European Review for Medical and Pharmacological Sciences 2023; 27: 9830-9837

Efficacy and safety of dupilumab plus topical tacrolimus for atopic dermatitis in 6- to 12-year-old patients

S.-S. GAO, M. CHEN, R. WANG, J.-G. CHEN

Taizhou Central Hospital, Taizhou University Hospital, Taizhou, China

Abstract. – OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of combining dupilumab with topical tacrolimus for the treatment of atopic dermatitis (AD) in children aged 6 to 12 years.

PATIENTS AND METHODS: A total of 168 pediatric (aged 6 to 12 years) patients with severe AD admitted to our hospital between April 2022 and April 2023 were included in this retrospective study. These patients are grouped according to different medication methods, assigned them to receive either tacrolimus plus topical corticosteroids (control group) or dupilumab combined with tacrolimus and topical corticosteroids (study group), with 84 patients in each group. Clinical efficacy and adverse reactions were primary clinical endpoints.

RESULTS: The use of dupilumab significantly increased the total effective rate for the patients by 14.29%, from 77.38% (65/84) in the control group to 91.67% (77/84) in the study group. Following treatment, patients given dupilumab showed a more significantly decreased peripheral blood eosinophils (EOS) and immunoglobulin E (IgE) levels than those without dupilumab treatment. Patients administered with dupilumab exhibited markedly lower scores on the Patient-oriented Eczema Measure (POEM) at weeks 12 and 16 and lower Eczema Area and Severity Index (EASI) scores at weeks 8, 12, and 16 when compared to those patients who did not receive dupilumab therapy. At the 16-week, 37 patients in the study group obtained a score of 1/0 on the Verified Investigator's Global Assessment (v-IGA) scale, whereas the control group had 24 such cases, indicating a significantly higher response rate provided by the protocol incorporating dupilumab. After 16 weeks of treatment, both groups demonstrated a marked decrease in itch numeric rating scale (NRS) scores and Dermatology Life Quality Index (DLQI) scores, with lower scores observed in the study group than in the control group. The absence of a significant difference in the incidence of adverse reactions between the two groups suggested a high safety profile of dupilumab.

CONCLUSIONS: The combination of dupilumab with topical tacrolimus demonstrated favorable efficacy in the management of AD in children aged 6 to 12 years. This treatment protocol effectively alleviates symptoms, enhances the quality of life of patients, and shows no increased risk of adverse reactions.

Key Words:

Atopic dermatitis, Dupilumab, Tacrolimus, Corticosteroids, Eczema area and severity index.

Introduction

Atopic dermatitis (AD) is the prevailing chronic inflammatory skin condition, distinguished by eczematous lesions and intense itching[1]. AD predominantly affects children, with a prevalence rate ranging from 10% to 20%, and there has been a noticeable upward trend in recent years, resulting in a substantial economic burden on both patients and their families[2,3]. Atopic dermatitis is closely related to skin barrier dysfunction and immune dysregulation, wherein interleukin-4 (IL-4) and IL-13 hold pivotal roles as inflammatory cytokines. They stimulate B cells to produce immunoglobulin E (IgE), induce eosinophil differentiation and migration into tissues, directly act on skin keratinocytes, leading to barrier disruption, and activate sensory neurons, thereby causing refractory itching[4]. In moderate to severe AD, extensive skin lesions with severe and persistent itching can lead to sleep disturbances, anxiety, and depression, resulting in a significantly compromised quality of life[5]. At present, treatment alternatives available for moderate to severe AD in children are scarce, and certain patients may experience ineffectiveness or poor tolerability with traditional systemic therapies[6].

Corresponding Author: Jinguang Chen, MD; e-mail: m15957626481@163.com

In recent years, biologic agents have been introduced for the management of atopic dermatitis, providing more effective and less toxic treatment alternatives. Dupilumab, a fully human monoclonal antibody, specifically binds to the shared alpha chain of the IL-4 and IL-13 receptors, leading to the inhibition of their signaling pathways[7,8]. Clinical trials of dupilumab have demonstrated that these cytokines are crucial and central driving factors in various type 2 inflammatory diseases. Previous research[9] has confirmed that subcutaneous injections of 300 mg once a week (q1w) or once every two weeks (q2w) markedly mitigated the objective signs and symptoms of AD, including itching, anxiety, depressive symptoms, and Dermatology Life Quality Index (DLQI) scores, compared to a placebo. As of 2022, dupilumab has been approved for the management of moderate to severe AD in children aged 6 to 12 years and adults in China. However, there remains a paucity of large-sample clinical studies and long-term follow-up data specifically focusing on children aged 6 to 12 years. To this end, the current research was performed to explore the effectiveness and safety of dupilumab in this group of AD children.

