

## ORIGINAL ARTICLE

# Concomitant use of dupilumab with glucocorticoid in bullous pemphigoid reduces disease severity: A preliminary study

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**Abstract**

**Objective:** To retrospectively analyze the efficacy and safety of dupilumab in the treatment of bullous pemphigoid.

**Methods:** From October 2020 to October 2022, the medical records of patients with bullous pemphigoid who were treated with dupilumab in our department were collected retrospectively to analyze the therapeutic effect and changes in laboratory indexes.

**Results:** The records of a total of 11 patients with bullous pemphigoid who were treated with dupilumab was reviewed. Within 2 weeks of the treatment, 10 (90.9%) of the 11 patients had complete or substantial control of the disease. The BPDAI scores of the patients decreased from baseline 113 (62, 181) to 37 (6, 130) at 2 weeks ( $p = .001$ ) and 4 (0, 37) at 12 weeks after treatment ( $p < .001$ ). In the 11 patients treated with dupilumab, the relief time of pruritus was 0–3 days (0.5, 7) days, and the pruritus was significantly alleviated after 2 weeks ( $t = 15.925$ ,  $p < .001$ ). The DLQI score decreased from ( $25.5 \pm 2.5$ ) before treatment, to ( $11.8 \pm 4.4$ ) at 2 weeks ( $t = 10.764$ ,  $p < .001$ ) and ( $2.1 \pm 1.9$ ) at 12 weeks ( $t = 30.038$ ,  $p < .001$ ). The patients had high eosinophil counts, high serum IgE levels, low serum total protein levels, and abnormal blood coagulation function. The aforementioned indicators gradually returned to normal after treatment. No adverse reactions occurred during the treatment.

**Conclusion:** Dupilumab can effectively control the condition of bullous pemphigoid, efficiently relieve pruritus symptoms, and is relatively safe.

**KEYWORDS**

blood coagulation function, dupilumab biologics, eosinophils, IL-13, IL-4, immunoglobulin E, pemphigoid, treatment

Lingyu Hu and Ruiting Huang contributed equally to this study.

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## 1 | BACKGROUND

Bullous pemphigoid (BP) is an autoimmune sub-epidermal vesicular disease wherein the autoantibodies destroy the connection between the epidermis and basement membrane, causing blisters and bullae. The incidence of BP is mainly among the elderly. The number of patients is increasing as society ages. Its typical rash is erythema or tension bullae on otherwise normal-looking skin, and patients frequently experience severe pruritus. Anti-inflammatory drugs, glucocorticoids, immunosuppressants, and potent topical hormones are currently the main treatment methods. BP patients are mostly the elderly, and they frequently have additional underlying diseases that limit their treatment options. Furthermore, some patients develop treatment resistance, making it difficult to control their condition even when using a variety of different treatment strategies. T helper 2 cell (Th2)-related cytokines and chemokines, primarily interleukin-4 (IL-4), IL-5, CCL-13, CCL-18, eotaxin, and others were found to be overexpressed in pemphigoid lesions.<sup>1</sup> Dupilumab works therapeutically by inhibiting the downstream inflammatory response by blocking the IL-4 receptor  $\alpha$  (IL-4R  $\alpha$ ) of IL-4 and IL-13.<sup>2</sup> In this study, we retrospectively analyzed patients who were treated with dupilumab in our outpatient and inpatient departments between October 2020 and October 2022. The patients were mostly elderly and several of them had significant comorbidities. We examine the use, efficacy, and safety of dupilumab in this paper.

## 2 | PATIENTS AND METHODS

### 2.1 | Research patients

From October 2020 to October 2022, BP patients were treated with dupilumab in the dermatology department of the Second Affiliated Hospital of Kunming Medical University. *Inclusion criteria:* ① BP patients who were diagnosed with clinical findings, histopathology, immunofluorescence and/or enzyme-linked immunosorbent assay showing positive anti-BP180 and/or BP230 antibodies; ② Complete clinical medical records. *Exclusion criteria:* Patients who did not complete a full 12 weeks of regular follow-up after dupilumab treatment.

