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# Systemic Immune-Inflammation Index (SII) and Neutrophil-Lymphocyte Ratio (NLR) as Systemic Inflammatory Predictors in the Diagnosis of Bullous Pemphigoid and Pemphigus Vulgaris

**Mulubwa Changa Chibesa, Mengqi Guan, Shanshan Li***

Department of Dermatology and Venerology, First Hospital of Jilin University, Changchun, China
Email: *lishans@jlu.edu.cn

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## Abstract

Introduction: Autoimmune blistering skin disorders such as Bullous Pemphigoid and Pemphigus Vulgaris present diagnostic challenges. The Systemic Immune-Inflammation Index (SII) and Neutrophil-Lymphocyte Ratio (NLR), are inflammatory markers used to assess the body's immune-inflammatory response. Objectives: The study aims to evaluate the significance of hematologic markers, specifically the Systemic Immune-Inflammation Index (SII) and Neutrophil-Lymphocyte Ratio (NLR), as diagnostic predictors of bullous pemphigoid (BP) and pemphigus vulgaris (PV). Methods: A retrospective study of 64 patients (36 with BP and 28 with PV). Patient clinical data: age, gender, complete blood count, autoimmune antibody levels (Dsg1, 3 and BP180, 230), IgE and C-reactive protein, and history of hypertension, diabetes, brain infarction, and coronary heart disease. The data was analyzed using SPSS. Results: The study involved 36 (56.3%) diagnosed with bullous pemphigoid (BP) and 28 (43.75%) with pemphigus vulgaris (PV). The average age in BP was 71 ± 8 and 52 ± 13 in PV. Laboratory findings showed high levels of Dsg1, Dsg3, neutrophil count, and lymphocyte count in PV, while high levels of eosinophils with a significant increase in C-reactive protein (CRP) in BP. Blood biomarkers, including NLR, PLR, SII, MPV, CRP, and IgE, proved an overall of 84.4% in disease prediction. Dsg1, Dsg3, BP180, and BP230 showed an overall of 88.1%. No significant relationship was noted between NLR, SII, and patients with comorbidities. Conclusion: The study highlights the diagnostic potential of SII and NLR in addition to hematologic markers in BP and PV, emphasizing their role in early diagnosis and therapeutic interventions, requiring further validation in larger patient cohorts.

**Keywords**

Pemphigoid, Vulgaris, Neutrophil-Lymphocyte, Immune-Inflammation, Autoimmune

## 1. Introduction

Bullous pemphigoid (BP) and pemphigus are autoimmune blistering skin disorders caused by the formation of blisters and erosions on the skin and mucous membranes due to autoantibodies targeting specific proteins. The mechanisms underlying their pathophysiology and their pathological characteristics vary [1] [2]. There are two major types of pemphigus: pemphigus vulgaris (PV) and pemphigus foliaceus (PF) and rarer subgroups such as paraneoplastic pemphigus, IgA pemphigus, and pemphigus foliaceus [1].

Bullous pemphigoid (BP) is the most common autoimmune blistering disorder characterized by antibodies targeting proteins called BP180 and BP230, components of the skin's basement membrane [3] [4]. It presents with intense, itchy, large, and tense blisters on the skin often starting with urticarial plaques and involving the trunk and extremities, rarely with oral involvement [2] [4]. With a global annual incidence ranging from 2.5 to 75 cases per million, it is more common in older individuals aged 60 - 80 years [2] [5], and has a 1-year mortality rate varying between 19% to 41% in Europe and 6% to 12% in the United States [4] [6].

Pemphigus vulgaris is characterized by autoantibodies targeting desmoglein (Dsg) 1 and 3, adhesive proteins in the skin's epidermis. It presents with painful blisters in the mucous membranes, especially the mouth. Skin involvement can occur with fragile blisters that rupture rapidly. It is more common in individuals of Ashkenazi Jewish, Mediterranean, Indian, Malaysian, Chinese, and Japanese descent [7], primarily affecting individuals aged 45 - 65 years with a peak incidence of 30 - 60 years [8] [9]. It has a high mortality rate of 60% - 90% and can lead to severe complications like sepsis, fluid and electrolyte imbalances, and impaired thermoregulation [3] [4] [10].