Patients and Methods

Baseline Profiles

A total of 168 pediatric (aged 6 to 12 years) patients with severe AD admitted to our hospital between April 2022 and April 2023 were included in this retrospective study. These patients were grouped according to different medication methods according to a retrospective randomization criterion. Those who received either tacrolimus plus topical corticosteroids were in the control group, and those who received dupilumab combined with tacrolimus and topical corticosteroids were in the study group, with 84 patients in each group. This study was approved by the Medical Ethics Committee of our hospital and complied with the ethical principles outlined in the Helsinki Declaration.

Inclusion and Exclusion Criteria

Inclusion criteria: 1) Patients aged 6 to 12 years, with a body weight of 30-60 pounds regardless of gender; 2) Diagnosis of AD following the criteria set by Eichenfield et al[10]; 3) Moderate to severe AD, with Eczema Area and Severity Index (EASI) ≥ 16 and a weekly average most severe itching Numeric Rating Scale (NRS) ≥ 4; 4) Guardians of the patients provided informed consent, and the patients exhibited good compliance.

Exclusion criteria: 1) Patients in the acute exacerbation stage with exudation, erosion, or secondary infections; 2) Patients who received topical medication within 14 days before enrollment, including calcineurin inhibitors (topical tacrolimus or pimecrolimus), corticosteroids, and topical antihistamines; 3) Presence of diseases that may confound disease status assessment (e.g., skin atrophy, ichthyosis, fungal infections, contact dermatitis); 4) Allergy to dupilumab or any of its components.

Treatment Protocols

All patients received basic moisturizing skincare at least twice daily, and the affected skin areas were topically treated with 0.03% tacrolimus ointment (Zhejiang Wansheng Pharmaceutical Co., Ltd.; NMPA approval number: H20133243) twice daily. Additionally, all patients regularly applied hydrocortisone-17-butyrate (Tianjin Jinyao Pharmaceutical Co., Ltd.; NMPA approval number: H10940095) once in the morning and once at night to the affected skin areas one week after enrollment. A daily oral dose of 10 ml levocetirizine oral solution (Chongqing Huabang Pharmaceutical Co., Ltd.; NMPA approval number: H20061289) was administered before meals.

The study group received dupilumab in addition to the above treatment regimen. An initial subcutaneous injection of 400 mg was administered, followed by 200 mg subcutaneous injections every two weeks (q2w) until a minimum treatment period of 16 weeks. Injection sites were rotated, and precautions were observed to avoid injection into areas of thin or compromised skin, as well as areas with bruising or scarring.

Outcome Measures

Clinical efficacy assessment

Clinical efficacy was assessed using the Scoring Atopic Dermatitis (SCORAD) index[11]. SCORAD includes three aspects: extent of skin lesions, severity of skin lesions, and intensity of pruritus. The score ranges from 0 to 103 points. Clinical efficacy was assessed by calculating the percentage reduction in SCORAD score [(post-treatment score – pre-treatment score) / pre-treatment score]. Marked effectiveness was defined as symptom disappearance with a reduction rate of 60-90% in the SCORAD score, effec-

tiveness was defined as symptom mitigated with a reduction rate of 20-59%, and ineffectiveness was defined as symptoms unchanged or worsened with a reduction rate < 20%. The total effective rate was calculated as (marked of effective cases + effective cases) / total number of cases × 100%.

Serological indicators

Peripheral blood eosinophil count (EOS) and total serum IgE (T-IgE) levels were measured in all patients after enrollment and at 16 weeks of treatment using an automatic hematology analyzer.

Symptom and sign assessment

Patients' symptoms were evaluated using the Patient-oriented Eczema Measure (POEM)[12]. POEM comprehensively assesses the severity of seven symptoms experienced by patients over the past week. The maximum score of POEM is 28 points, with higher scores indicating more severe clinical symptoms. The severity of signs was assessed using the Eczema Area and Severity Index (EASI)[13]. EASI is a comprehensive score based on the range and severity of AD skin lesions at each anatomical site, including erythema, edema/papulation, excoriation, and lichenification. The score ranges from 0 to 72 points, with higher scores indicating more severe disease. The EASI index was calculated as follows: EASI score = 20% of the affected area on the upper limbs (erythema + edema/papulation + excoriation + lichenification) + 40% of the affected area on the lower limbs + 30% of the affected area on the trunk + 10% of the affected area on the head/neck.

