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## Original Article

### Clinical Features between Young and Elderly Patients with Bullous Pemphigoid: An Age-Matched Case Control Retrospective Study

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#### SUMMARY

**Background:** Bullous pemphigoid (BP) mainly happens in elderly patients but also young patients. As the disease could have an early onset in young individuals, this study aimed to determine the clinical features between young and elderly BP patients.

**Method:** This is a retrospective study on inpatients firstly diagnosed with BP in two university-affiliated hospitals from 1990 to 2019. Clinical manifestations, laboratory examinations, treatment, complications, length of hospital stay (LOHS) and prognosis were compared among the three groups: young patient group (age < 40), middle-aged patient group (40 ≤ age < 60), and elderly patient group (age ≥ 60).

**Results:** 192 BP patients were included in total: 14 cases in the young patient group, 38 cases in the middle-aged patient group and 140 cases in the elderly patient group. Among these three groups, there was a significant difference in lesions involving the skin of head (LISH), disease-controlled maximum dosage of corticosteroid (DCMDC) and the complications. The LISH in the young, middle-aged and elderly groups were 9.1%, 22.1% and 68.8% respectively. The results of this study further showed that BP was more likely to involve the head and skin at a higher age ( $\chi^2 = 9.742, p = 0.045$ ). BP patients at different ages require different DCMDC to control the disease progression ( $\chi^2 = 3.427, p = 0.035$ ). Multivariate logistic regression analysis showed that the rate of complications increased along with the age of patients ( $p = 0.004$ ).

**Conclusion:** Together, the data of this study revealed that patients presented different clinical features of BP among different age groups.

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## 1. Introduction

Bullous pemphigoid (BP) is one of the most common types of autoimmune subepidermal blistering diseases,<sup>1</sup> which are especially prevalent in the elderly population over 60 years old.<sup>2</sup> Clinical manifestations of BP majorly include severe itching and tension blisters with erosion and escharosis. Auto-antibodies are present in the epidermal dermal junction, mainly targeting the hemidesmosome antigen BP180 and BP230, leading to the formation of sub-epidermal blisters.<sup>3</sup> Systemic or/and local corticosteroid therapy are the primary choices for the treatment of BP.<sup>4</sup> Immunosuppressive agents such as methotrexate, azathioprine, cyclophosphamide or dapsone are also selected as the adjuvant therapy in severe cases.<sup>5</sup> Nevertheless, the mortality rate of BP is still high (13%~38% per year according to literature).<sup>6</sup>

In comparison with those under 60 years old, a 300-fold higher relative risk was found in patients over 90 years of age.<sup>7</sup> The incidence rate of BP in different regions was different from 2.6 to 14 per 100,000 people per year.<sup>8,9</sup> In central Europe, the incidence rate was 4.5 to 14 per 1 million people per year and in North America, as the most frequently occurring autoimmune blistering disease,<sup>10</sup> BP had an incidence rate of 6 to 7 per million people per year. Moreover, the incidence rate had been growing gradually without regional differences,<sup>11</sup> which warrants an expanded awareness of the disease. BP also occurs in young adults and children although it is a disease that primarily involves the elderly.<sup>5,12</sup> Ralph et al. reported a case of BP in an eight-year-old boy with characterization of the BP 180 and 230 antigens in the year 1991.<sup>13</sup> Geyer et al. also reported a sixteen-year-old boy who developed this disease.<sup>14</sup>

As the disease could happen early in young people, this study conducted a retrospective study on 192 inpatients firstly diagnosed with BP from two university-affiliated hospitals in the course of 29 years. As patients over 60 years accounted for the majority, this study took 20 years as an age interval to analyze the relationship

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between age and treatment response. The general conditions, clinical manifestations, laboratory examination findings, treatment, complications and prognosis among the study groups were compared to determine the difference of treatment efficacy and prognosis.

## 2. Materials and methods

This study was approved by Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College. No informed consent was needed due to the fact that this was a retrospective analysis.

### 2.1. Patients

192 inpatients that were firstly diagnosed with BP from January 1<sup>st</sup>, 2016 to December 31<sup>st</sup>, 2018 were enrolled in the clinic of Peking Union Medical College Hospital. The diagnosis relied on clinical manifestations, pathological examinations and the results of direct and indirect immunofluorescence detection (DIF, IIF). The patients were confirmed by skin pathology and/or immunofluorescence or by experienced experts. Patients with other critical diseases at the time of admission or those considered unsuitable by physicians were excluded from this study. All patients were divided into three groups according to their ages: young group (age < 40), middle-age group (40 ≤ age < 60), and elderly group (age ≥ 60). According to bullous pemphigoid disease area index (BPDAI), which is the main index to evaluate the severity of disease,<sup>15</sup> BP was divided into mild group (< 10%), moderate group (10%–50%) and severe group (> 50%). The total BPDAI activity score is the summary of the 3 subcomponents – cutaneous blisters/erosions, cutaneous urticaria/erythema, and mucosal blisters/erosions. Lesions are determined based on the sites affected. BP scores can range from 0 to 360 for BPDAI total activity (maximum 240 for total skin activity and 120 for mucosal activity), and 0 to 12 for BPDAI damage, with higher scores indicating greater disease.