### 2.2 | Treatment and follow-up

For the treatment with dupilumab, the atopic dermatitis treatment plan in the drug manual was consulted. The initial dose was 600 mg subcutaneously injected,

followed by 300 mg injected every 2 weeks. Some patients with severe conditions were given medication weekly at first, then every two weeks after their disease was under control. Past use of hormones, immunosuppressants, anti-inflammatory drugs (minocycline), and topical drugs by patients remained unchanged, and the dosage was adjusted based on changes in the disease. Following the initial administration, all patients were followed-up once every 1–2 weeks, and then once every 2–4 weeks after 1 month. Details about skin lesions, pruritus degree, bullous pemphigoid disease area index (BPDAI) score, peripheral blood eosinophil count, total serum IgE concentration, liver and kidney function, blood coagulation function, other test indexes, and possible adverse drug reactions were collected at each follow-up.

### 2.3 | Evaluation of the therapeutic effect

The disease process is defined as follows: (1) Treatment baseline: The time when doctors began BP treatment with dupilumab; (2) Disease control stage: There are no new active lesions, and the existing lesions have begun to heal or recover; (3) Consolidation treatment stage: No new lesions appeared within at least 2 weeks, approximately 80% of the lesions had healed, and the pruritus symptoms were mild. (4) Complete remission following treatment: The patient had no new rash or pruritus in the original rash at least 2 months after discontinuing the drug treatment.<sup>3</sup>

Definition of therapeutic effect: (1) Fully controlled: The area of active skin lesions decreased by more than 90% when compared to the baseline; (2) Mostly controlled: The area of active skin lesions decreased by 50%–90% when compared to the baseline; (3) Partially controlled: The area of active skin lesions decreased by 50% when compared to the baseline; (4) Uncontrolled: The original skin lesions did not change or were aggravated. (5) Treatment failure: The discontinuation of dupilumab treatment was due to disease progression, adverse reactions, or death.<sup>4,5</sup> The short-term and medium-term efficacy rates of dupilumab were assessed 2 and 12 weeks after the initial injection, respectively.

### 2.4 | Statistical method

SPSS 26.0 statistical software was used to process the data in this study. The measurement data were expressed by M (Q1, Q3) when it did not accord with the normal distribution, and by ( $\bar{x} \pm s$ ) when it was consistent with the normal distribution. The paired t-test was used to

compare measurement data that fit the normal distribution, while Wilcoxon and Friedman's tests were used to compare measurement data that did not fit the normal distribution. The difference was statistically significant at  $p < .05$ .

### 3 | RESULTS

#### 3.1 | Clinical data baseline characteristics

Data on 11 BP patients (4 males and 7 females) treated with dupilumab were collected, with a median age of 79 (45, 92) years, a median disease duration of 2 (1, 180) months, a BPDAI score of 113 (62, 181), and a pemphigoid pruritus visual analog scale score of  $(24.9091 \pm 4.98908)$  (Table 1).

During the course of the dupilumab treatment, one patient was not treated with hormones, while the other patients received hormone treatment. The minimum dose (prednisone equivalent) was 20 mg and the maximum dose was 100 mg. Except for one patient, all others received topical hormone therapy (halometasone ointment or halometasone/triclosan ointment). Minocycline hydrochloride capsule was used concurrently with the aforementioned topical hormone in nine patients; intravenous human immunoglobulin 25 g/day (for 2 days) was used concurrently in one patient, and cyclosporine, a soft capsule was used concurrently in one patient. The majority of patients had one or more comorbidities, with only one patient having no comorbidity. Comorbidities recorded included hypertension, myocardial infarction, pulmonary infection, old pulmonary tuberculosis, cerebral hemorrhage, cerebral infarction, brain atrophy, lower limb atherosclerosis, pleural effusion, pericardial effusion, mediastinal lymph node enlargement, pleural adhesion, pleural calcification, hepatic cyst, renal cyst, atrial tachycardia, atrial premature beat, complete right bundle branch block, abnormal electrocardiogram, hypoproteinemia, hypocalcemia, hyponatremia, digestive tract ulcer, diabetes, cataract, and others.

#### 3.2 | Disease control

##### 3.2.1 | BPDAI score

The patients quickly entered the disease control stage after receiving dupilumab treatment for BP. After 2 weeks of treatment with dupilumab, the rash in 10 (90.91%) of the 11 cases was fully or mostly controlled.