Severity score

The Verified Investigator's Global Assessment (v-IGA)[14] was used to evaluate the severity of patients' conditions. v-IGA is a physician's subjective rating. At each time point, the number of patients (cases) and their percentage (%) who had an IGA score of 0/1 (IGA score of 0 or 1) were recorded. The IGA score uses a 5-point scale, with physicians evaluating the patient's symptoms, signs, severity, and impact on their daily work and life. An IGA score of 0 indicates no signs of atopic dermatitis (no erythema, no edema/papulation, no lichenification, no exudation/crusting), with the possibility of post-inflammatory pigment deposition and/or hypopigmentation. A score of 1 indicates almost imperceptible erythema, almost imperceptible edema/papulation, and/or very mild lichenification, without exudation or crust. A score of 2 indicates mild but noticeable erythema (pink), slight but noticeable edema/papulation, and/or slight but noticeable lichenification, without exudation or crust. A score of 3 indicates moderate and obvious erythema (dark or bright red), obvious edema/papulation, and/or obvious lichenification, with possible exudation and crusting. A score of 4 indicates marked erythema (deep or bright red), marked edema/papulation, and/or marked lichenification, with widely present lesions and possible exudation or crusting.

Itch severity assessment

The Numeric Rating Scale (NRS) was employed to evaluate the severity of itching in patients. NRS is a patient-reported assessment of the most severe itching experienced over the past 24 hours, with 0 indicating no itching and 10 indicating the most severe itching.

Quality of life assessment

The Dermatology Life Quality Index (DLQI)[15] was adopted to assess patients' quality of life. DLQI measures the impact of skin lesions on patients' quality of life over the past week and is reported by the patients themselves. DLQI scores range from 0 to 30 points, with higher scores indicating a more compromised quality of life.

Safety and long-term follow-up

The incidence of various adverse reactions, such as conjunctivitis, injection site reactions, upper respiratory tract infections, herpes, and erythema, was recorded and calculated during the treatment.

Statistical Analysis

Data were entered and statistically analyzed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). Count data were expressed as rates (%), and measurement data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data were expressed as means ± standard deviations and analyzed using paired *t*-tests. Kaplan-Meier survival curves were employed to evaluate patient relapse-free survival. $p < 0.05$ suggested statistical significance.

Results

Baseline Patient Profiles

In the control group, there were 48 male and 36 female patients, with an average age of 8.23

Table I. Clinical baseline features.

	Control group	Study group	t/χ^2	p
N	84	84		
Gender (male/female)			0.221	0.638
Male	48	51		
Female	36	33		
Age (mean ± SD, y)	8.23 ± 1.61	7.96 ± 1.85	1.009	0.314
Disease duration (mean ± SD, y)	3.11 ± 0.85	2.96 ± 0.72	1.234	0.219
Weight (mean ± SD, kg)	44.05 ± 9.40	46.36 ± 8.91	1.635	0.104
Complicated with allergic diseases			0.720	0.396
Yes	62	57		
No	22	27		

± 1.61 years, a disease duration of 3.11 ± 0.85 years, a body weight of 44.05 ± 9.40 kg, and 62 cases with accompanying allergic diseases. In the study group, there were 51 male and 33 female patients, with an average age of 7.96 ± 1.85 years, a disease duration of 2.96 ± 0.72 years, a body weight of 46.36 ± 8.91 kg, and 57 cases with accompanying allergic diseases. The two groups were well-balanced in terms of baseline features ($p > 0.05$) (Table I).

Clinical Efficacy

In the control group, 12 cases showed marked effectiveness, 53 cases were effective, and 19 cases were ineffective, resulting in a total effectiveness rate of 77.38% (65/84). In the study group, 25 cases showed marked effectiveness, 52 cases were effective, and 7 cases were ineffective, resulting in a total effectiveness rate of 91.67% (77/84). The use of dupilumab significantly increased the total effective rate for the patients by 14.29% ($p < 0.05$, Table II).

