

Research Article

Clinical Response Predictive Model for Omalizumab in Moderate-to-Severe Asthma Patients

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Objective. Our study aimed to develop a predictive model for evaluating the clinical response of omalizumab treatment in moderate-to-severe asthma patients. **Methods.** This single-center, prospective study collected patients who meet the diagnostic criteria for moderate-to-severe bronchial asthma set by the National Asthma Prevention and Treatment Group in 2016 in the first hospital affiliated with Soochow University. Patients recruited were treated with omalizumab once per four weeks; at the beginning of each injection, blood eosinophils and the level of total serum IgE (IU/mL) were tested. After four injections of omalizumab, asthma control test (ACT), the 15-item Mini Asthma Quality of Life Questionnaire (MiniAQLQ), global treatment effectiveness (GETE), and lung function of all patients were evaluated in the 16th week. We used the selection operator method to build a logistic model and evaluated the clinical response of omalizumab in these patients. **Results.** This study included 108 moderate-to-severe patients (aged 39.86 ± 14.59 years). Eighty-nine patients finished treatment for 16 weeks, and 74 patients (83.1%) had an excellent or good response. The serum level of total IgE increased significantly after injection of omalizumab, while blood eosinophils count decreased significantly from baseline. Using the GETE as a clinical outcome, several clinical variables were significant predictors of clinical response. The corrected AUC and Brier scores were 0.872 and 0.111, which showed good discrimination. Significant variables included age, weight, family allergic history, acute exacerbations, the ratio of total serum IgE level at the 4th week to the baseline level, forced expiratory volume in one second/forced vital capacity (FEV1/FVC), and commodities of rhinitis. Using the improvement in maximal expiratory flow 25% of the measured value to the predicted value (MEF25%pre) as clinical outcome, the significant variables included weight, duration of asthma, use of oral corticosteroids (OCS), total serum IgE level at the 4th week, and history of rhinitis. Its corrected AUC and Brier scores were 0.674 and 0.225 after internal validation. **Conclusion.** Omalizumab treatment remarkably improved asthma control and pulmonary function in Chinese patients with moderate-to-severe asthma. The response prediction model we developed provides convenient approaches to help identify better clinical response patients to omalizumab treatment.

1. Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and causes symptoms of wheezing, shortness of breath, chest tightness, and cough. The immunoglobulin E (IgE) bound to the surface of mast cells or basophils plays an important role in the Th2 pathway leading to airway allergic responses. The binding of allergens to IgE

triggers cross-linking and aggregation of IgE receptors, which in turn promotes the release of histamine, tryptase, prostaglandins, leukotrienes, and cytokines [1].

Omalizumab is a humanized monoclonal antibody designed to treat IgE-mediated disease by inhibiting the binding of IgE to high-affinity receptors on proinflammatory cells. It was applied as add-on therapy to patients previously accepted inhaled corticosteroids (ICS) and long-acting β_2 -

adrenaline receptor agonist (LABA) treatment while still inadequately controlled and has been widely recommended by guidelines [2]. It was shown that omalizumab significantly reduced the annualized rate of severe exacerbations [3]. Recent studies showed that global evaluation of treatment effectiveness (GETE) was good/excellent in 77% of patients at 16 weeks. The mean improvement in forced expiratory volume in 1 second (FEV1) was 160 mL at 16 weeks. However, physicians agreed that not all patients respond to omalizumab significantly and its cost is still high. Some patients may also experience a relapse of symptoms after withdrawal of the drug. Many efforts have been tried to find predictors to estimate which people should be prioritized for omalizumab treatment, but ended with conflicting results. Studies showed that omalizumab responders had significantly younger age in the adult subgroup, higher pretreatment total serum IgE level, percent predicted FEV1, and fractional exhaled nitric oxide (FeNO) than non-responders [4]. Other studies indicated responsiveness of omalizumab is not associated with pretreatment clinical biomarkers, including FeNO, serum total IgE, FEV1, and blood eosinophils [5]. So far there is no consensus opinion. Therefore, individualized precision treatment using clinical variable parameters must be developed. The treatment of patients with asthma should be “tailored to patient’s” clinical or biochemical characteristics, based on predictors of response to treatment.

The GETE score is one of the commonly applied tools to evaluate the efficacy of biologically targeted therapies for asthma in numerous studies. In addition to the GETE score, various studies have assessed treatment response using criteria such as a 40–50% reduction in asthma attacks, a 3-point increase or more than a 20-point improvement in the asthma control test (ACT), or a 120 ml or greater increase in spirometric FEV1. Therefore, we have also included the improvement of small airway function as another predictive outcome. These studies yielded divergent outcomes, particularly regarding the impact of type 2 inflammation, characterized by elevated fractional exhaled nitric oxide (FeNO) and eosinophil levels, on treatment efficacy [6]. The STELLAIR study, a real-world investigation, found comparable efficacy in patients with high ($\geq 300/\mu\text{L}$) and low ($< 300/\mu\text{L}$) eosinophil counts when using the GETE scale, a 40% reduction in attacks, and both measures combined [7]. In contrast, the recent PROSPERO study evaluated the treatment response based on a 50% reduction in attacks, ACT improvement, and FEV1 enhancement, revealing that patients with elevated baseline eosinophil levels were more likely to respond only to ACT improvements [8]. However, a post hoc analysis of the INNOVATE study observed no decrease in attacks following omalizumab treatment if the serum total IgE level was 75 IU/mL and the peripheral eosinophil count was 150/ μL [9]. The EXTRA study, which featured a higher attack frequency in the placebo group, was re-examined and showed no significant differences in exacerbation frequency between high- and low-biomarker subgroups treated with omalizumab [10].

So in this context, we built an observational study monitoring the change of total serum IgE and eosinophils during omalizumab treatment every 4 weeks. A score system for predicting response was constructed. The improvement in lung function after omalizumab injection was also evaluated.

2. Methods

2.1. Study Population. This is a prospective study to evaluate the intervention of omalizumab treatment. We recruited outpatients who had moderate-to-severe persistent allergic asthma from April 2020 to December 2021 at the First Affiliated Hospital of Soochow University. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) [2]. The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for moderate-to-severe bronchial asthma established by the GINA, and the duration after the first diagnosis was more than 3 months. (2) Patients with moderate-to-severe allergic asthma whose treatment is not effectively controlled after treated with inhaled corticosteroids (ICS) and long-acting β_2 -adrenaline receptor agonist (LABA). (3) Patients who voluntarily sign our informed consent. The exclusion criteria were as follows: (1) patients aged less than 6 years. (2) Patients with acute exacerbation within the past 4 weeks and the possibility of pregnancy. (3) The patient has contraindications listed in the locally approved instructions. (4) Patients who are allergic to the active ingredient of the vaccine or to any dressing. (5) Patients who are combined with other respiratory diseases, such as allergic bronchopulmonary aspergillosis, hypersensitivity pneumonia, pulmonary malignancy, pulmonary, bronchiectasis, tuberculosis, idiopathic pulmonary interstitial fibrosis, and pulmonary sarcoidosis. In addition, inhalation technique and compliance were checked.