One case had poor rash control after 3 weeks of dupilumab treatment, but the rash was controlled when prednisone tablets (30 mg/day) were used concurrently. The rash in one patient completely disappeared in the eighth week of follow-up but the patient refused to continue treatment and was treated with prednisone 15 mg alone; there was no recurrence of the rash after 24 weeks of follow-up and the treatment was continued with hormone 7.5 mg. No new lesions appeared in the patients during the consolidation treatment stage. At present, all drug treatments have been discontinued for at least 2 months, and there has been no recurrence. Following treatment, three patients achieved complete remission. The BPDAI score dropped from 113 (62, 181) at baseline to 37 (6, 130) at 2 weeks ( $Z = -3.059$ ,  $p = .002$ ), and decreased to 4 (0, 37) at 12 weeks after treatment ( $Z = -2.937$ ,  $p = .003$ ,  $p = .003$ ; Figure 1).

##### 3.2.2 | Pemphigoid pruritus visual analog scale (VAS) score

At baseline, all patients had varying degrees of pruritus with the most severe case scoring a full 30 points. After treatment with dupilumab, the pruritus sensation of the skin rash was quickly relieved. The 11 patients experienced relief from pruritus after receiving dupilumab for 0–3 days (0.5, 7) days. Pruritus began to subside to varying degrees in 8 patients after 1 day of treatment with dupilumab. The pruritus in all patients improved significantly after 2 weeks of treatment ( $t = 15.925$ ,  $p < .001$ , Figure 2).

##### 3.2.3 | Dermatology life quality index (DLQI) score

The dermatology life quality of pemphigoid patients was significantly improved. The DLQI score of pemphigoid patients decreased from  $(25.5 \pm 2.5)$  at the time of diagnosis to  $(11.8 \pm 4.4)$  at 2 weeks ( $t = 10.764$ ,  $p < .001$ ), and to  $(2.1 \pm 1.9)$  at 12 weeks ( $t = 30.038$ ,  $p < .001$ ) (Figure 3).

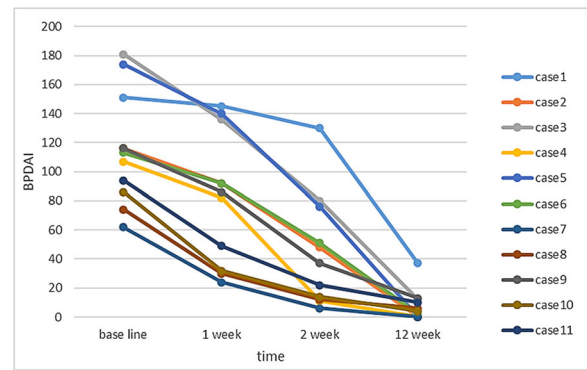
#### 3.3 | Changes in laboratory indicators

##### 3.3.1 | Changes in the eosinophil count and total IgE

The changes in the peripheral blood eosinophil count and total IgE were recorded for 10 patients. Among

TABLE 1 Therapeutic drug use of patients at baseline.

| Patient code | Sex    | Age | Course of disease (month) | Glucocorticoid use at baseline (as calculated by prednisone) | Therapeutic drug use of patients at baseline |             |              |                       | Topical drug (cream halometasone/triclosan) |         |
|--------------|--------|-----|---------------------------|--|--|-------------|--------------|-----------------------|---|---------|
|              |        |     |                           |  | Minoocycline hydrochloride                   | Niacinamide | Cyclosporine | Mycophenolate mofetil |   | Albumin |
| Case1        | Female | 76  | 3                         | 0  |  |             |              |                       | ✓   |         |
| Case2        | Female | 73  | 12                        | 30 mg  | ✓  |             |              |                       | ✓   |         |
| Case3        | Male   | 91  | 180                       | 37.5 mg  | ✓  | ✓           |              |                       | ✓   |         |
| Case4        | Female | 79  | 1                         | 37.5 mg  | ✓  | ✓           | ✓            |                       | ✓   |         |
| Case5        | Female | 45  | 6                         | 150 mg   | ✓  | ✓           |              | ✓                     | ✓   |         |
| Case6        | Male   | 80  |                           | 30 mg  |  |             |              |                       | ✓   |         |
| Case7        | Female | 84  | 1                         | 30 mg  |  |             |              | ✓                     | ✓   |         |
| Case8        | Female | 90  | 4                         | 50 mg  |  |             |              |                       | ✓   |         |
| Case9        | Female | 67  | 5                         | 50 mg  |  |             |              |                       | ✓   |         |
| Case10       | Male   | 81  | 3                         | 50 mg  | ✓  |             |              | ✓                     | ✓   |         |
| Case11       | Male   | 69  | 2                         | 0  | ✓  |             |              | ✓                     | ✓   |         |



