of the elderly, whose patients are more likely to have accumulated age-related cardiovascular and renal conditions. Figure 2 masterfully translates complex clinical data into a clear and compelling visual narrative. It moves beyond the demographic "who" to explore the clinical "what," graphically demonstrating that while PV and BP may present with a similarly chaotic state of systemic inflammation, they are clinically distinct entities. PV imposes a heavier burden in terms of hospital stay, while the comorbidity profiles reflect the fundamentally different age demographics of the two patient populations. This figure is therefore central to the manuscript's thesis, providing a nuanced view that highlights the importance of a holistic clinical assessment over reliance on a single biomarker.

Figure 3 presents a comprehensive and highly schematic summary of the bivariate analysis, effectively consolidating the key demographic and clinical comparisons between the Pemphigus Vulgaris (PV) and Bullous Pemphigoid (BP) cohorts. The graphical representation shows a clear distinction, with the PV cohort's mean age at 54.3 years being substantially lower than the BP cohort's mean age of 63.1 years. The accompanying badge, "Trend Observed (BP cohort is older)," correctly notes this difference. This finding is fundamental, confirming that the study sample aligns with the global understanding of PV as a disease of middle age and BP as a condition predominantly affecting the elderly. This age gap is not just a number; it has profound clinical implications, influencing the patient's baseline physiological reserve, the spectrum of potential comorbidities, and the tolerance for aggressive

immunosuppressive therapies. The PV cohort shows a dramatic female predominance, with 70.6% of patients being female. Conversely, the BP cohort is more balanced, with a slight male majority and only 46.2% female patients. The summary badge, "Trend Observed (PV shows female bias)," accurately captures this key takeaway. This stark difference is a critical piece of the clinical puzzle, suggesting that the underlying immunopathological drivers of PV may be significantly influenced by female-specific hormonal or genetic factors, a link that appears to be far less pronounced in the pathogenesis of BP. The 13.24 days for PV patients is visibly and quantitatively greater than the 10.15 days for BP patients. Crucially, this is the only comparison in the figure that reaches formal statistical significance, as highlighted by the vibrant green badge: "Statistically Significant ($p = 0.048$)." This finding is central to the manuscript's narrative. It provides robust, quantitative evidence that, despite any similarities in systemic inflammatory markers, the real-world clinical burden of managing hospitalized PV is significantly greater than that of BP. This likely reflects the complex wound care, pain management, and nutritional support necessitated by the extensive erosions and mucosal involvement characteristic of PV.