### 2.2. Methods

The information of all 192 patients was collected, including gender, age of onset, lesions involving the skin of head (LISH), disease-

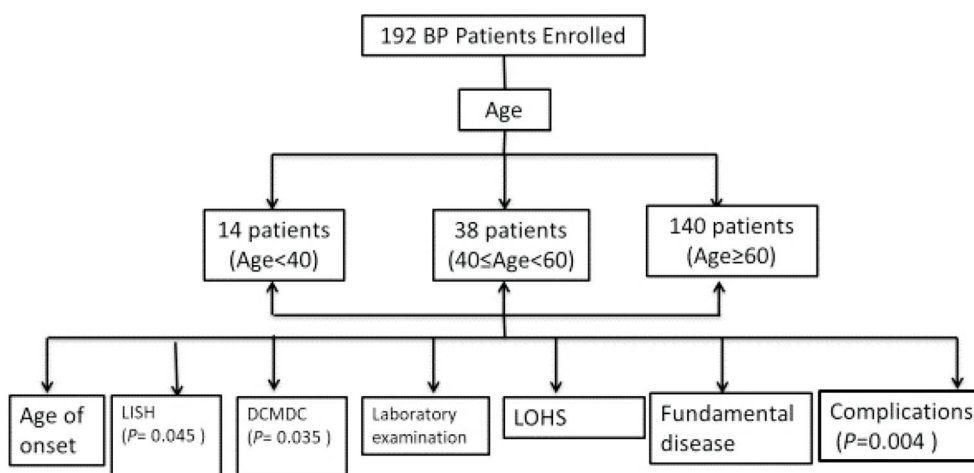
controlled maximum dosage of corticosteroid (DCMDC), laboratory examinations, length of hospital stay (LOHS), fundamental diseases, complications and treatment response (Figure 1).

Age of onset is defined as the age of the patient when BP was firstly diagnosed by an experienced dermatologist. LOHS was counted in days from the first day of hospitalization to the day patients met the discharge standard, which is defined as less than 3 new onset blisters per day. Fundamental diseases including respiratory disease, circulatory system disease, digestive system disease, nervous system disease, immune system disease, endocrine disease, cancer, diabetes, and other skin diseases were taken into consideration. The corresponding diagnosis was made by an experienced specialist. Complications refer to another disease or several diseases associated with the disease in the course of treatment and medical care, including infection, abnormal liver and kidney function, hypoproteinemia, electrolyte abnormalities, and abnormal blood glucose. DCMDC was determined as the amount of corticosteroid required to improve the condition of the original lesions or control new lesions based on the following guidelines.

The main treatment method of BP is systemic corticosteroid therapy, including prednisone or the equivalent dose of dexamethasone and methylprednisolone. The dosage of corticosteroid was reduced if the condition of lesions was controlled for two weeks. If newly-formed lesions or exudation of the original lesions were still observed within one-week usage of corticosteroid, the dose should be increased by 1/3–1/2. If the conventional dose did not control the progression of the lesions, a pulse therapy (500 mg–1000 mg methylprednisolone intravenously daily for 3 days) or a combination of immunosuppressive agents therapy should be considered. Assistance of steroid therapy with symptomatic supportive treatment should be provided, such as giving nutritional support, maintaining electrolyte balance, managing infectious diseases, etc.

The standard of treatment response was established according to an international standard,<sup>16</sup> that is, clearance of the original lesions (including the erythema, blisters, bullae, and erosions) or no emergence of newly formed lesions after the corresponding treatments. The criteria were mainly based on the following conditions: Recovery: All the original lesions vanished, with no newly formed blisters;

Improvement: 80% of the original lesions vanished or crusted, with no or few newly formed blisters;



**Figure 1.** The flow chart of the study. 192 inpatients diagnosed with BP were recruited and divided into 3 age groups. The study compared them regarding lesions involving the skin of head (LISH), disease-controlled maximum dosage of corticosteroid (DCMDC), laboratory examinations, length of hospital stay (LOHS), fundamental diseases, complications among the three groups and age of onset between gender of the patients. The statistical significance between the three groups was found in DCMDC (in the young and middle-aged groups was significantly higher than in the elderly group), LISH and the occurrence of complications (both increased with the age of the patient).