Environmental factors like medications, infections, allergens, radiation therapy, diet, and stress can induce immune dysregulation in BP and PV, potentially leading to disease flares and triggering autoimmunity in genetically predisposed individuals. Genetic predisposition isn't always enough to cause pemphigus or pemphigoid [9].

Chronic conditions like BP and PV require long-term management to manage symptoms, prevent complications, and enhance quality of life. Treatments like immunosuppressive medications, corticosteroids, and glucocorticoids are used [4] [11] [12].

Recent studies have shown an association between the systemic immune-inflammation index (SII) and neutrophil-lymphocyte ratio (NLR) in autoimmune blister diseases. However, the comparability of these indices in bullous

pemphigoid (BP) and pemphigus vulgaris (PV) remains uncertain, potentially reflecting distinct levels of systemic inflammation and disease progression. This research aims to explore the association and diagnostic potential of the hematologic markers SII and NLR in BP and PV. The study evaluates the correlation and clinical attributes of SII and NLR showing their potential as prognostic indicators in predicting disease outcomes and monitoring for enhanced patient management and whether SII or NLR outperforms conventional laboratory biomarkers in clinical practice.

## 2. Sample

This research was conducted at the First Hospital of Jilin University, located in Changchun City, Jilin, China, from October 2021 to June 2023. Patient data was retrospectively retrieved from the electronic medical database. Patient inclusion criteria depended on completed treatment, no relapse, and the availability of comprehensive, complete laboratory investigations. Those with incomplete or missing Complete Blood Count (CBC) results were excluded. A total of 64 patients were part of the study, consisting of 36 patients with BP and 28 patients with PV. The study adhered to the principles of the Declaration of Helsinki and gained approval from the Research Ethics Committee of the First Hospital of Jilin University. Patient consent was waived since the data was collected retrospectively. Collected clinical data included patient age, gender, specific autoimmune bullous disease type, disease duration, and comorbidities. Additionally, laboratory data retrieved included a complete blood count (CBC), C-reactive protein (CRP), Immunoglobulin E (IgE), Dsg1, Dsg3, BP180, and BP230.

## 3. Hematologic Immune Indices

Neutrophil-lymphocyte ratios (NLR) and platelet-lymphocyte ratios (PLR) were calculated from the CBC results as absolute neutrophil count divided by absolute lymphocyte count (#N ÷ #L) and absolute platelet count divided by absolute lymphocyte count (#P ÷ #L), respectively, while systemic immune-inflammation indices (SII) were calculated from the platelet count (PLT), neutrophil count, and lymphocyte count as #P × (#N ÷ #L).

## 4. Data Analysis

Data analysis was conducted using Microsoft Excel software version 2016 (Microsoft Inc., USA) and Statistical Package for the Social Sciences (SPSS) version 25. (IBM Inc., USA). Continuous variables were summarized as mean ± standard deviation (SD), while categorical variables were summarized as numbers and percentages. The independent T-test was used to evaluate the difference among group means for continuous data, while Pearson's Chi-square test or Fischer's exact test was used to determine the differences between categorical variables, and the statistical significance was set at a two-sided $p < 0.05$ consideration of $p < 0.01$ as being statistically highly significant among the two groups

and $p > 0.05$ was considered not to be statistically significant.

## 5. Results

### 5.1. Patient Characteristics

Our research involved a total of 64 patients, with 36 diagnosed with BP and 28 with PV. BP was the predominant diagnosis, accounting for 56.3% of cases. Of these participants, 48 (56.47%) were males and 37 (43.53%) were females. The average age, denoted as mean ± SD, for BP was 71 ± 8, and 52 ± 13 for PV. Age was noted to be a significant factor in the diagnosis of disease ($p = 0.000$). Among the BP patients, 28 (77.78%) had comorbidities, and 14 (38.89%) experienced complications. In contrast, 8 (28.57%) PV patients had comorbidities and 9 (32.14%) faced complications, with brain infarction (BI) emerging as a more significant factor. Detailed patient information is available in Table 1.