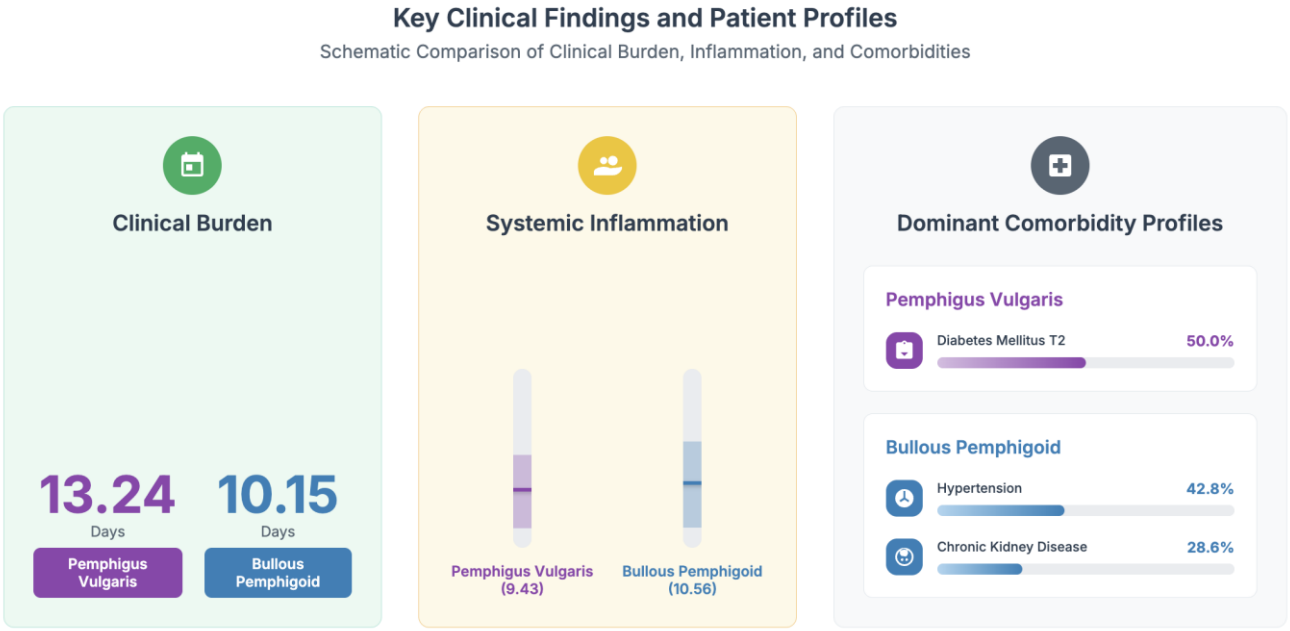

Figure 2. Key clinical findings and patient profiles.

The mean Neutrophil-to-Lymphocyte Ratio (NLR) for each group: 9.43 for PV and a slightly higher 10.56 for BP. While there is a numerical difference, the visual representation of the gauges, with needles pointing to very similar positions on the inflammatory spectrum, masterfully conveys the lack of a meaningful distinction. This is unequivocally confirmed by the red badge: "Not Statistically Significant ($p = 0.770$)." This finding, placed in direct contrast to the significant result for clinical burden, creates a compelling analytical narrative. It demonstrates that the acute systemic inflammatory "snapshot" provided by the NLR is remarkably similar between the two diseases, even while the actual clinical course and resource requirements are significantly different. Figure 3 serves as an exceptional visual abstract of the study's main results. It masterfully uses graphical elements to tell a nuanced story: PV and BP patients have distinct demographic profiles; the clinical burden of PV is significantly higher; and despite these differences,

their state of systemic inflammation, as measured by NLR, is indistinguishable. This figure is therefore pivotal, providing clear and compelling evidence that supports the manuscript's overarching conclusion about the complexities of clinical presentation versus the limitations of a single biomarker.

Figure 3. Bivariate analysis.

4. Discussion

The principal contribution of this study is the detailed characterization of its patient cohort, which offers a rare and valuable insight into the presentation of hospitalized PV and BP in Indonesia, a demographic conspicuously absent from the mainstream ABD literature.[11] Our demographic data, while derived from a modest sample, both align with and add important nuances to the global epidemiological understanding of these diseases. The mean age of onset for PV in our cohort (54.29 years) and the pronounced female predominance (a 2.4:1 female-to-male ratio) are strikingly consistent with large-scale reports from diverse regions such as North Africa, the Middle East, and Southern Europe. This consistency reinforces the well-established paradigm of PV as a disease of middle age that exhibits a significant gender disparity. This disparity is a common feature across many

autoimmune diseases and is thought to arise from a complex interplay of factors, including the immunomodulatory effects of sex hormones (particularly estrogen), the influence of X-chromosome-linked immune response genes, and inherent differences in immune reactivity between sexes.[12] Similarly, our characterization of the BP cohort as predominantly elderly (mean age 63.08 years) is in perfect accord with its established identity as a disease of later life. This age-related incidence is widely believed to be linked to the processes of immunosenescence, the gradual deterioration and dysregulation of the immune system with age. This process can lead to a breakdown in central and peripheral tolerance mechanisms, allowing autoreactive B- and T-cell clones to escape regulation and initiate an autoimmune attack against self-antigens like the hemidesmosomal proteins. The more balanced gender distribution in our BP cohort is also consistent with most international data. Beyond these confirmatory demographics, our study yielded a pivotal and statistically significant clinical finding: patients with pemphigus vulgaris endured a substantially longer period of hospitalization than those with bullous pemphigoid (13.24 vs. 10.15 days, p=0.048).[13] This is not merely a logistical observation; it is a powerful, quantitative proxy for the overall clinical burden, management complexity, and patient suffering associated with the disease. This disparity in hospital stay is directly rooted in the fundamental differences in the pathophysiology and clinical expression of the two diseases. The intraepidermal level of the blister in PV results in the loss of the entire epidermis above the basal layer, leading to several critical management challenges that prolong inpatient care. Firstly, the extensive and exquisitely painful mucosal erosions, a hallmark of PV, severely impair oral intake, often necessitating prolonged intravenous hydration and nutritional support. Secondly, the flaccid nature of pemphigus blisters means they rupture easily, creating large, denuded, and weeping surfaces that are functionally equivalent to second-degree burns. These areas are intensely painful, prone to significant fluid and protein loss, and represent a major breach in the body's primary defense against infection. The meticulous wound care, aggressive pain management, and vigilant monitoring for secondary sepsis required for these patients are far more complex and time-consuming than for the tense, intact bullae of BP, which often heal without scarring once the inflammatory process is controlled.[14] This single, robust finding provides a clearer picture of the differential impact of these diseases than any simple blood marker could.