Uncured: 80% of the original lesions still present, or massive newly formed blisters;  
 Death: Death due to poor response to treatment during hospitalization.

### 2.3. Statistical analysis

Data were analyzed using SPSS19.0 software and were expressed as mean  $\pm$  standard deviation or number (percentage). *t* test or  $\chi^2$  test were used for the comparisons among groups. Multivariate logistic regression was used to analyze the influence factor of complicates of BP.  $p < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. General conditions

Out of the 192 patients, 117 (60.9%) were male and 75 (39.1%) were female. Ratio of male to female was 1.56: 1. The age of onset ranged from 1 to 93 years old (average:  $65.83 \pm 15.381$ ). There were 14 cases in the young patient group (age  $< 40$ ), 38 cases in the middle-aged patient group ( $40 \leq \text{age} < 60$ ), and 140 cases in the elderly patient group (age  $\geq 60$ ), respectively. The average age of onset was  $70.80 \pm 13.38$  in males and  $64.03 \pm 17.22$  in females, without a significant difference ( $t = 1.89$ ,  $p = 0.064$ ).

The most common primary site of lesions was the torso. In this study, 77 patients had lesions on the head (LISH) (40.1%). The young patient group, middle-aged patient group, and elderly patient group accounted for 7, 17, and 53 cases, respectively ( $\chi^2 = 9.742$ ,  $p = 0.045$ ). 45 cases (23.43%) had lesions involving the mucosa: 1 case in young patient group, 10 cases in middle-age patient group, and 34 cases in elderly patient group ( $\chi^2 = 7.944$ ,  $p = 0.094$ ). According to BPDAl, all of the patients had severe BP. Out of the 192 patients, 6 (3.13%) had positive Nickolsky sign, while the other 186 (96.88%) were negative.

Circulatory system diseases were one of the most common fundamental diseases in BP patients (55 cases, 28.65%), including hypertension, coronary heart disease, rheumatic heart disease and arrhythmia. The other diseases were neuropathy, diabetes, digestive system disease, thyroid disease and tumor. Other cases were complicated with another skin disease, including chronic idiopathic urticaria, stucco keratosis, eczema, psoriasis and vitiligo.

### 3.2. Laboratory examination

DIF and IIF detection of the pathological section and peripheral eosinophil count were conducted routinely in BP patients. The results showed no significant difference in the performed examinations among the three different age groups ( $p = 0.454$ ,  $0.354$ ).

**Table 1**

Lesion areas, DCMDC and LOHS among 3 groups.

	Group			$\chi^2/F$	<i>p</i>
	Age $< 40$ (n = 14)	$40 \leq \text{age} < 60$ (n = 38)	$60 \leq \text{age}$ (n = 140)		
Lesions present on the skin of the head, N (%)	7 (9.1)	17 (22.1)	53 (68.8)	9.742	0.045
Lesions involving the mucosa, N(%)	1 (2.2)	10 (22.2)	34 (75.6)	7.944	0.094
DCMDC	$61.67 \pm 40.16$	$63.93 \pm 22.97$	$54.00 \pm 24.45$	3.427	0.035
LOHS	$37.33 \pm 24.90$	$19.50 \pm 11.28$	$21.66 \pm 13.29$	2.004	0.138

A significant difference in lesions involving the skin of head (LISH) among the three groups. In the same group, there was the higher number of lesions involving the mucosa but with no statistical significance. Disease-controlled maximum dosage of corticosteroid (DCMDC) was significantly higher in young and middle-age group. Length of hospital stay (LOHS) was higher in young group, but without statistical significance.

### 3.3. DCMDC and LOHS

A significant difference of LISH was observed among the three groups ( $\chi^2 = 9.742$ ,  $p = 0.045$ ). In the same group, there was the higher number of lesions involving the mucosa but with no statistical significance. DCMDC was  $61.67 \pm 40.16$  mg/d in the young group (age  $< 40$ ),  $63.93 \pm 22.975$  mg/d in the middle-aged group ( $40 \leq \text{age} < 60$ ) and  $54.00 \pm 24.45$  mg/d in the elderly group (age  $\geq 60$ ). The DCMDC in the young and middle-aged groups were significantly higher than that in the elderly group ( $\chi^2 = 3.427$ ,  $p = 0.035$ ).