**FIGURE 1** Changes in the BPDAI score after dupilumab treatment: With the passage of time, the BPDAI score gradually decreased. The Friedman test revealed that the BPDAI score decreased significantly 1 week after treatment ( $Z = -2.936$ ,  $p = .003$ ), and at 12 weeks, the majority of patients were fully or mostly controlled ( $Z = -2.937$ ,  $p = .03$ ). BPDAI, bullous pemphigoid disease area index.

them, two patients had elevated peripheral blood eosinophils and two patients had a higher baseline total IgE concentration than the normal value. In these 4 patients, peripheral blood eosinophil count and total IgE levels decreased after treatment with dupilumab.

### 3.3.2 | Changes in blood coagulation function

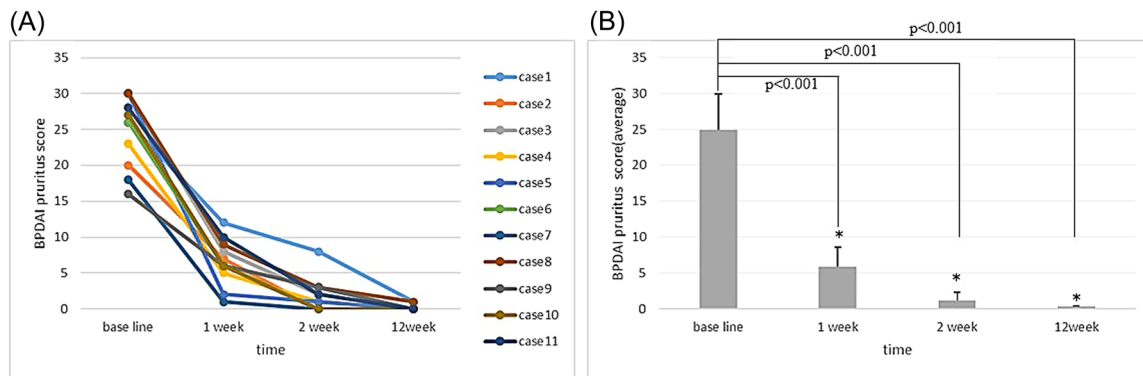
Nine of the patients had abnormal indexes of blood coagulation function, and eight of the nine patients had simultaneous elevations of prothrombin activity, fibrinogen degradation products (FDPs), and thrombus dissolved dimer (DD). In one of the nine patients, the prothrombin activity was slightly elevated. The corresponding indicators tended to be normal after treatment and as the disease improved.

### 3.3.3 | Changes in total blood protein

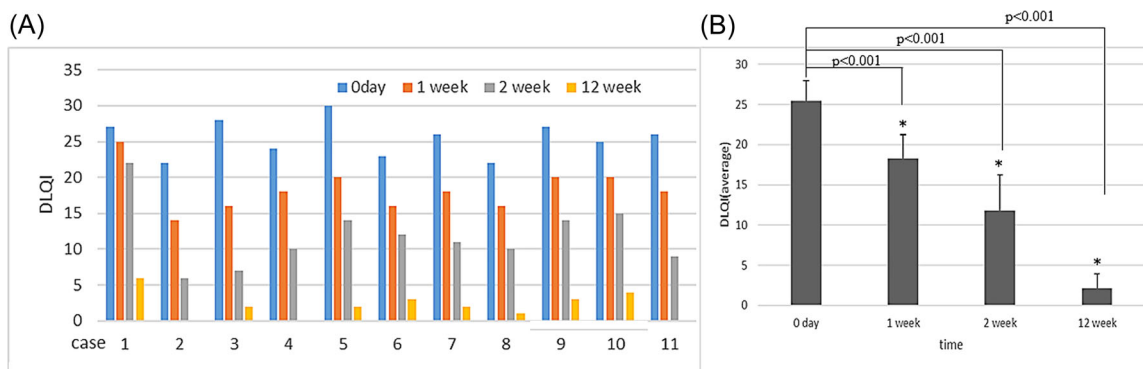
Total blood protein decreased in 10 patients to varying degrees, while albumin decreased in three cases.