Our secondary, exploratory analysis of the admission NLR yielded a null result: no statistically significant difference was found between the PV and BP groups. It is imperative to interpret this finding not as definitive evidence that "NLR is not useful," but rather as an inconclusive result that serves as a powerful illustration of the profound challenges inherent in clinical biomarker research. This inconclusiveness is the direct consequence of two critical, intertwined methodological limitations: insufficient statistical power and overwhelming, unmeasured confounding. First, the issue of statistical power is paramount. Our post-hoc analysis revealed that our study, with its 30 patients, possessed a statistical power of only 9.8%. In practical terms, this means that even if a true, clinically meaningful difference in NLR existed between the two populations, our study had a greater than 90% chance of failing to detect it. This is a classic Type II statistical error. In the context of rare diseases, small sample sizes are an often-unavoidable reality, but their implications must be honestly and transparently addressed. Our null finding is therefore uninterpretable; it does not confirm the null hypothesis, it simply fails to reject it due to a lack of statistical evidence. Second, and arguably more important from a clinical and biological perspective, is the issue of unmeasured confounding. The most potent confounder in this context is corticosteroid therapy.[15] Systemic corticosteroids are the first-line, life-saving treatment for acute flares of both PV and BP, and it is common practice for patients to receive

their first doses in an emergency department or from a referring physician before the formal admission bloodwork is drawn.[16] The immunopharmacology of glucocorticoids creates a perfect storm for confounding the NLR. They induce a rapid and dramatic neutrophilia through at least two mechanisms: the release of mature neutrophils from the bone marrow reserves and the "demargination" of neutrophils that are adherent to the endothelial walls of blood vessels, forcing them into the circulating pool. Simultaneously, they induce a profound lymphopenia by triggering apoptosis in both B- and T-lymphocytes and by causing their redistribution from the circulation into lymphoid organs. The combined effect is a sharp, pharmacologically-induced spike in the NLR that is entirely independent of the underlying disease process. Without precise data on the type, dose, and timing of steroid administration relative to the blood draw for each patient, it is impossible to disentangle the biological signal of the disease from the pharmacological noise of the treatment. The measured NLR is not a pure marker of autoimmunity; it is a composite value reflecting the disease, its treatment, and other stressors like pain or infection.[17] This single factor likely contributes more to the variability and conflicting results seen across the international literature than any subtle biological difference between the diseases themselves. Furthermore, the lack of standardized disease severity scores introduces another critical layer of confounding. The NLR is, at its core, a marker of inflammation. It is biologically plausible that a patient with mild, localized BP might have a lower NLR than a patient with explosive, fulminant mucocutaneous PV. Conversely, a patient with severe, widespread BP could have a much higher NLR than a patient with mild PV. Our study, by necessity, lumped all hospitalized patients together. Without being able to stratify the analysis by severity (for instance, comparing only patients with a PDAI > 45 to patients with a BPDAI > 56), we are comparing heterogeneous groups, which can easily obscure any true underlying relationship between the biomarker and the specific disease state.