After identifying eligible patients, we collected baseline parameters, including their demographic information, course of asthma, family history, medical history, and comorbidities. Then, omalizumab was injected into 108 patients, dosage and dosing intervals were based on weight and the baseline level of total serum IgE (IU/mL) as described in the prescribing information [11]. Some patients with high IgE levels requested to adjust the interval to 4 weeks due to inconvenient medical visits, and the patient group receiving omalizumab treatment every 2 weeks was excluded from the study. Patients received the first injection of omalizumab and were told to come for the second injection 4 weeks later. At each beginning injection of omalizumab, participants were arranged with laboratory tests including blood eosinophils (EOS) count and level of total serum IgE examination (IU/mL). 16 weeks later, at the beginning of the fifth injection, patients underwent a lung function test by a professional technician and were issued an official clinical lung function report. Data including FEV1, FEV1 percentage of predicted (FEV1%pre), forced vital capacity (FVC), peak expiratory flow (PEF), maximal expiratory flow after 75% of FVC has not been exhaled (MEF75%), maximal mid-expiratory flow (MMEF 75/25), and their percentages of predicted were collected. Fractional

exhaled nitric oxide (FeNO) was also evaluated. Physician-assessed evaluation of global treatment effectiveness (GETE: excellent, good, moderate, poor, and worsened) and evaluation of asthma control with the asthma control test (ACT) and the 15-item Mini Asthma Quality of Life Questionnaire (MiniAQLQ) are also collected. A flow diagram illustrating patient selection and grouping is shown in Figure 1. This study was approved by the research ethics committee of the First Affiliated Hospital at Soochow University (No. 2019118).

2.2. Clinical Prognostic Clinical Predictive Model. Clinical prognostic clinical predictive modelling refers to the use of mathematical and statistical methods to construct an idealized mathematical model that describes the association between a set of clinical characteristics and outcomes based on a large number of observed patients and their final outcomes. Nomograms have been found to be a reliable tool for creating simple and intuitive graphs for statistical prediction models. Mathematical prediction models take into account all the information about the patient and quantify this information so as to predict the probability of the outcome occurring through a set of readable combinations of variables, independent of the clinician's individual subjective clinical experience, with a more precise and reproducible assessment. The specific steps of predictive model building are as follows: identification of the clinical problem and predictive model type, data collection and data processing, variable screening and model construction, assessment of model performance, model testing, and model presentation and reporting.

2.3. Outcomes. Our outcome was responders to omalizumab, who were rated as good or excellent by GETE after 16 weeks of treatment. MEF25%pre is traditionally considered to reflect the function of small airways. All pulmonary function tests were conducted according to ATS/ERS (American Thoracic Society/European Respiratory Society) criteria [12].

2.4. Variables' Selection and Construction of Nomograms. We developed the risk-prediction model for the possibility of response and airflow function improvement after omalizumab treatment following the transparent reporting of a multivariable-prediction model for Individual Prognosis or Diagnosis guidelines [13]. The median value for the duration of asthma and baseline blood eosinophils was used to provide an approximately similar distribution of data across subgroups. The restricted cubic spline was used to flexibly model and verify the linear relationship between continuous variable and outcome. Multiple imputations with chained equations were used to replace missing values with the "mice" package. In the imputation model, we included all predictor variables, along with characteristics and laboratory results, and the outcome indicator. The LASSO (least absolute shrinkage and selection operator) technique entails applying a penalty to the absolute

magnitude of the coefficients in a regression model, which is determined by a tuning parameter, denoted as λ [14]. The larger the applied penalty, the more the estimates decrease toward zero. Therefore, the coefficients of irrelevant variables are zero, which can exclude noninfluential predictors from the final model, thereby improving predictive performance.

The model was developed based on the selected features and refitted to avoid model overfitting. A nomogram was then constructed by using a linear combination of the selected features weighted by their regression coefficients. "Points" indicates the score of the corresponding factor below and "Total Points" indicates the summation of all the scores of factors above. Both models were developed by this process [15].

The discriminative ability of the nomogram was evaluated using the area under the receiver operating characteristic curve (AUC). Furthermore, a calibration curve was plotted and the Brier score was calculated to evaluate the calibrating ability of the nomogram. When the Brier score was ≤ 0.25 , the model was considered to have favorable calibration. Internal validity and adjustment for overfitting of the nomogram were implemented with a bootstrap resampling (1000 times) analysis. The AUC and Brier score after adjustment were also calculated. The decision curve analysis (DCA) and clinical impact curve (CIC) were applied to evaluate the clinical value of the model.

2.5. Statistical Analysis. Continuous variables were expressed as mean standard deviation or median interquartile range, while categorical values were expressed using relative frequencies and proportions. Comparisons of parameters between 2 different groups were conducted with the *t*-test and the Mann-Whitney *U* test for continuous variables with or without normal distribution. Categorical variables were evaluated using the chi-square test or Fisher exact test. Data were analyzed using SPSS software (version 24.0) and R software (version 4.1.0). A *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline Clinical Characteristics of Patients and Response to Omalizumab Treatment. As the inclusion criteria, we treated 108 uncontrolled allergic asthma patients with omalizumab. 89 patients finished treatment for 16 weeks. 74 patients (83.1%) had an excellent or good response; 15 patients (16.9%) showed no response after 16 weeks of treatment. Patients, who have a family history of allergic diseases or aggravated more than 2 times during the last year or with rash, are more likely to be responders ($P < 0.01$, Table 1). After the first injection, 9 patients withdrew for economic reasons, 2 patients discontinued treatment due to adverse events, and 1 patient withdrew for pregnancy after the second injection. After the third injection, 3 patients withdrew for economic reasons, 3 patients withdrew considering no obvious effects, and 1 patient broke up for pneumonia treatment.