### 5.2. Laboratory Findings and the Systemic Immune Inflammation Index (SII), Neutrophil-Lymphocyte Ratio (NLR)

All patients included in the study had complete blood count (CBC) records in addition to other laboratory findings. In PV, the results showed a strong statistical significance ($p < 0.01$) with high values for Dsg1 (**$p = 0.000$), Dsg3 (**$p = 0.000$), lymphocyte count (**$p = 0.006$), and a significant (*$p < 0.05$) neutrophil count ($p = 0.04$).

Table 1. Clinical characteristics of patients with bullous pemphigus and pemphigus vulgaris.

| | | BP | PV | P Value |
|---|---|---|---|---|
| | | (n = 36) | (n = 28) | |
| Age (years) | | 71 ± 8 | 52 ± 13 | 0.000** |
| Gender | Male | 21 (58.3) | 11 (39.3) | 0.135 |
| | Female | 15 (41.7) | 17 (60.7) | |
| Diabetes | Yes | 3 (8.3) | 1 (3.6) | 0.443 |
| | No | 33 (91.7) | 27 (96.4) | |
| Hypertension | Yes | 14 (38.9) | 6 (21.4) | 0.139 |
| | No | 22 (61.1) | 22 (78.6) | |
| Coronary Heart Disease | Yes | 3 (8.3) | 0 (0) | 0.121 |
| | No | 33 (91.7) | 28 (100) | |
| Brain Infarction | Yes | 8 (22.2) | 1 (3.6) | 0.034* |
| | No | 28 (77.8) | 27 (96.4) | |
| Complications | Yes | 14 (38.9) | 9 (32.1) | 0.584 |
| | No | 22 (61.1) | 19 (67.9) | |
| Cod (days) | | 75 (30 - 255) | 165 (37.5 - 638.75) | 0.080 |

**strongly significant findings $p < 0.01$, *significant findings $p < 0.05$, Not significant findings $p > 0.05$, Cod: Course of disease duration.

Although certain parameters such as white blood cells (WBC), platelet count, neutrophil (%), mean platelet volume (MPV), NLR, eosinophil count, and SII were observed to be higher in the PV group, no statistically significant differences between the two groups were found ($p > 0.05$).

In the BP group, there was a statistical difference with high values for Bp180, Eosinophil (%), and CRP, with Eosinophil (%) and BP180 being strongly significant ($p < 0.01$) and CRP showing significance of $p < 0.05$. PLR, BP230, PLT, RDW (%), and IgE were elevated but did not reach statistical significance ($p > 0.05$). For more details on the laboratory findings, refer to Table 2.