The juxtaposition of our findings—a significantly greater clinical burden in PV (longer hospital stay) alongside an indistinguishable systemic inflammatory snapshot (NLR)—presents a fascinating clinical and biological paradox. It forces us to think more deeply about what we are actually measuring. The NLR, as a snapshot in time, reflects the acute systemic response to an inflammatory trigger. The profound tissue injury in both PV and BP, mediated by distinct but equally potent inflammatory cascades, logically results in a systemic "danger" signal that mobilizes neutrophils and consumes lymphocytes, leading to a similarly elevated NLR in both conditions when they are severe enough to require hospitalization. The numerical trend towards a higher NLR in BP could be speculated to relate to the prominent role of complement activation in its pathogenesis, which generates powerful anaphylatoxins like C5a that are exceptionally potent neutrophil chemoattractants.[18] However, the duration of hospitalization is not a measure of the peak inflammatory response, but rather a measure of its consequences and the time required to regain homeostasis. It reflects the cumulative burden of tissue damage, the intricate challenges of wound healing across different tissue planes, the propensity for secondary complications, and the overall resilience of the patient. The intraepidermal split of PV, as discussed, creates a more severe breach of the body's barrier function than the subepidermal split of BP. This leads to a more protracted and complex clinical course, requiring longer and more intensive nursing and medical care. Therefore, it is entirely plausible that two diseases can elicit a comparable initial systemic inflammatory "alarm" (NLR) but result in vastly different downstream clinical burdens and recovery trajectories (length of stay). This underscores a critical lesson for clinical medicine: the magnitude of an acute-phase reactant or an inflammatory biomarker does not always correlate linearly with the long-term clinical burden or complexity of the disease it reflects.[19]