The LOHS in the young group, middle-aged group and the elderly group were  $37.33 \pm 24.90$  days,  $19.50 \pm 11.28$  days and  $21.66 \pm 13.29$  days, respectively. Statistical analysis indicated no significant difference among groups ( $\chi^2 = 2.004$ ,  $p = 0.138$ ) (Table 1).

### 3.4. Complications

During corticosteroid treatment, the most common complications were hypokalemia, hypocalcemia and hyperglycemia. In addition, fungal and bacterial infection of the skin and bacterial infection of the lung, osteoporosis and osteonecrosis of the femoral head were found. The difference in complications appearance among the three groups was found to be statistically significant ( $\chi^2 = 11.087$ ,  $p = 0.004$ ) and increasing with the age of the patient ( $\chi^2 = 11.087$ ,  $p = 0.004$ ) (Table 2). Additionally, multivariate logistic regression showed that age is an influence factor for the rate of complications ( $p = 0.004$ ).

## 4. Discussion

The study recruited 192 inpatients diagnosed with BP from 1990 and 2019. Patients were selected and enrolled in this period for the following reasons. On the one hand, after several years of follow-up, the condition changes were observed, and most of the patients had better control of the disease. On the other hand, overall basic treatments were the same, without large-scale use of biological agents, dialysis, plasma exchange, etc. Lastly, the probability of sample bias was small. Among these patients, elderly patients accounted for the majority and 140 of the 192 were male while 75

**Table 2**

Rates of complications in different age groups.

Groups	Complications (%)
age $< 40$	4 (40.0)
$40 \leq \text{age} < 60$	16 (72.7)
$60 \leq \text{age}$	88 (83.8)

Complications refer to other disease(s) associated with the disease during treatment and medical care. The difference in complications appearance among the three groups was found to be statistically significant ( $\chi^2 = 11.087$ ,  $p = 0.004$ ) and increasing with the age of the patient.

were female. Ratio of male to female was 1.56:1, which was consistent with that in literature.<sup>7</sup>

The study results revealed that DCMDC in young and middle-aged group was higher. The LISH was significantly lower in the young patient group. Moreover, the study data showed an increased tendency of complications with increased age of the patients. Higher DCMDC, but lower LISH and fewer complications in the young group suggested that besides these patients often present with a clinically less lesions and less severe course of the disease, their disease was not well controlled with the same dose of medications as in the elderly groups.

It has been reported that patients with specific autoantibodies to BP180 hemidesmosomal components were more vulnerable to develop oral mucosal lesions and had a relatively more severe disease with poor treatment responsiveness.<sup>17</sup> In this study, 45 patients developed mucosal lesions, of which the incidence rate did not have a significant difference between the younger group and elderly group, indicating that mucosal involvement was not associated with the poor response in the treatment of the younger group. In addition, there was no difference in the IIF results among these three groups, indicating that the titer of antibody was not related to the treatment response. The increased treatment resistance in younger patients is likely related to the genetic susceptibility to a more severe variant of BP.<sup>18,19</sup> In the future, gene susceptibility of younger BP patients might be of great help to better elucidate the mechanisms responsible for treatment resistance.

The severity of young BP patients and the response to treatment was the focus of this study. There have been similar publication before, but the sample size and observation time were insufficient to obtain consistent results. A previous publication suggested that bullous pemphigoid among young people was more severe and more active than the usual form in the elderly.<sup>20</sup> This present study evaluated whether young BP patients had different responses from the elderly, with the aim to improve the treatment experience in this rare condition. This study is retrospective, age-matched, case-control, multi-centered. A key limitation is the long-time period (29 years) of the study, in which treatments have been improved and guidelines have changed, leading to different treatment regimens. Moreover, a multi-center and big sample size is prone to reduce the selection bias. However, this study enrolled elderly patients in close proximity to the young ones in the same time period to try to avoid treatment bias. Enrolling BP patients and tracking them within a multi-center study will improve performance in ongoing patient monitoring and improve the attention to treatments and the response to the selected treatment regimens. BP mainly occurred in patients over 60 years old. Considering the lower incidence rates for BP in young patients<sup>21</sup> and their lack of complications and increased mobility compared to their elderly counterparts, targeted therapy may lead to better outcomes and may be cost-effective. Finding a more reasonable treating option for these young BP patients would be of great value.

In conclusion, our data reveals that patients often present with different clinical features of BP among different age groups. Especially, younger BP patients require a higher dosage of corticosteroids to control BP. In clinical practice, more attention to these patients should be given, including complications such as hypoproteinemia, hypokalemia, hypocalcemia, hyperglycemia due to steroid usage.

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## Disclosure of conflict of interest

The authors declare that they have no competing interests.

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