**Table 2.** Routine blood test with biomarkers for Bullous pemphigoid and pemphigus vulgaris.

| | BP (n = 36) | PV (n = 28) | P Value |
|---|---|---|---|
| WBC ($10^9$/L) | 8.688 ± 4.164 | 10.200 ± 4.969 | 0.190 |
| Neutrophil (%) | 0.654 ± 0.125 | 0.692 ± 0.123 | 0.233 |
| Lymphocyte (%) | 0.187 ± 0.971 | 0.215 ± 0.101 | 0.259 |
| Eosinophil (%) | 0.067 (0.024 - 0.137) | 0.008 (0.000 - 0.020) | 0.001** |
| Neutrophil count ($10^9$/L) | 4.885 (3.223 - 7.185) | 6.715 (3.853 - 8.898) | 0.040* |
| Lymphocyte count ($10^9$/L) | 1.205 (0.823 - 1.905) | 1.860 (1.375 - 2.493) | 0.006* |
| Eosinophil count ($10^9$/L) | 0.395 (0.170 - 1.028) | 0.70 (0.003 - 0.135) | 0.038* |
| RDW (%) | 14.117 ± 1.686 | 13.700 ± 1.679 | 0.330 |
| PLT ($10^9$/L) | 231.86 ± 76.226 | 262.50 ± 62.402 | 0.090 |
| MPV (fL) | 9.747 ± 1.067 | 9.939 ± 0.773 | 0.425 |
| CRP (mg/L) | 13.475 (2.875 - 38.760) | 2.720 (0.9175 - 11.015) | 0.033* |
| IgE (mg/L) | 291.500 (101.175 - 1095.000) | 43.250 (18.475 - 81.250) | 0.084 |
| Dsg1 (RU/mL) | 25.37 ± 60.064 | 149.67 ± 82.923 | 0.000** |
| Dsg3 (RU/mL) | 12.77± 36.775 | 103.55 ± 103.108 | 0.000** |
| BP180 (kDa) | 86.958 ± 87.037 | 9.644 ± 34.152 | 0.000** |
| BP230 (kDa) | 24.74 ± 78.823 | 4.32 ± 4.930 | 0.177 |
| SII | 853.435 (579.388 - 1521.289) | 915.467 (456.896 - 1450.640) | 0.707 |
| NLR | 3.893 (2.562 - 5.969) | 4.0 (1.965 - 5.303) | 0.456 |
| PLR | 201.543 (115.564 - 286.223) | 165.783 (102.733 - 192.682) | 0.054 |

***statistically highly significant findings $p < 0.01$, *Statistically Significant findings $p < 0.05$, Not significant findings $p > 0.05$, WBC: White blood cells; RDW: Red distribution width; PLT: platelets; MPV: Mean platelet volume; CRP: C-reactive protein; IgE: immunoglobulin E; SII: Systemic immune inflammation index; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; p-value: significance.

### 5.3. Desmoglein (Dsg) Proteins (1, 3), Anti-BP (180, 230), C-Reactive Protein (CRP)

Abnormalities in Dsg1 and Dsg3 are commonly observed in PV, while BP180, BP230, and CPR are frequently associated with BP. Elevated CRP levels are commonly found in various conditions, such as autoimmune disorders, diabetes, cardiovascular disease, and neurodegenerative diseases. We evaluated Dsg1, Dsg3, BP180, and BP230, which are target antigens for autoantibodies, as well as plasma CRP levels in patients with PV and BP.

The mean total values of Dsg1 and Dsg3 were significantly higher in PV, while CRP levels were found to be higher in BP. We assessed the mean and median of these and other biomarkers to compare patients with BP and PV. Detailed information can be found in Table 2.

### 5.4. Biomarkers in Disease Prediction

**1) Hematology markers**

The calculations for disease prediction using blood biomarkers demonstrated that CRP (OR: 0.984), NLR (OR: 0.462), and PLR (OR: 0.989) were linked to a decrease in the odds of the outcome by roughly 1.6%, 53.8%, and 1.1%, respectively, for each unit increase, but these associations lacked statistical significance ($p > 0.05$). Notably, the confidence interval (C.I.) for NLR was wide and included 1, indicating a degree of uncertainty. Conversely, the odds of the outcome were associated with a decrease in IgE (OR: 0.993) concentration by about 0.7% for each unit increase, and this result achieved statistical significance ($p < 0.05$). On the other hand, the odds of the outcome increased by approximately 0.4% for each unit increase in SII (OR: 1.004), and this association was statistically significant ($p < 0.05$). When considering MPV, the odds of the outcome increased by approximately 58.6% for each unit increase, yet the wide C.I. and the non-significant p-value ($p = 0.328$) were uncertain as shown in Table 3(a). The sensitivity was 80% and the specificity was 89.3%, with an overall score of 84.4% on disease prediction.