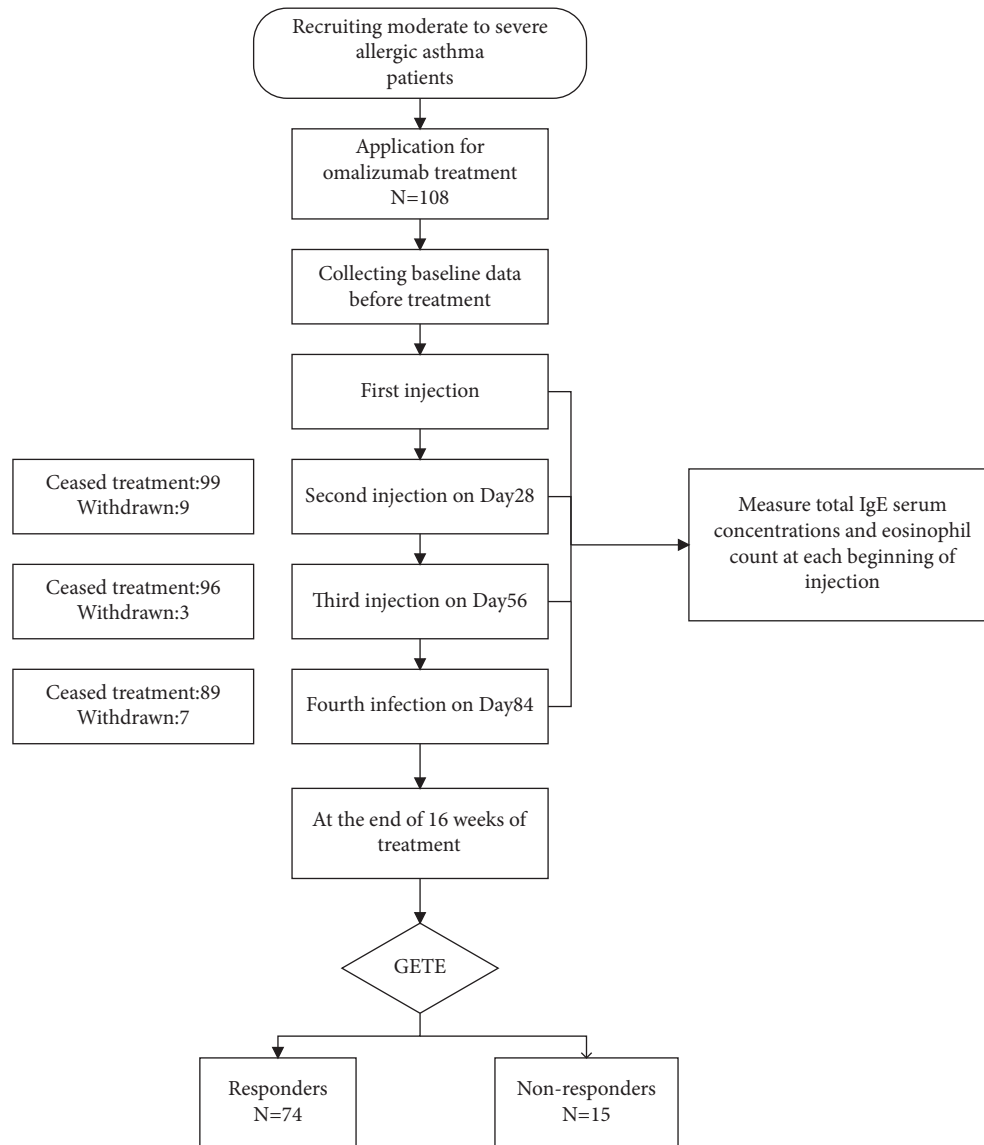


FIGURE 1: Flow diagram of participants in this study.

None of the severe adverse events appeared. Most adverse events reported were consistent with the omalizumab scientific leaflet. Seven patients showed local wheals around the injection site and 5 patients appeared with generalized rash. One patient showed transient drop in blood pressure. One patient showed hypertension. Two patients reported myalgia after injection.

Lung function parameters including FEV₁, FEV₁%pre, FEV₁/FVC, PEF%pre, MEF75%pre, MEF50%pre, MMEF%pre, and FeNO showed improvements after treatment with omalizumab (Table 2). The baseline ACT in responders was 18 (16.5, 19). The baseline MiniAQLQ score was 70.49 ± 10.39 . After 16 weeks of treatment, the average increase in ACT score was 4.31 and the average rise in MiniAQLQ score was 16.05 (both, $P < 0.01$). Figure 2 shows a quantitative distribution change of FEV₁ (Figure 2(a)), FeNO (Figure 2(b)), asthma control (Figure 2(c)), and life

quality score (Figure 2(d)) of all patients after 16 weeks. 19 patients used oral glucocorticoids regularly at baseline. After omalizumab treatment for 16 weeks, 5 patients' dosages have been gradually reduced and 6 patients abandon oral glucocorticoids gradually. Three patients reduced the dosage of ICS after omalizumab.

3.2. The Change of IgE Levels and Blood Eosinophils during the 16 Weeks of Treatment. Participants exhibited a significant increase in the total level of serum IgE at 4 weeks after the first omalizumab injection. The total level of serum IgE decreased since the 8th week gradually compared to the baseline level of serum IgE. The blood EOS count showed a significant decrease at 4 weeks after the first omalizumab injection and then increased slightly during the following treatment (Figure 3).

TABLE 1: Baseline characteristics of participants recruited in this study.

| Characteristics | N = 108 | Responders | Nonresponders | t/Z/ χ^2 | P value |
|--|------------------------|------------------------|--------------------|---------------|--------------|
| Age at visit 1 (years old) | 39.86 ± 14.59 | 40.27 ± 14.58 | 35.28 ± 13.58 | -1.326 | 0.188 |
| Male, n (%) | 61 (56.48%) | 47 (63.51%) | 8 (53.33%) | 1.352 | 0.245 |
| Weight (kg) | 68.34 ± 10.28 | 69.29 ± 10.44 | 64.22 ± 9.19 | 1.900 | 0.060 |
| Course of asthma (years) | 5 (2-10) | 5 (2-10) | 8.5 (5-14) | -1.382 | 0.167 |
| Family history of allergic diseases, n (%) | 58 (53.7%) | 47 (92.2%) | 4 (25.67%) | 8.168 | 0.004 |
| Ocs, n (%) | 19 (17.6%) | 15 (88.2%) | 2 (13.33%) | | 0.731 |
| Concomitant asthma medications, n (%) | 46 (42.6%) | 29 (74.4%) | 10 (66.67%) | 2.166 | 0.141 |
| No. of protocol-defined exacerbations during the past year | | | | 7.078 | 0.008 |
| <2 times | 54 (50.00%) | 33 (44.59%) | 12 (80.00%) | | |
| ≥2 times | 54 (50.00%) | 41 (55.41%) | 3 (20.00%) | | |
| HBP, n (%) | 18 (16.7%) | 12 (16.22%) | 1 (6.67%) | | 0.456 |
| DM, n (%) | 5 (4.6%) | 4 (5.41%) | 0 (0.00%) | | 1.000 |
| Rhinitis, n (%) | 101 (93.5%) | 71 (95.95%) | 13 (86.67%) | | 0.308 |
| Rash, n (%) | 37 (34.3%) | 23 (31.08%) | 9 (60.00%) | 4.081 | 0.043 |
| Omalizumab dose (mg) | | | | 2.251 | 0.530 |
| 150 | 22 (20.4%) | 11 (14.86%) | 4 (26.67%) | | |
| 300 | 37 (34.3%) | 31 (41.89%) | 3 (20.00%) | | |
| 450 | 29 (26.9%) | 21 (28.38%) | 4 (26.67%) | | |
| 600 | 20 (18.5%) | 11 (14.86%) | 4 (26.67%) | | |
| EOS | 0.24 (0.10-0.43) | 0.24 (0.10-0.44) | 0.24 (0.08-0.31) | | 0.385 |
| IgE | 260.98 (116.74-449.58) | 270.76 (140.47-432.64) | 250 (65.99-398.01) | | 0.517 |

HBP: high blood pressure; DM: diabetes mellitus. The bold values indicate that the differences observed are statistically significant ($p < 0.05$).