Serum Markers

Following treatment, patients given dupilumab showed a more significantly decreased peripheral blood EOS and IgE levels than those without dupilumab treatment ($p < 0.05$) (Figure 1).

Table II. Clinical efficiency (n).

	N	Significantly effective	Effective	Ineffective	Total effective rate
Control group	84	12	53	19	65 (77.38%)
Study group	84	25	52	7	77 (91.67%)
χ^2					6.553
p					0.011

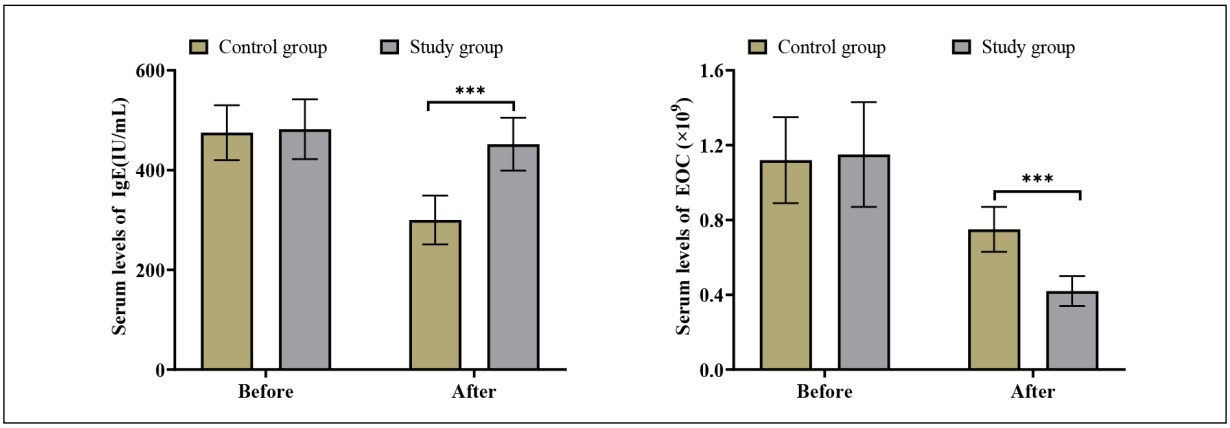

Figure 1. Serum levels of EOS and T-IgE. ***Indicated $p < 0.001$.

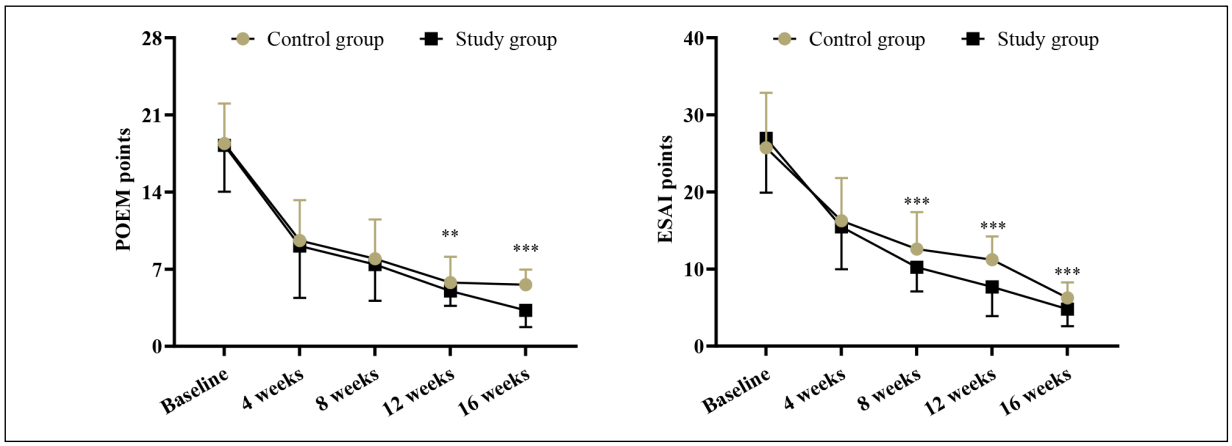

Figure 2. POEM and ESAI points. **Indicated $p < 0.01$, ***Indicated $p < 0.001$.

Symptom and Sign Assessment

As the treatment duration extended, both groups of patients showed a significant decrease in POEM and EASI scores. Patients administered with dupilumab exhibited markedly lower scores on the POEM at weeks 12 and 16 and lower EASI scores at weeks 8, 12, and 16 when compared to those patients without dupilumab therapy (all $p < 0.05$) (Figure 2).