**2) Specific or target biomarkers for disease prediction**

The odds of the outcome were linked to an increase of about 1.3% and 1.8% for each unit increase in Dsg1 (OR: 1.013) and Dsg3 (OR: 1.018), respectively. These results demonstrated statistical significance in disease prediction ($p < 0.05$). Conversely, the odds of the outcome associated with BP180 (OR 0.970) decreased by approximately 3.0% for each unit increase, with a p-value ($p = 0.068$) slightly exceeding the typical significance ($p < 0.05$), indicating a borderline association. In the case of BP230 (OR: 0.003), the odds changed by approximately 0.7% for each unit increase, but this result was not statistically significant ($p > 0.05$), suggesting no meaningful association between BP230 and the outcome of disease as shown in Table 3(b). Sensitivity was 87.5% and specificity was 88.9%, with an overall prediction of 88.1%.

**Table 3.** (a) Hematology markers in disease prediction, (b) Specific biomarkers for disease prediction.

| | (a) | | | |
|---|---|---|---|---|
| | 95% C.I for EXP(B) | | | |
| | Odd Ratio | lower | Upper | P Value |
| CRP | 0.984 | 0.964 | 1.004 | 0.121 |
| IgE | 0.993 | 0.988 | 0.999 | 0.014* |
| SII | 1.004 | 1.001 | 1.008 | 0.013* |
| NLR | 0.462 | 0.192 | 1.111 | 0.085 |
| PLR | 0.989 | 0.975 | 1.003 | 0.111 |
| MPV | 1.586 | 0.629 | 3.999 | 0.328 |
| | (b) | | | |
| | 95% CI for EXP(B) | | | |
| | Odd Ratio | Lower | upper | P Value |
| Dsg1 | 1.013 | 1.003 | 1.024 | 0.017* |
| Dsg3 | 1.018 | 1.003 | 1.033 | 0.016* |
| BP180 | 0.970 | 0.939 | 1.002 | 0.068 |
| BP230 | 0.993 | 0.932 | 1.058 | 0.832 |

(a) Note: *statistically significant findings $p < 0.05$, Not statistical finding $p > 0.05$, CRP: C-reactive protein; IgE: immunoglobulin E; SII: Systemic immune inflammation index; NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume; p-value: significance; C.I: Confidence interval. (b) Note: *Significant findings $p < 0.05$, Not significant findings $p > 0.05$, CI: Confidence interval; Dsg: Desmoglein; BP: Antibodies to bullous pemphigoid.

### 5.5. Systemic Inflammation-Immune Index (SII) and Neutrophil-Lymphocyte Ratio (NLR)

From CBC results, neutrophil counts, lymphocyte counts, and platelet counts, SII was determined as $P \times (\#N \div \#L)$, where P is the platelet count, N is the neutrophil count, and L is the lymphocyte count, and NLR was determined by neutrophil count ÷ lymphocyte count as $N \div L$. The median SII (IQR) for BP was 853.435 (579.388 - 1521.289) and 915.467 (456.896 - 1450.640) for PV. Although the median SII was higher in PV, the difference was not statistically significant ($p = 0.707$). The median neutrophil count in PV was slightly higher but not statistically significant ($p > 0.05$).

A Mann-Whitney U test was conducted to explore the relationship between SII and NLR with diabetes, brain infarction, hypertension, coronary heart disease, and patients that had complications (more than one comorbidity) in patients with BP and PV. The mean and P-value were calculated, and the results indicated no significant relationship between NLR and SII with comorbidities or complications as shown in Table 4(a) and Table 4(b).

**Table 4.** (a) Systemic immune inflammatory response index (SII) with comorbidity, (b) Neutrophil-lymphocyte ratio (NLR) with comorbidity.