TABLE 2: Change in clinical values between baseline and 16 weeks for omalizumab treatment.

| | Baseline (n = 89) | After omalizumab treatment for 16 weeks (n = 89) | t/Z | P value |
|----------------|------------------------|--|--------|--------------|
| FEV1 | 2.78 ± 0.85 | 2.99 ± 0.85 | -4.29 | ≤0.001 |
| FEV1% | 86.65 ± 19.55 | 92.33 ± 17.77 | -4.68 | ≤0.001 |
| FEV1/FVC | 74.39 ± 13.16 | 77.34 ± 12.21 | -4.82 | ≤0.001 |
| FVC | 3.80 ± 0.98 | 3.89 ± 1.00 | 2.23 | 0.029 |
| PEF | 7.58 ± 2.49 | 7.85 ± 2.35 | 2.19 | 0.032 |
| PEF%pre | 95.68 ± 27.16 | 99.32 ± 24.61 | 2.25 | 0.027 |
| MEF 75%pre | 78.15 ± 35.95 | 83.44 ± 34.78 | 2.92 | 0.005 |
| MEF 50%pre | 62.84 ± 37.55 | 65.64 ± 36.26 | 1.89 | 0.062 |
| MEF 25%pre | 51.61 ± 37.49 | 53.78 ± 36.23 | 1.25 | 0.215 |
| MMEF 75/25%pre | 57.73 ± 35.43 | 60.72 ± 34.29 | 2.18 | 0.033 |
| FeNO | 34 (21–62.75) | 22 (17–37) | -5.86 | ≤0.001 |
| ACT | 18 (16.5–19) | 23 (21–23) | -7.98 | ≤0.001 |
| ACQ | 1.78 ± 0.58 | 0.94 ± 0.48 | -17.72 | ≤0.001 |
| MiniAQLQ | 70.58 ± 10.42 | 86.03 ± 7.34 | 13.94 | ≤0.001 |
| EOS | 0.21 (0.10–0.40) | 0.15 (0.09–0.27) | -4.11 | ≤0.001 |
| IgE | 271.85 (131.00–426.80) | 743.10 (405.85–1104.00) | -7.57 | ≤0.001 |

FEV1: forced expiratory volume in one second; FEV1%: FEV1 percentage of predicted; FVC: forced vital capacity; PEF: peak expiratory flow; PEF%pre: PEF percentage of predicted; MEF75%pre: maximal expiratory flow after 75% of FVC (MEF75) has not been exhaled percentage of predicted; MEF50%pre: maximal expiratory flow after 50% of FVC has not been exhaled (MEF50) percentage of predicted; MEF25%pre: maximal expiratory flow after 25% of FVC has not been exhaled (MEF25) percentage of predicted; MMEF 75/25%pre: maximal mid-expiratory flow (MMEF 75/25) percentages of predicted; FeNO: fractional exhaled nitric oxide; ACT: asthma control test; MiniAQLQ: the 15-item Mini Asthma Quality of Life Questionnaire. The bold values indicate that the differences observed are statistically significant ($p < 0.05$).

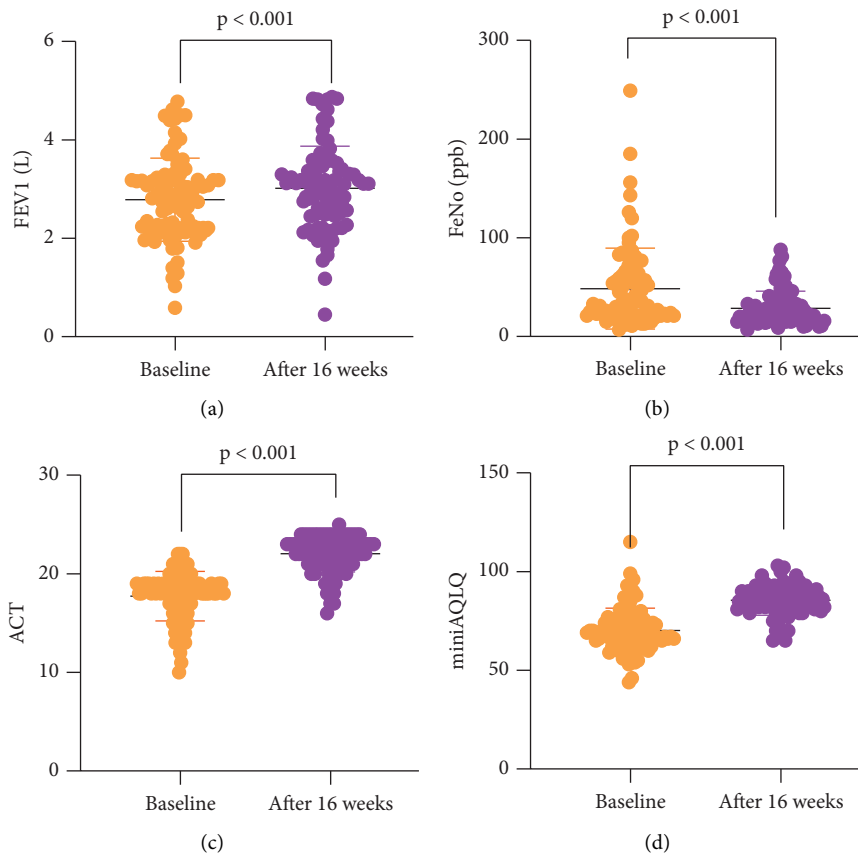


FIGURE 2: Quantitative distribution change of FEV1, FeNo, ACT scores, and MiniAQLQ scores before and after omalizumab treatment: (a) FEV1; (b) FeNo; (c) ACT scores; (d) MiniAQLQ scores.

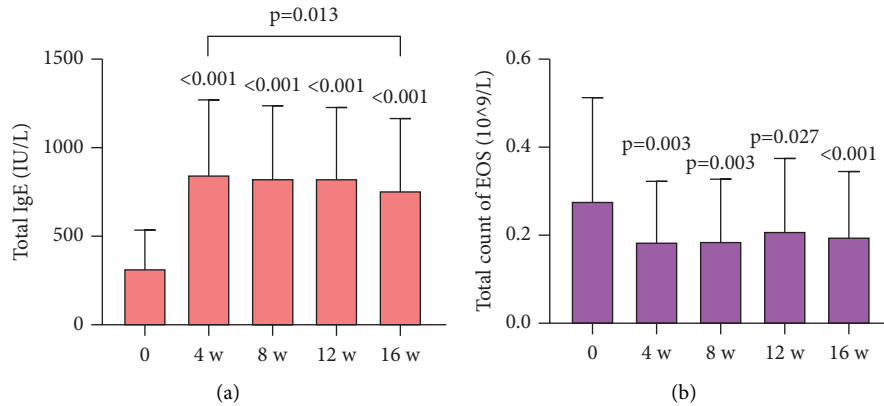


FIGURE 3: The change of total level of serum IgE and blood eosinophils counts from baseline to 4 weeks, 8 weeks, 12 weeks, and 16 weeks: (a) total level of serum IgE; (b) blood eosinophils counts.