Severity Assessment

At the 16-week mark, 37 patients in the study group achieved a score of 1/0 on the v-IGA scale, whereas the control group had 24 such cases, indicating a significantly higher response rate provided by the protocol incorporating dupilumab ($p < 0.05$) (Figure 3).

Severity of Itching and Quality of Life

After 16 weeks of treatment, both groups showed a significant reduction in itch NRS scores and DLQI scores, with lower scores observed in the study group *vs.* the control group ($p < 0.001$) (Figure 4).

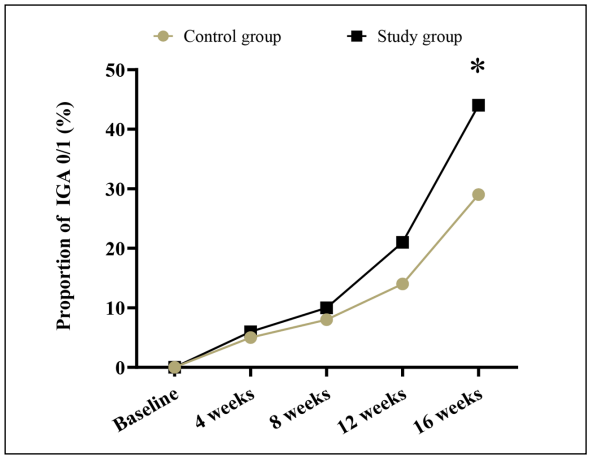

Figure 3. Proportion IGA 0/1. *Indicated $p < 0.05$.

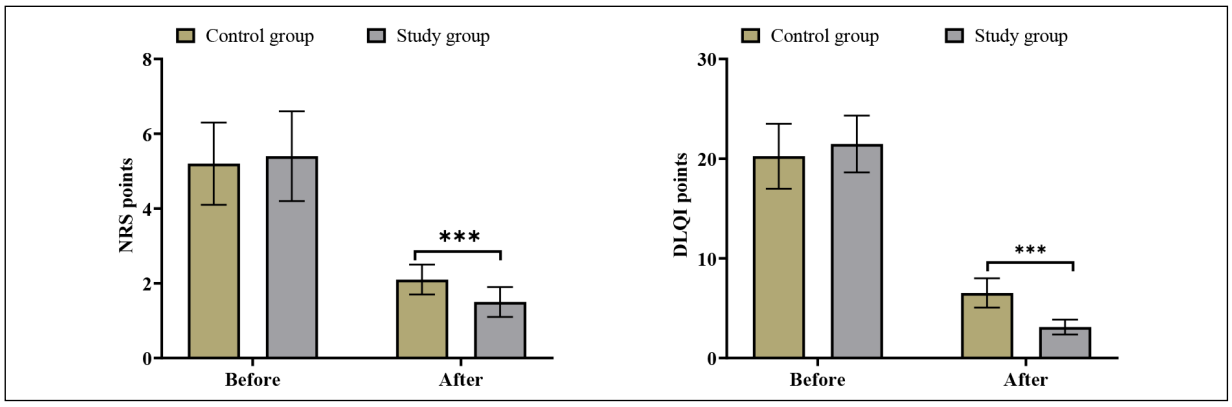

Figure 4. NRS and DLQI points. ***Indicated $p < 0.001$.

Adverse Events

Among the 168 patients in this study, a total of 28 patients experienced varying degrees of adverse reactions during the treatment process. Among them, there were 11 cases in the control group and 17 cases in the study group. The absence of a significant difference ($p > 0.05$) in the incidence of adverse reactions between the two groups suggested a high safety profile of dupilumab. Furthermore, all adverse reactions were mild, and they resolved spontaneously without the need to discontinue the treatment in any patient (Table III).

Discussion

AD is the most prevalent chronic inflammatory skin disease globally, with a higher prevalence (over 20%) in children than in other population groups[16]. The severity and incidence of AD vary with age, gender, socioeconomic characteristics, geographical location, and race. The age range of 6 to 12 years is the school-age period when children begin school and establish early social relationships. This period is crucial for psychological and social development. Affliction with AD and the accompanying itching, sleep disturbances, and attention difficulties may result in significantly compromised psychological health and quality of life of the affected children[17].