(a)

| Comorbidity | | BP | P Value | PV | P Value |
|---|---|---|---|---|---|
| Diabetes | Yes | 1723.01 (1260.89) | 0.375 | 2782.20 (0) | 0.155 |
| | No | 1044.8 (667.85) | | 1119.50 (870.82) | |
| Hypertension | Yes | 1296.56 (890.86) | 0.399 | 945.73 (932.72) | 0.240 |
| | No | 977.09 (598.69) | | 1242.47 (915.93) | |
| Coronary heart disease | Yes | 1255.79 (808.82) | 0.627 | 0 | - |
| | No | 1087.28 (735.93) | | 1178.88 (910.49) | |
| Brain infarction | Yes | 1149.68 (563.96) | 0.594 | 550.14 (550.14) | 0.496 |
| | No | 1087.51 (780.96) | | 1202.17 (919.29) | |
| Complications | Yes | 1235.90 (703.79) | 0.173 | 1009.11 (914.83) | |
| | No | 1015.69 (751.62) | | 1259.3 (962.89) | 0.313 |

(b)

| Comorbidity | | BP | P Value | PV | P Value |
|---|---|---|---|---|---|
| Diabetes | Yes | 6.35 (4.13) | 0.548 | 8.21 | 0.155 |
| | No | 4.83 (3.81) | | 4.16 (2.87) | |
| Hypertension | Yes | 6.14 (4.76) | 0.183 | 3.60 (2.70) | 0.401 |
| | No | 4.20 (2.92) | | 4.50 (3.00) | |
| Coronary heart disease | Yes | 7.50 (4.39) | 0.129 | 0 | - |
| | No | 4.73 (3.74) | | 4.31 (2.91) | |
| Brain infarction | Yes | 5.17 (2.22) | 0.171 | 2.04 | 0.421 |
| | No | 4.90 (4.18) | | 4.39 (2.93) | |
| Complications | Yes | 5.66 (4.78) | 0.455 | 3.416 (2.27) | 0.248 |
| | No | 4.51 (3.07) | | 4.73 (3.14) | |

(a) Note: Not significant findings $p > 0.05$, Significant findings $p < 0.05$. (b) Note: Not significant findings $p > 0.05$, Significant findings $p < 0.05$.

## 6. Discussion

The skin is a vital organ in the protection of the body against dehydration and infections. Bullous skin conditions like pemphigus and BP can be life-threatening due to their impact on the skin and oral mucosa. They are divided into two categories based on the epidermis, or epidermal-dermal interphase [13].

Diagnosis of BP and PV relies on clinical manifestations, physical examination, instruments such as the Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), Pemphigus Disease Area Index (PDAI), and Bullous Pemphigoid Disease Area Index (BPDAI), laboratory tests and histology with direct immunof-

luorescence (DIF) and indirect immunofluorescence (IIF), and ELISA studies to assess disease severity and treatment response to aid in diagnosis [3] [7] [8] [14].

Histologically, PV is a condition characterized by acantholysis in the epidermis and mucous membranes, resulting in suprabasilar blisters associated with IgG deposits and it often presents with the Nikolsky sign. In contrast, BP causes basal keratinocytes to adhere to basement membranes, leading to complement-mediated inflammation resulting in linear IgG/C3 deposits along the dermal-epidermal junction [1] [4] [7] [9].

The study revealed that the mean age at diagnosis for BP was 71 ± 8, with a higher range for females, whereas PV was 52 ± 13, with a higher age range for males. These findings align with prior research, reflecting similar age distributions in both conditions, with a mean age of 70 years for BP and 50 years for PV. Notably, these diseases are rarely observed in children. In addition, a higher prevalence of PV among females (60.7%) and of BP among males (58.3%) was noted, consistent with most studies, although some variations have been reported in gender distribution and prevalence. We established statistical significance regarding age (**p = 0.000) in disease diagnosis but found no significant gender difference (p = 0.135) [4] [5] [7] [10] [11] [12] [15].

PV occurs at an annual rate of 1 - 5 cases per million, with a higher prevalence among individuals of Ashkenazi Jewish, Mediterranean, Indian, Malaysian, Chinese, and Japanese descent. The mortality rate is around 5% - 10%, with an incidence range of 0.098 to 5 cases per 100,000 individuals, while BP varies from 0.21 to 7.63 cases per 100,000. The prevalence of PV falls between 0.38 and 30 cases per 100,000, and BP ranges from 1.46 to 47.99 per 100,000, averaging at about 21.84 per 100,000 individuals. While infection is a recognized risk factor, cardiovascular and thromboembolic events significantly contribute to BP patient mortality, potentially including cerebrovascular events [4] [5] [6] [16] [17] [18].