3.3. Predictive Model for Clinical Response of Omalizumab Treatment. Incorporating all baseline characteristics as variables, the LASSO regression analysis was employed, and the optimal λ value was selected to filter out the significant predictors. It resulted in eight variables for building the prediction model. According to the multivariable analysis, the final formula was $\text{Logit}(P) = -7.249 + 0.125 * \text{age} + 0.091 * \text{weight} + 4.633 * \text{familyhistory} + 0.154 * \text{AE} - 0.094 * \text{FEV1\%FVC} + 4.826 * \text{rhinitis} - 3.815 * \text{rash} + 2.354 * \text{Ig}$ (4w IgE: baseline IgE). To estimate the likelihood of clinical response for the treatment of omalizumab, a nomogram was constructed using the results of the multivariate logistic analysis (Figure 4). The area under the curve (AUC) clinical scores were assigned to the 8 independent factors and the estimated risk of progression was calculated by summing the scores of each factor. The final score ranged from a minimum of zero points to a maximum of 400 points, where a straight line is drawn to determine the probability of a response. For example, a 40-year-old man with allergic asthma weighs 70 kg and had a family history of allergic diseases. He underwent twice protocol-defined exacerbations over the last year, combined with rhinitis but without rash. His baseline FEV1/FVC was 80% and total IgE was 180 IU/ml, while it increased to 523 IU/ml at week 4 after treatment. The total score was about 254, indicating that his risk of response was over 90%.

After the construction, the area under the curve of this model was 0.941 (Figure 5(a)). The model results were validated by generating a new dataset through 1000 iterations of bootstrap resampling from the test set, thereby correcting the overfitted model. Postbootstrapping, the model's stability was confirmed with an adjusted AUC of 0.872. The refined Brier score was recorded at 0.111, indicating a commendable level of accuracy, as it is below the threshold of 0.25. The calibration curve showed good agreement between the predictive and actual response of omalizumab treatment (Figure 5(b)). The decision curve analysis (DCA) utilized to evaluate the clinical utility of the nomogram is plotted in Figure 5(c). It showed that intervention of omalizumab in identified patients using the predictive model could lead to better outcomes than

alternative strategies. To evaluate the clinical effects of the nomogram model more visually, the clinical impact curve (CIC) on the ground of the DCA curve was drawn. The "number high risk" curve fits very close to the "number high risk with event" curve. It indicated that the nomogram model owns extraordinary predictive power (Figure 5(d)).

3.4. Predictive Model for the Improvement of Small Airway Function. Increase of MEF25%pre after 16 weeks treatment of omalizumab reflected the improvement of small airway function. 50 imputations were carried out to replace missing values considering the proportion of missing data and errors in databases after imputation. The LASSO regression analysis was used to select predictors and the final formula was $\text{Logit}(P) = 3.966 - 0.023 * \text{weight} + 0.704 * \text{duration of asthma} + 0.601 * \text{ocs usage} - 0.005 * \text{Week4 IgE} - 2.232 * \text{rhinitis}$. A score-based nomogram was constructed to visually estimate the possibility for asthma patients to achieve lung function benefit from omalizumab (Figure 6).

The stability of the model was verified after 1000 bootstrapping and the overfitting corrected AUC was 0.674 (95% CI: 0.660–0.691, Figure 7(a)). Brier score after correction was 0.225, close to 0.25, which represented normal calibration. The calibration curve revealed normal predictive accuracy between the actual probability and predicted probability (Figure 7(b)). The DCA curve and CIC curve were also drawn to evaluate the clinical benefit (Figures 7(c) and 7(d)). It indicated that the nomogram had a good clinical value.

4. Discussion

Our study further verifies the improvement in lung function, asthma control, and quality of life after treated with omalizumab, which is the same as some previously reported studies [16]. This is the first study that develops a nomogram to identify patients more likely to respond to omalizumab. Our study revealed that patients with increased age, weight, higher ratio of total serum IgE over baseline, and more exacerbations before may have higher possibility to respond.