This study investigated the effectiveness of dupilumab in children aged 6 to 12 years with moderate to severe AD, and the results showed favorable efficacy of dupilumab treatment for 16 weeks in these patients. In this study, combined therapy of dupilumab, corticosteroids, and calcineurin inhibitors was adopted. Topical corticosteroids remain the main anti-inflammatory treatment for AD, and medium-potency topical corticosteroids such as 0.25% fluticasone propionate and 0.1% mometasone furoate are commonly used in older children, adolescents, and adults. Moreover, corticosteroids should only be used for a short duration under medical supervision. Previous studies[18] have shown that proactive corticosteroid treatment, defined as the use of topical anti-inflammatory agents on the recurrently susceptible areas twice weekly for a long-term maintenance interval after visible lesions have healed, can reduce the risk of relapse and the need for corticosteroids, without increasing the risk of skin atrophy and other side effects. Calcineurin inhibitors such as tacrolimus are commonly used anti-inflammatory drugs for the management of AD. These medications possess favorable skin penetration while exhibiting minimal systemic absorption, rendering them suitable for long-term usage with fewer adverse reactions and without causing skin atrophy[19]. Additionally, tacrolimus can promote the synthesis of skin collagen, restore the skin barrier function, and thus, play a therapeutic role in atopic dermatitis. It can also inhibit the expression and release of inflammatory mediators and various cytokines, exerting a strong inhibitory effect on skin infections[20]. Dupilumab targets the IL-4 receptor α subunit, which can bind specifically to IL-4 and IL-13, thereby inhibiting their signaling pathways[8]. Dupilumab is currently the only biological therapy approved for the management of moderate to severe AD in children aged 6 years and older and has been shown[21] to be effective and safe in severe AD children with inadequate local control.

In the present study, the study group showed markedly lower levels of EOS and T-IgE than the control group after 16 weeks of treatment. This suggested that dupilumab treatment might decrease the serum T-IgE levels, mainly due to the blockade of type II inflammatory cytokines IL-4 and IL-13, which are usually involved in the induction of IgE production[22]. EOS and T-IgE are key clinical indicators of type II inflammation, and the results indicated that the combined treatment of dupilumab and topical tacrolimus might enhance the immune response and alleviate inflammatory reactions in patients with atopic der-

Table III. Adverse reactions (n).

	N	Conjunctivitis	Respiratory tract infections	Herpes and erythema	Injection site reactions	Others	Total adverse reactions
Control group	84	4	0	3	2	2	11
Study group	84	6	3	2	2	4	17
χ^2							1.543
p							0.214

matitis. Furthermore, it has been reported[23] that dupilumab significantly reduces the IgE concentrations of specific food allergens such as milk, egg, and peanut, as well as aeroallergens. In the current research study, various relevant indicators related to AD symptoms, signs, and quality of life, such as POEM, ESAI, v-IGA, NRS, and DLQI, were evaluated, and the patients receiving dupilumab achieved better treatment outcomes than those without dupilumab treatment. The findings of the current study were similar to previous findings[24,25]. During the treatment, 20.23% of patients in the study group reported treatment-related adverse events, with conjunctivitis and injection site reactions being the most common. All observed adverse reactions were mild and self-resolving, indicating good short-term safety of dupilumab in children. Nevertheless, further large-scale clinical trials are required to explore the duration of medication, tapering and cessation timing, and current and potential adverse reactions.

Conclusions

The combination of dupilumab with topical tacrolimus demonstrates favorable efficacy in the management of AD in children aged 6 to 12 years. This treatment protocol effectively alleviates symptoms, enhances the quality of life of patients, and shows no increased risk of adverse reactions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

Jinguang Chen and Shuangshuang Gao conceived the structure of manuscript. Meng Chen did the experiments and made the figures. Rui Wang reviewed and edited the manuscript. All authors read and approved the final manuscript.

ORCID ID

Chen Jinguang: 0009-0008-2915-5387.

Funding

Research Project of Taizhou Federation of Social Sciences (22YB14); Hospital level project of Taizhou Central Hospital (22YB14).

Availability of Data and Materials

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

Ethics Approval

This study was conducted in accordance with the ethical regulations of the Declaration of Helsinki. The study was admitted to the Ethics Committee of the Taizhou Central Hospital. The number of the Ethics Committee acceptance is: 2023L-0709.

Informed Consent

Not applicable.

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