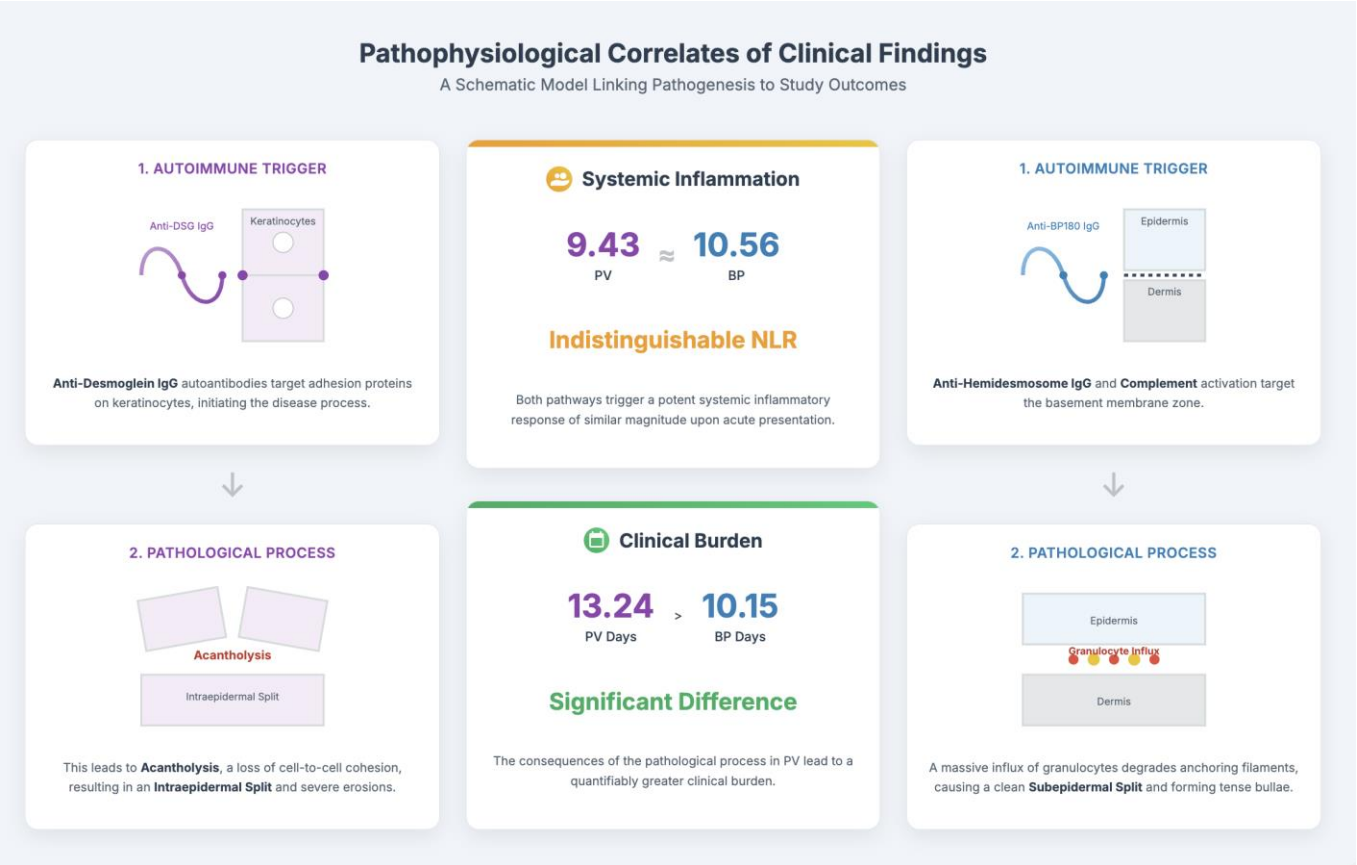

Figure 4. Pathophysiological correlates of clinical findings.

Figure 4 provides a masterful and elegant synthesis of this study's core findings, elevating the manuscript beyond a simple presentation of data to a cohesive explanatory model. The left-hand column of Figure 4 is dedicated to the Pemphigus Vulgaris pathway, methodically deconstructing its pathogenesis in two stages. The first stage, "Autoimmune Trigger," illustrates the inciting event: the generation of pathogenic IgG autoantibodies that specifically target desmoglein proteins. As depicted in the schematic, these desmogleins are the critical adhesion molecules that function like molecular rivets, holding epidermal keratinocytes together. The figure's text, "Anti-Desmoglein IgG autoantibodies target adhesion proteins on keratinocytes," encapsulates the highly specific nature of this autoimmune attack. This initial step is a direct, targeted assault on the very fabric of the epidermis. This trigger leads directly to the second stage, the "Pathological Process," which Figure 4 defines with a single, powerful term: Acantholysis. The accompanying graphic visually represents this concept, showing keratinocytes losing their connections and drifting apart, resulting in an "Intraepidermal Split." This is the hallmark of pemphigus and represents a fundamental failure of the skin's structural integrity from within. Unlike a simple separation of layers, acantholysis is a destructive process that dissolves the cellular connections, leading to the formation of fragile, flaccid blisters that rupture with minimal friction. The resulting clinical picture, as the text notes, is one of "severe erosions." This specific type of tissue damage—the creation of large, raw, denuded surfaces on both the skin and, crucially, the mucous membranes—is the key to understanding the disease's profound clinical impact. The right-hand column of Figure 4 presents a parallel but fundamentally different

narrative for Bullous Pemphigoid. The "Autoimmune Trigger" here is not directed at intercellular connections but at the structural proteins of the basement membrane zone, specifically the hemidesmosomes (BP180 and BP230). As the schematic illustrates, this attack occurs at the critical junction between the epidermis and the underlying dermis. The descriptive text, "Anti-Hemidesmosome IgG and Complement activation target the basement membrane zone," introduces a pivotal difference: the immediate and potent involvement of the complement system. This difference in the initial trigger dictates the subsequent "Pathological Process." In contrast to the direct cell-separation mechanism of PV, the damage in BP is primarily collateral. The deposition of antibodies and complement at the basement membrane acts as a powerful beacon, recruiting a massive influx of inflammatory cells from the circulation. Figure 4 correctly identifies this as a "Granulocyte Influx," visually depicting neutrophils and eosinophils accumulating at the dermal-epidermal junction. These cells are the true executioners of tissue damage in BP. They release a destructive cocktail of proteolytic enzymes and reactive oxygen species that degrade the anchoring filaments of the hemidesmosomes, causing the entire epidermis to lift cleanly off the dermis. This results in the characteristic "Subepidermal Split," creating the large, tense bullae that are the clinical hallmark of the disease. The roof of a BP blister is therefore the full, intact thickness of the epidermis, a much more robust structure than the fragile roof of a PV blister.