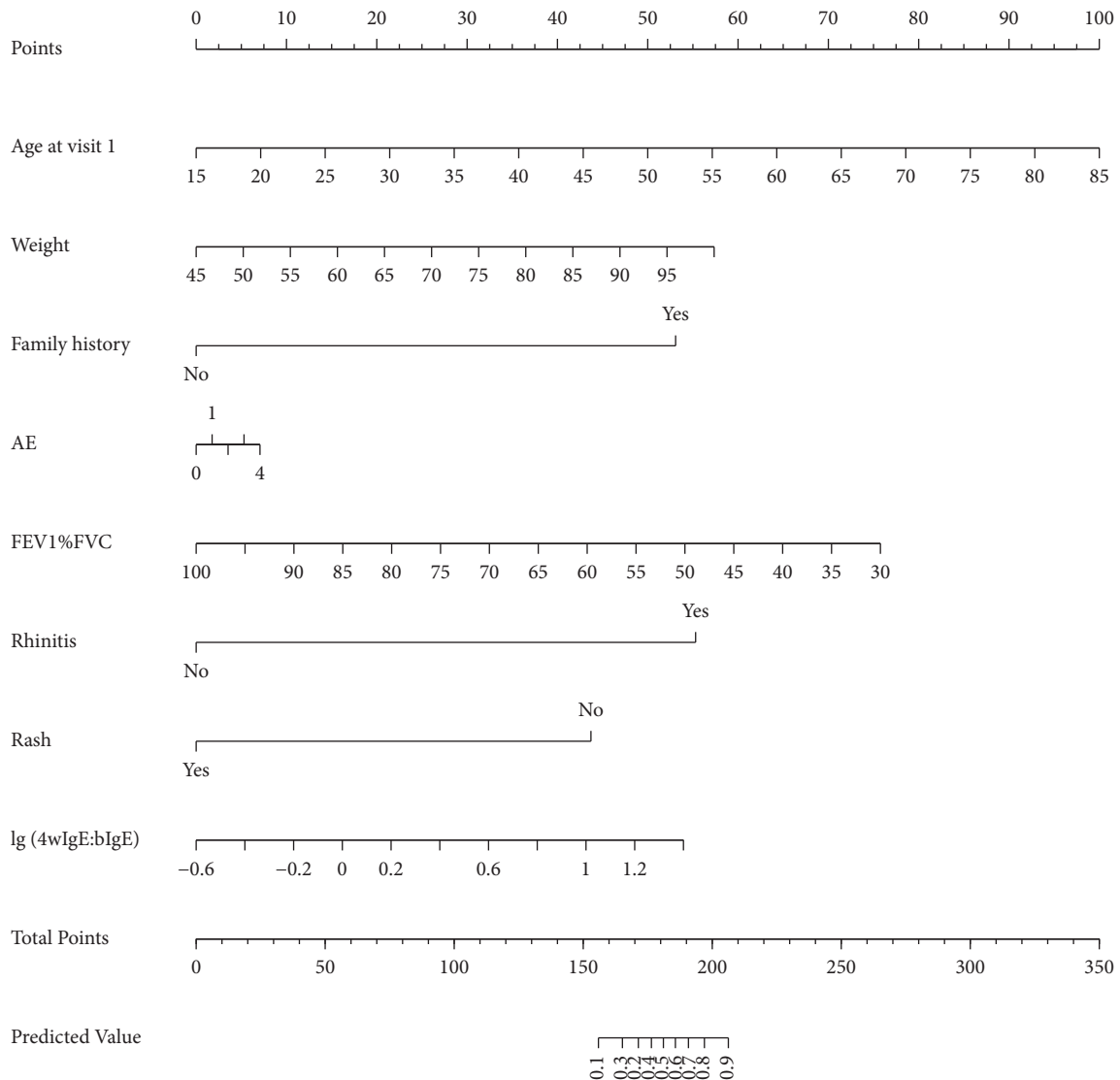


FIGURE 4: Nomogram predictive model for clinical response of omalizumab to moderate-to-severe asthma. Values for each variable are individually plotted and correspond to point values assigned from the point scale (top). These point values are then totaled and plotted on the total point scale (bottom), which is used to assign a corresponding value for prediction. (AE: protocol-defined exacerbations during the past year; FEV1%FVC: FEV1 percentage of forced vital capacity; 4wIgE: bIgE: the week 4: baseline IgE ratio).

Furthermore, we demonstrated that patients with a longer duration of asthma and taking OCS regularly were more likely to benefit from small airway function after 16 weeks of treatment. This model could help make appropriate interruption at an early stage of moderate-to-severe asthma patients.

Reduction in OCS/ICS doses during 16 weeks was observed after omalizumab injection. Our participants had moderate-to-severe and symptomatic asthma, with a history of at least 3 months suffering from asthma. Most participants had poor symptom control, marked impairment of quality of life, and a high prevalence of allergic comorbidities. After 16 weeks of treatment, the overall response rate to omalizumab was high at 83.1%, which is similar to the previous results of 77% as reported by a meta-analysis [3]. A significant improvement in lung function, asthma control, and

quality of life from baseline was observed, which was consistent with previously reported studies [17–19]. And there was a significant lowering of OCS/ICS dose at 4 months, and these results are in line with the eXpeRIence registry [20].

Total serum IgE increased significantly after the first injection of omalizumab and will decrease gradually later, while eosinophils decreased gradually after injection. The mechanism underlying the phenomenon may include that the build-up of the omalizumab-IgE complex has a slower clearance compared with free IgE. The current clinical technique is unable to differentiate between omalizumab-IgE complexes and free IgE after the application of omalizumab under the current clinical technician [21]. This could be the underlying mechanism of the decreased serum IgE level at the later stage after using omalizumab. Furthermore,

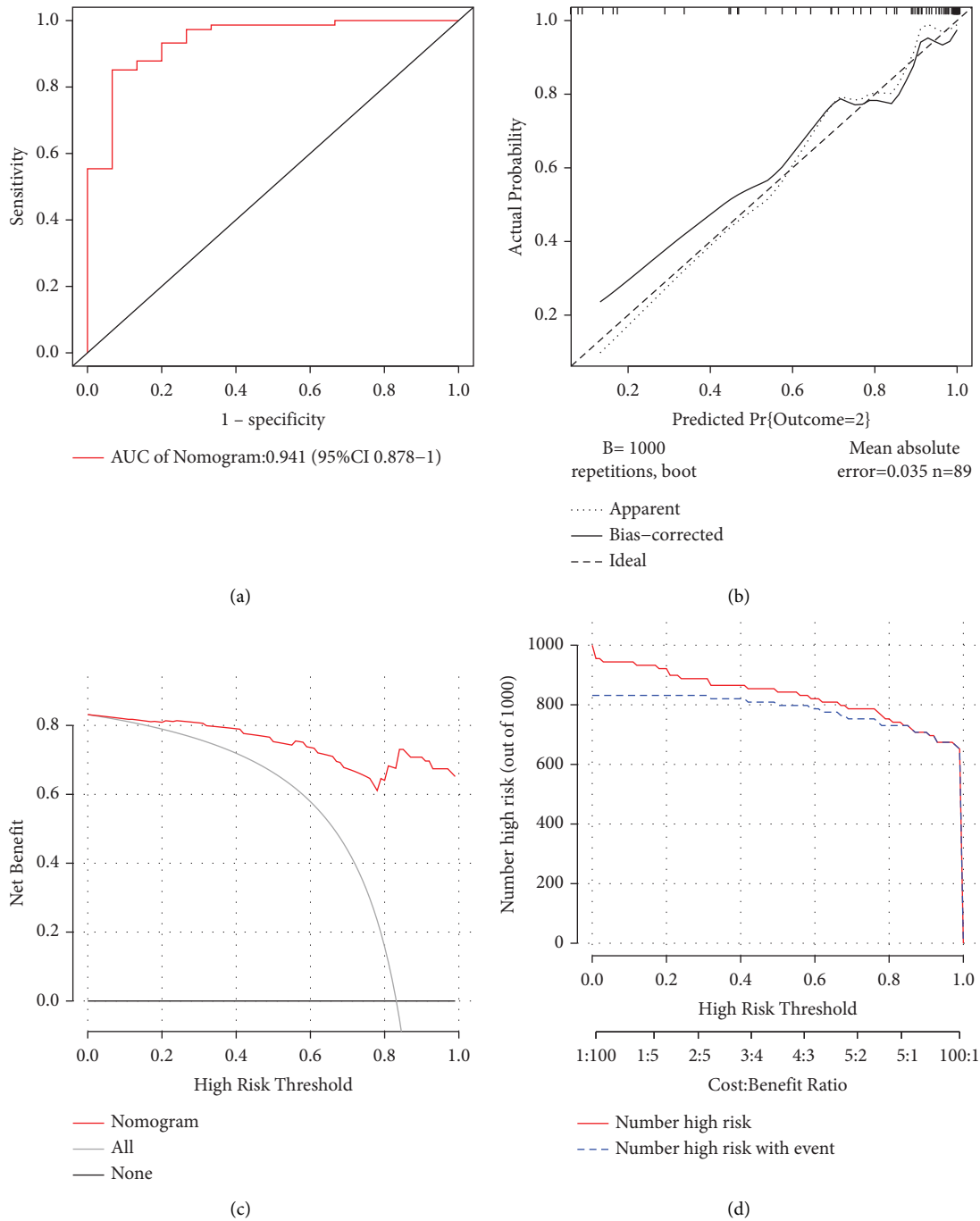


FIGURE 5: Effectiveness evaluation of nomogram predictive model: (a) ROC curve; (b) calibration plot; (c) decision curve analysis; (d) clinical impact curve.

the antidrug antibody response, off-target binding, and glycosylation pattern can inhibit the binding of omalizumab and IgE [22]. Li et al. measured total and free IgE levels separately and proved that all patients who were treated with omalizumab achieved free IgE levels below 50 ng/mL 7 days later, while the total IgE kept remarkably higher than baseline [23]. Meanwhile, a pooled analysis demonstrated that the reduction of serum-free IgE by omalizumab is associated with a reduction in peripheral eosinophil counts in patients [24].