## 3.4 | Adverse reactions

No adverse reactions such as conjunctivitis, blepharitis, eye pruritus, allergic reaction at the injection site, headache, eosinophilia, and oral herpes were detected in the 11 patients.



**FIGURE 2** Changes in the pruritus score on the visual analog scale in pemphigoid patients: (A) changes in pruritus score on the visual analog scale of patients at baseline, 1 week after treatment and 2 weeks after treatment; (B) after treatment, the skin pruritus was significantly different from baseline at 1 week ( $t = 13.177$ ,  $p < .001$ ) and 2 weeks ( $t = 15.925$ ,  $p < .001$ ).



**FIGURE 3** Changes in the dermatology life quality index (DLQI) of the 11 patients: (A) The dermatology life quality of 11 pemphigoid patients was severely impacted. (B) The DLQI score of the patients decreased from ( $25.5 \pm 2.5$ ) at the time of the diagnosis to ( $11.8 \pm 4.4$ ) at 2 weeks ( $t = 10.764$ ,  $p < .001$ ), and to ( $2.1 \pm 1.9$ ) at 12 weeks ( $t = 30.038$ ,  $p < .001$ ).

### 3.5 | Follow-up treatment plan

Two patients stopped taking dupilumab after a full 40-week treatment (involving 21 drugs). After 60 weeks of follow-up, these 2 patients had no recurrences and stopped taking all the medications. One patient's rash was resolved completely by the eighth week of follow-up. The patient refused maintenance therapy and was only given prednisone 15 mg. There was no recurrence of the rash after 24 weeks of follow up, and this patient experienced complete relief from the ailment and stopped taking medication. One patient was treated with dupilumab alone for 4 weeks. Although there was no new rash, the old rash did not subside. The rash began to improve after prednisone tablets of 30 mg/day were given. Before starting dupilumab, one patient received a methylprednisolone injection of 80 mg/day, and a large number of new rashes continued to develop. There was some relief from the trunk rash after treatment with dupilumab, but there were still a large number of new blisters on limbs, hands, and feet. Following that, the hormone dosage was

increased to 120 mg/day of methylprednisolone injection and to 300 mg/week of dupilumab. The rash was then controlled, and the pruritus was relieved.

## 4 | DISCUSSION

The production of autoantibodies against hemidesmosome components is central to the pathogenesis of BP. Antibody production and function are closely linked to the inflammatory response mediated by Th2. Activated Th2 cells can secrete cytokines such as IL-4, IL-5, IL-13, IL-31, and chemokines. On the one hand, they can recruit eosinophils and other inflammatory cells and promote B cells to convert and secrete IgE. The release of inflammatory factors, on the other hand, maintains the continuous activation of the inflammatory response via positive feedback. Furthermore, cytokines like IL-4 and IL-31 can sensitize peripheral nerves causing them to mediate pruritus sensation.<sup>6</sup> Dupilumab has the ability to

bind to the IL-4 R  $\alpha$  receptor, inhibit the action of IL-4 and IL-13, and inhibit downstream signal transduction, thereby inhibiting inflammatory response, reducing pruritus, and preventing disease progression.<sup>7</sup> Dupilumab is not currently approved for the treatment of BP. However, due to the role of Th2-mediated inflammation in the pathogenesis of BP, research initiatives around the world<sup>8–23</sup> and within China<sup>24–27</sup> have used dupilumab to treat refractory or moderate to severe BP.

We attempted to use dupilumab to treat 11 BP patients whose underlying diseases made conventional treatment ineffective or who had poor responses to conventional treatment, and we achieved positive results. In terms of dupilumab use in BP, we currently referred to its use in the treatment of atopic dermatitis. Ten of the 11 patients were treated with hormones concurrently. However, the reduction in hormone dosage after disease control was faster than that for the patient who was conventionally treated with hormones alone, and there was no disease rebound. As a result, the use of dupilumab is of immense significance in reducing hormone dosage and rapidly reducing hormone frequency. The condition of a 43-year-old patient was out of control following an active radical treatment protocol. We achieved good results by shortening the dupilumab use cycle and switching to weekly dosing when adding dupilumab. It is worth noting that a 91-year-old patient had more than 80% skin involvement. Erythema, blisters, blood blisters, and bullae were widely distributed all over the skin. The rash could not be controlled with dupilumab and topical halometasone cream for 4 weeks. The rash was controlled with 30 mg/day prednisone tablets. This suggests that combining hormones and dupilumab could be an effective way to control the disease in patients with severe conditions and obvious inflammatory responses to rash. However, due to the small number of cases, the sample size must be increased for further observations and analysis.