Typically, studies have shown BP resolves within months but can last up to 5 years, while PV is chronic and requires long-term management. Our disease duration was 75 days (30 - 255) for BP and 165 days (37.3 - 638.75) for PV for PV. All the patients received treatment and were relieved of symptoms in less than 5 years with no relapse or statistical difference between the diseases' course in relation to *Huang et al.*, who reported a mean average disease duration of 3.8 ± 2.1 years (equivalent to 45.6 months) for all patients [11].

Research is ongoing to understand the impact of PV and BP on inflammatory and immune status, with PV linked to hypertension and diabetes and BP linked to cardiovascular and neurological conditions like diabetes, ischemic heart disease, hypertension, and commonly neurological disorders such as cerebrovascular disease and dementia [4] [19].

Our study found that patients with BP had a higher incidence of hypertension, cardiovascular disease, diabetes, coronary heart disease, and brain infarction than PV, with hypertension and brain infarction being more prominent in BP and Hypertension in PV with an equal number of patients affected with diabetes and brain infarction. Moreover, a significant number of BP patients had multiple

comorbidities compared to PV patients. This is attributed to BP commonly affecting the elderly and the effects of long-term treatment, increasing their risk of comorbidities. This highlights the importance of closely monitoring patients by ensuring regular check-ups and monitoring for early signs of comorbidities, implementing routine screening protocols, tailoring medication to minimize the risk of side effects, and educating patients about the risks associated with their condition, encouraging proactive health management. This is in relation to other studies that suggest both diseases are more susceptible to hypertension, diabetes, and brain infarction, with hypertension and brain infarction being more prominent [6] [11] [18] [20] [21] [22] [23] [24]. Additionally, studies from Asian areas, including Taiwan (China), Thailand, and Japan, have linked BP to conditions like psoriasis and diabetes [16].

Acute inflammation is the body's rapid response to infection or injury and is crucial for disease diagnosis, treatment, and progression. Routine hematology markers like lymphocyte count, neutrophil count, platelet count, NLR, eosinophil count, MPV, WBC, SII, and PLR serve as reliable indicators of infection and inflammation. Significant hematological biomarkers for disease severity, prognosis, and management were found to be neutrophil count, lymphocyte count, eosinophil count (all $p < 0.05$) in PV, and eosinophil (%) ($p < 0.05$) in BP. Previous research showed leukocytosis and eosinophilia being more frequent in BP patients than PV patients [8]. The study found leukocytosis more prevalent in PV than in BP patients but significant in both diseases. The role of eosinophil in blister formation is well-known in PV [4] and BP [12].

CRP, IgE, and MPV are widely used hematology biomarkers, while inexpensive indices like NLR, PLR, and SII have emerged as promising prognostic indicators in various diseases [25] [26]. We conducted investigations to examine the link between the hematological markers SII and NLR, which are systemic inflammation and immune response in BP and PV patients. SII and NLR showed elevated levels in PV patients compared to BP patients, indicating a potentially high immune response and inflammation in PV. However, no statistically significant differences ($p > 0.05$) were noted, encouraging the need for more research with a larger sample size. BP exhibited elevated levels of BP180, CRP, and IgE, which have the potential to predict relapses after treatment. BP180 and CRP are significantly associated with disease severity, while BP230 showed no significant correlation. High IgE levels do not show statistical significance in the severity. These findings suggest a connection between coagulation markers and circulating BP180 and BP230 autoantibodies, suggesting coagulation activation in BP pathophysiology. PV showed higher concentrations of Dsg1 and Dsg3, holding strong significance.