In our study, we proved that eosinophil counts significantly decreased in the 4th week after omalizumab injection. In the pooled analysis of 5 studies, circulating eosinophils were reduced by a median of 18.8% in the group of omalizumab intervention, and the reduction was maintained independent of the reduction in glucocorticoids dose [24, 25]. Decreased eosinophils were observed to be related to improved clinical outcomes [24]. A slight increase in the 12th week was observed, which is probably due to the short-term response caused by glucocorticoids reduction or allergens' exposure.

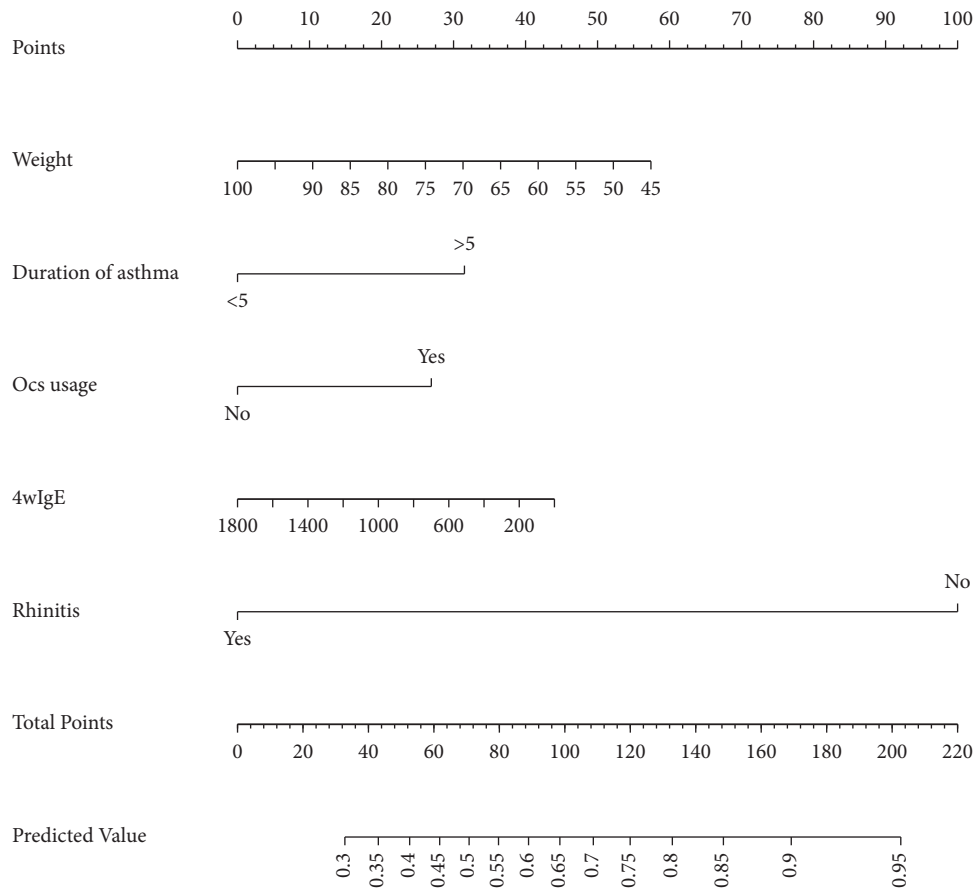


FIGURE 6: Nomogram predictive model for the improvement of small airway function.

Predicting response to omalizumab in patients with uncontrolled asthma is of great clinical relevance. Stopping therapy early in nonresponders will minimize unwarranted drug exposure and healthcare expenditure. Our study developed and validated the nomogram predictive model of clinical response. GETE is widely used for evaluating the response to omalizumab [26, 27]. Our results showed that elder and heavier patients with worse lung function, more frequent exacerbations, family allergic history, or rhinitis are more likely to respond to omalizumab treatment. In addition, the nomogram also pointed out the ratio of total serum IgE in 4th week over baseline to be a predictive factor of response. Previous studies reported age and allergic medical history to be predictors of omalizumab treatment response [28]. The nomogram's reference to rhinitis pertains to individuals suffering from concurrent chronic rhinitis or nasal polyps. Omalizumab demonstrates efficacy not only in the management of allergic asthma but also exerts a modulating influence on sinusitis when it is associated with asthma. This medication enhances nasal symptomatology and overall quality of life in individuals with chronic sinusitis that is recurrent and accompanied by nasal polyps (CRSwNP), diminishes the size of nasal polyps, and lessens the count of eosinophils in peripheral blood [29]. Nevertheless, chronic rhinitis and nasal polyps were not categorized in our analysis due to the limited sample size. The term "rash" within the context of our study alludes to the patients' histories of

atopic dermatitis and chronic urticaria. Studies in real-world settings have indicated that omalizumab can effectively alleviate symptoms of chronic urticaria and atopic dermatitis [30]. However, there is limited discussion on how the presence of concomitant dermatitis or urticaria affects the response to asthma symptoms. Al-Ahmad et al. observed no significant difference in response based on the presence or absence of eczema or urticaria in their research [31]. In this model, it is suggested that patients without a history of dermatitis or urticaria may be more likely to benefit, although the number of cases is relatively small, which may introduce certain biases. Further validation with larger sample size studies is warranted to confirm these findings. In addition, Cakmak et al.'s research revealed that an elevated baseline FEV1 (%) is correlated with a positive response to omalizumab treatment [32]. However, our model suggests that patients with poor lung function and frequent exacerbations respond better to omalizumab. In the WATCH study, patients with frequent attacks but few acute healthcare encounters and those who did not require steroids were independently associated with omalizumab response [33]. The severity of asthma attacks requiring healthcare intervention or steroid use was not delineated in our study, but few of our participants required emergency care or intravenous steroids during the follow-up period. Patients with poor lung function and frequent exacerbations are relatively more characterized by type 2 inflammation. These