The first benefit that patients noticed after receiving dupilumab treatment was the improvement in pruritus. This medication controlled BP pruritus symptoms faster than it improved skin lesions. Except for one patient, pruritus in the other patients were relieved to varying degrees on the day of medication and was completely relieved within 2 weeks. The relief from pruritus improved the sleep quality of patients and effectively improved their life quality.

In recent years, there has been increasing evidence on the important role eosinophils (EOS) and immunoglobulin E (IgE) play in the pathogenesis of BP. EOS is a cell essential for blister formation mediated by IgE autoantibodies.<sup>28</sup> It was reported that 50% of BP patients had elevated EOS in their peripheral blood.<sup>29</sup> In untreated BP patients, the number of EOS cells was linearly correlated with disease severity.<sup>30</sup> Only two

patients in this study had eosinophilia, which may be attributable to the small sample size. On the other hand, it could be due to the fact that most of these patients had used glucocorticoids before admission. The peripheral blood eosinophil count and total IgE were elevated, which may be related to the small sample size. Following treatment, the blood eosinophil count and total IgE concentration of the two patients returned to normal, which was consistent with the other cases.

Furthermore, the enrolled patients had varying degrees of blood coagulation dysfunction, primarily an increase in D dimer and fibrinogen degradation products (FDPs). The skin is closely related to the hemorrhagic and blood coagulation systems. Skin epidermal cells can secrete tissue factors that induce blood coagulation. At the same time, the fibrinolytic system can be activated to help with anticoagulation. Blood coagulation and the fibrinolytic system activation in the peripheral blood of BP patients leads to increased vascular permeability, making it easier for inflammatory cells to migrate from blood vessels to skin tissues. Infiltration of skin inflammatory cells can aggravate local inflammatory response, promoting blister formation,<sup>31</sup> but it also increases the risk of thrombosis.<sup>32</sup> D dimer and FDPs are specific fibrinolysis markers. D-dimer and FDPs increased during disease activity and decreased to normal after disease remission in the patients studied, indicating that blood coagulation and fibrinolytic function were activated and abnormal while the disease was active. The specific mechanism remains unclear.

Total blood protein decreased to varying degrees in 10 of the patients, while albumin decreased concurrently in 3 patients. With disease remission, blood protein levels gradually returned to normal. A large area of skin rash, erosion, ulceration, protein loss, malnutrition, and increased consumption were the main considerations for the above changes. Following disease relief, the condition gradually returned to normal.

## 5 | CONCLUSION

To summarize, dupilumab therapy can achieve disease control in BP, effectively relieve pruritus symptoms, and is relatively safe. The excellent safety profile of dupilumab, which does not suppress immunity, unlike other therapeutic options. It can effectively reduce the dosage of hormones and shorten the use cycle for patients on hormone medication, providing a new treatment option for patients with poor control or intolerance to conventional treatment. However, given the short history of dupilumab in the treatment of BP, the long-term efficacy of the drug must be monitored. The following limitations

apply to this study: small sample size, no control group, and short follow-up time. Future research should increase the sample size, implement reasonable controls, and investigate the specific use of dupilumab.

### AUTHOR CONTRIBUTIONS

**Lingyu Hu:** Data curation; resources; writing—original draft; writing—review & editing. **Ruiting Huang:** Data curation; methodology; resources; writing—review & editing. **Fuqiong Jiang:** Formal analysis; funding acquisition; methodology; resources; writing—original draft; writing—review & editing. **Shuqiong You:** Data curation; formal analysis; resources; writing—original draft. **Qian Wu:** Data curation; methodology; resources; writing—review & editing.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### ETHICS STATEMENT

This study was conducted with approval from the Ethics Committee of Second Affiliated Hospital of Kunming Medical University. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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