Similar phenomena have been observed in other inflammatory conditions such as psoriasis, systemic lupus erythematosus, and rheumatoid arthritis [4] [7] [9] [27] [28] [29] [30].

SII and NLR are inexpensive, non-invasive, inflammatory markers currently being explored for their potential to predict and monitor disease activity. Ele-

vated levels can indicate increased systemic inflammation and immune response, and a poor prognosis. Dsg1, Dsg3, BP180, and BP230 are widely used proteins as antigens in serological tests to detect circulating autoantibodies in BP (BP180 and BP230) or PV (Dsg1 and Dsg3). While these tests are widely used, they are expensive, invasive, have limitations in monitoring disease and activity, and are still ongoing research to improve their sensitivity, specificity, and accuracy in diagnosis. The study examines specific and hematological biomarkers for disease prediction and their confidence intervals. It found that the Dsg1 and Dsg3 have significant predictive capabilities for disease outcomes, while BP180 and BP230 showed less predictive potential. The hematological markers showed that IgE and SII were significant indicators for disease prediction, distinguishing between PV and BP, aligning with previous studies [31] [32] [33]. There is no gold standard for the diagnosis of BP and PV because the sensitivity and specificity vary. The study sensitivity for specific markers (Dsg1, Dsg3, BP180, and BP230) was 87.5% and a specificity of 88.9% with an overall prediction of 88.1%. Hematological markers (SII, NLR, MPV, IgE, PLR, CRP) indicated a sensitivity of 80% and a specificity of 89.3% with an overall prediction of 84.4% indicating the prediction potential.

NLR is often elevated in various inflammatory conditions like psoriasis, atopic dermatitis, PV, and BP. A study by Lyakhovitsky A *et al.* found a connection between NLR and PLR to be similar in both groups. A higher NLR at initial presentation with leukocytosis and eosinophilia was more frequent in BP patients. With limited disease diagnosis, this information offers valuable insights into diagnosing these challenging skin disorders, despite some diagnostic limitations [13]. Notably, a high NLR was independently associated with mortality in Thai BP patients, underscoring its potential as a valuable prognostic indicator [15]. This study showed NLR was high in PV, but no correlation was noted.

SII and NLR were used to determine the relationship between BP and PV, in patients with and without comorbidities and/or complications. No significant relationship ($p > 0.05$) was noted in all parameters between BP and PV. Other studies have found that SII is a stronger predictor of survival in synchronic colorectal peritoneal Carcinoma and cerebral small vessel disease patients compared to NLR and PLR. SII is also positively associated with hypertension, diabetes, current smoking, and high-sensitivity CRP [34] [35].

## 7. Conclusions

In summary, this study found that while there was no significant difference, SII and NLR were higher in PV than in BP, suggesting a greater inflammatory response, increased disease severity, and potentially a poor prognosis, thus encouraging further research with a larger cohort.

SII and IgE were significant in disease prediction, with SII linked to an increased disease risk, and their predictive accuracy enhanced when combined with other clinical assessments, and diagnostic tools. The high specificity indicates the ability to rule out those without BP and PV.

No association was found between NLR and SII with hypertension, diabetes, coronary heart disease, and brain infarction in BP and PV patients.

While SII and NLR are promising indicators, previous studies have suggested a connection with these diseases. Because they can easily be calculated using complete blood count tests. This study shows their potential relevance in these diseases. Further research is needed to validate their clinical utility and diagnostic performance in a larger population.

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## Author Contribution

Chibesa Changa Mulubwa conducted data analysis and drafting of the manuscript. Mengqi Guan conducted the data collection and Li Shanshan conceptualized the study and supervised the entire process.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Abbreviations and Acronyms

SII: Systemic immune-inflammation indices
BP: Bullous pemphigoid
PV: Pemphigus vulgaris
NLR: Neutrophil-lymphocyte ratio
CBC: Complete blood count
CRP: C-reactive protein
IgE: Immunoglobulin E
Dsg: Desmoglein
BP: anti-BP