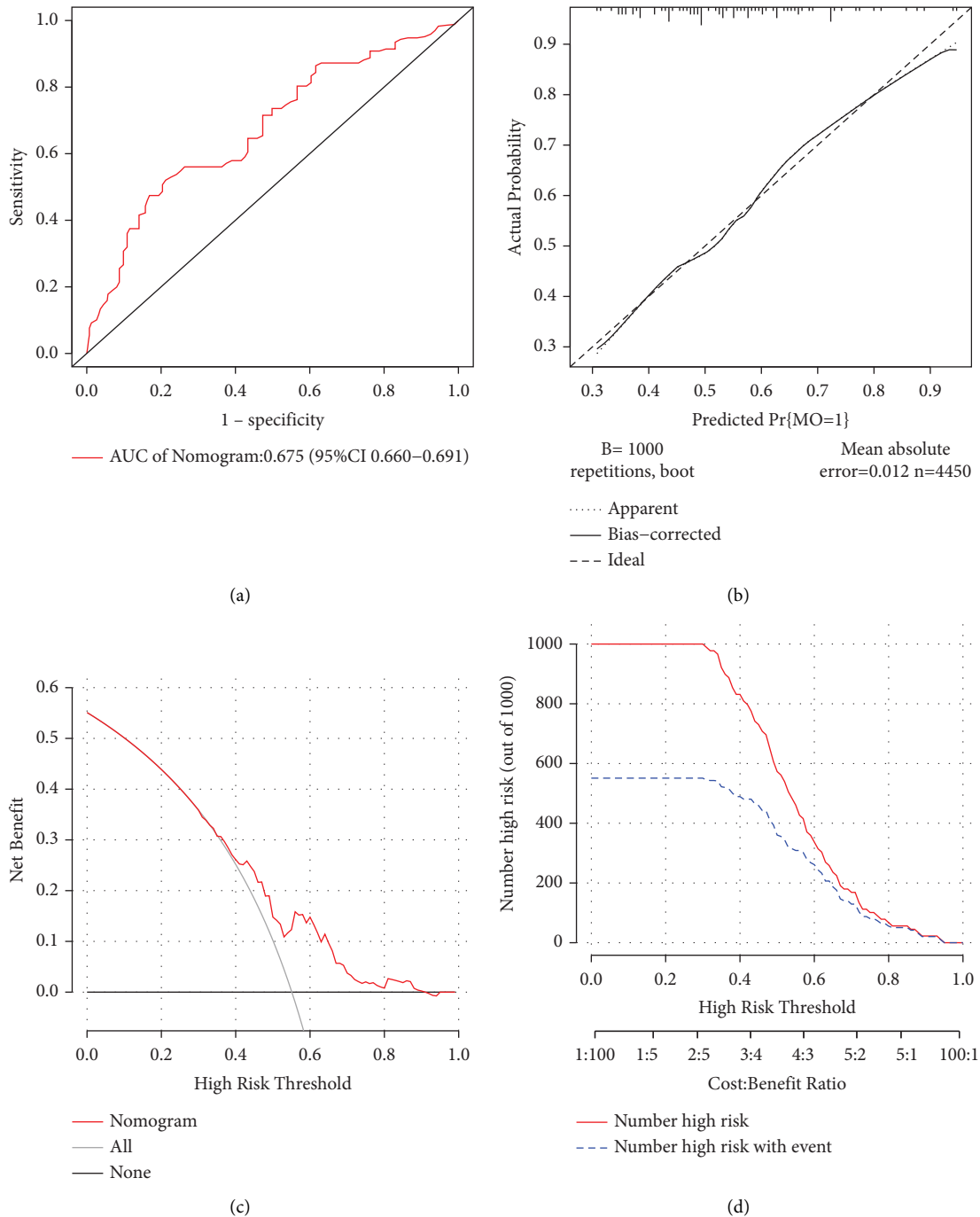


FIGURE 7: Effectiveness evaluation of nomogram predictive model: (a) ROC curve; (b) calibration plot; (c) DCA curve; (d) CIC curve.

patients tend to endure increased frequency of both diurnal and nocturnal symptoms, indicating a more substantial disease impact. Consequently, they are more likely to derive significant therapeutic advantages from targeted biological therapies.

Whether baseline total serum IgE level can be the predictor of response or not remained controversial [34]. Responders of omalizumab had a higher mean baseline total level of serum IgE. In the INNOVATE study, baseline total IgE was the only consistent predictor of response [9]. Many

studies, however, suggested that the difference in the baseline level of IgE was not the driving force for clinical response to omalizumab [23, 35]. The prescriptions of omalizumab are based on a dosing table accounting for total serum IgE and the body weight of the patient, which aimed to achieve an average serum-free IgE of 25 ng/mL that is associated with clinical improvement [36]. Other studies showed that the ratio of serum IgE at the 4th week over baseline was a better predictor of response, indicating that a more than 2-fold increase of this ratio can predict a good/

excellent response to omalizumab in patients with moderate-to-severe asthma [37]. The predictive value of the ratio is certified in our nomogram model.

Several studies have reported high FeNO, and high blood EOS counts were indirect markers of upregulated airway inflammation and could predict clinical response of omalizumab treatment [34, 38–40]; high blood eosinophil count is associated with poor response to omalizumab [41]. While some research studies demonstrated that the EOS counts were similar in responders and nonresponders [42–44], our study showed that blood eosinophil counts and FeNO were not related to GETE response. This nomogram showed satisfied discrimination and calibration performance, as well as a significant net benefit in predicting responders to omalizumab. It provides clinicians with scientific guidance and convenient approaches to identify individuals with a high possibility of response, thus improving the efficiency of treatment strategies.

Considering patients' hope for improvement in lung function as soon as possible, our study tried to develop a nomogram to predict the efficacy of improving small airway function. Predictors related to the efficacy included patients' weight, duration of asthma, use of OCS, total serum IgE level at 4th week, and history of rhinitis. Patients who have suffered from asthma symptoms for many years are supposed to have acute attacks frequently, which lead to constant chronic airway inflammation and prescription of additional glucocorticoids. Omalizumab treatment acts on the inflammation process by down-regulating cell degranulation and the release of inflammatory mediators [25], which probably is the reason for the improvement in airway function. Previous studies have shown that the history of allergic disease is related to the reduction of asthma exacerbations after treatment [38]. In our study, pretreatment total serum IgE was not a predictor of improvements of MEF25%pre, while total serum IgE at the 4th week after injection is more relative to the lung function improvement. This is the same as previous studies [3, 38]. Unexpectedly, the nomogram did not present excellent discrimination and calibration performance. It indicated that it is difficult to reliably predict lung function improvement from omalizumab therapy based on current baseline parameters, and more clinical characteristics needed to be analyzed in future study.

Limitations of this study should be mentioned. Firstly, this is a single-centered study, which leads to potential inevitable selection bias. Secondly, the sample size of this study is not large, and only internal verification is shown in the second predictive model (lung function model). Other factors such as the number and variety of allergens have not been incorporated into analysis. Further validation with large patient numbers and comprehensive variables are required. Thirdly, treatment was administered in an unblinded manner, and we used a symptom questionnaire to assess response (GETE). This could potentially lead to anticipation bias. Fourthly, the evaluation period of 4 months was relatively short.

5. Conclusion

Omalizumab treatment remarkably improved asthma control and pulmonary function in patients with moderate-to-severe asthma. In this study, a score model was developed to predict the response to omalizumab treatment in the short term (16 weeks). The model has good internal validity and high discrimination, providing great clinical value. It is not reliable to predict the improvements in lung function for asthma patients during the short 16 weeks, more data about long-term treatment need to be included in the future.

Data Availability

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

Ethical Approval

This study was approved by the Ethics Committee of the first affiliated hospital of Soochow University.

Consent

Informed consent was obtained from all participants (NO. 2019118).

Disclosure

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Xiuqin Zhang and Cuiping Fu are equal corresponding authors.

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