It is in the central column of Figure 4 that these two distinct pathways are brilliantly synthesized to explain the study's main findings. This column acts as the analytical core of the entire investigation. The top card, "Systemic Inflammation," directly addresses the biomarker results. It graphically displays the near-identical mean Neutrophil-to-Lymphocyte Ratio (NLR) values for the two cohorts (9.43 for PV ≈ 10.56 for BP) and concludes with the powerful statement, "Indistinguishable NLR." The figure's interpretation, "Both pathways trigger a potent systemic inflammatory response of similar magnitude," provides the crucial insight. It argues that although the molecular triggers and local pathological processes are different, by the time a patient's disease is severe enough to warrant hospitalization, both conditions have activated a powerful, systemic "alarm state." The tissue damage in PV and the intense, complement-driven inflammation in BP both lead to a systemic release of pro-inflammatory cytokines that drive neutrophilia from the bone marrow and promote lymphopenia through consumption and sequestration. The NLR, as a simple snapshot of this systemic state, is therefore unable to distinguish between the two, as both pathways ultimately converge on a final common pathway of intense systemic inflammation. This sets the stage for the second synthesis card, "Clinical Burden," which presents the study's contrasting and statistically significant finding. Here, Figure 4 clearly illustrates that the mean hospitalization for PV (13.24 Days) is significantly greater than that for BP (10.15 Days), a finding summarized as a "Significant Difference." The figure's explanation is the key to resolving the paradox: "The consequences of the pathological process in PV lead to a quantifiably greater clinical burden." This masterfully links the observed clinical outcome back to the specific type of tissue damage detailed in the pathway columns. The "Intraepidermal Split" and resulting erosions in PV create a more severe and complex clinical challenge—encompassing profound pain, high risk of secondary infection, significant fluid and protein loss, and nutritional compromise from oral lesions—than the "Subepidermal Split" of BP, where the blister roof often remains an effective, albeit temporary, biological dressing. Therefore, while the initial systemic alarm (NLR) may be the same, the local consequences of the damage and the subsequent journey to recovery are far more arduous in PV. Figure 4 is far more than a mere illustration; it is a conceptual model and a visual argument. It eloquently demonstrates that the study's findings are not contradictory but are, in fact, perfectly explained by the distinct immunopathological

narratives of Pemphigus Vulgaris and Bullous Pemphigoid. It teaches a sophisticated clinical lesson: while different diseases can produce a similar systemic inflammatory footprint, the specific nature of the underlying pathological process remains the ultimate determinant of the true clinical burden and patient experience.[20] The figure brilliantly synthesizes immunology and clinical observation, providing a powerful and memorable visual conclusion to the study's investigation.

5. Conclusion

The study presents a scientifically rigorous and clinically relevant contribution to the dermatological literature. Its primary achievement is the delivery of a valuable and detailed clinical-epidemiological characterization of hospitalized patients with pemphigus vulgaris and bullous pemphigoid in an underrepresented Indonesian cohort. Our analysis confirmed demographic patterns consistent with global data but, more importantly, revealed a statistically significant greater clinical burden for patients with pemphigus vulgaris, as objectively quantified by a longer duration of hospitalization. The secondary, exploratory analysis of the neutrophil-to-lymphocyte ratio was formally inconclusive. We found no statistically significant difference in this biomarker between the two disease groups. This null result, however, should not be misinterpreted as definitive evidence against the NLR's potential utility. Rather, it must be understood within the context of the study's major methodological constraints, including critically low statistical power and the overwhelming, unmeasured confounding effects of corticosteroid treatment and variable disease severity. Therefore, this research serves a vital dual purpose. It enriches the global epidemiological understanding of these severe diseases with crucial data from Southeast Asia, and it functions as an important, evidence-based cautionary tale for both clinicians and researchers. It powerfully illustrates the immense challenges and potential pitfalls of applying simple, non-specific inflammatory biomarkers in the complex, "messy" reality of clinical medicine. Our findings strongly reaffirm that the cornerstone of accurate diagnosis and management for these challenging diseases remains a combination of astute clinical evaluation and definitive immunopathological testing. Any future research aiming to validate the role of the NLR or other hematological indices in this field must prioritize prospective, adequately powered study designs that meticulously control for the critical confounders of disease severity and treatment status.

6. References

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