RESEARCH ARTICLE

Relationship between serum immunological biomarkers and small airway obstruction in patients with mild-to-moderate asthma and allergic rhinitis and their prognostic value

Jing Xue[1], Xin Liu[2,3], Cairong Bai[3], Yali Zuo[3], Wendong Hao[2,3]

Abstract

Objective: To evaluate the correlation between various serum immunological biomarkers and small airway obstruction in children, and the prognostic value of the markers.

Method: This study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University, Yulin, China, from February 2023 to March 2024, and comprised children aged 4-15 years diagnosed with asthma, who were divided into asthma group A and asthma with allergic rhinitis group B. Peripheral venous blood was collected from all the subjects to measure serum levels of total immunoglobulin E, C-reactive protein, eosinophil and interleukin-6 using enzyme-linked immunosorbent assay and standardised laboratory assays. All participants underwent pulmonary function testing, including forced expiratory volume in 1 second, forced vital capacity, forced expiratory volume in 1 second/forced vital capacity ratio, and peak expiratory flow measurements. Data was analysed using SPSS 19 and GraphPad Prism 5.

Results: Of the 295 patients, 178(60.3%) were in group A; 105(59%) girls and 73(41%) boys with mean age 8.5±1.8 years. The other 117(39.7%) patients were in group B; 72(61.5%) girls and 45(38.5%) boys with mean age 8.9±2.2 years ($p>0.05$). A significant negative correlation was found between serum interleukin-6 levels and the small airway obstruction parameters mean mid-expiratory flow between 25-75% of forced vital capacity % predicted (r=-0.564, $p<0.05$) and forced expiratory flow % 50 predicted (r=-0.521, $p<0.05$) in group B. The cut-off values for total immunoglobulin E, C-reactive protein and interleukin-6 were 337.80IU/mL, 24.51mg/L and 38.75pg/mL, respectively. The area under the curve, sensitivity and specificity values of the combined diagnosis of total immunoglobulin E, C-reactive protein and interleukin-6 were 0.885, 78.51% and 89.26%, respectively.

Conclusion: Biomarkers total immunoglobulin E, C-reactive protein and interleukin-6 were found to be associated with small airway obstruction, and their combination demonstrated high diagnostic power for identifying paediatric patients with both asthma and allergic rhinitis.

Keywords: Asthma, Allergic rhinitis, Interleukin-6, Small airway obstruction. (JPMA 76: 535; 2026)

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Introduction

Asthma is a common chronic inflammatory disease of the airways that affects individuals of all ages, with a significant prevalence in children. It is characterised by recurrent episodes that can vary in severity and frequency. Asthma symptoms, such as wheezing, chest tightness, etc., can be triggered or exacerbated by various factors, leading to significant variability in disease presentation and management. A variety of inflammatory mediators are involved in the pathophysiological processes of asthma, contributing to airway inflammation, hyper-responsiveness and remodelling. The phrase "One Airway, One Disease" encapsulates the understanding that asthma and allergic rhinitis are interconnected conditions affecting the respiratory system.[1] This concept highlights how inflammation and symptoms in one part of the airway can influence the other, leading to a more comprehensive view of airway diseases.

Small airways are defined as those with a diameter of ≤2mm. These include bronchioles that lead into the alveolar region.[2] Small airways are easily overlooked because of their many branches, large cross-sectional area, relatively slow airflow, and the fact that they often have no significant respiratory symptoms in the early stages of small airway obstruction (SAO).[3] However, Poiseuille's law[4] illustrates the critical relationship between airway diameter and resistance in the respiratory system. The inverse relationship highlights how even small changes in airway size can have significant effects on airflow, which is particularly relevant in conditions like asthma. Therefore, even minor narrowing of small airways leads to

[1]Department of Internal Medicine , Jingbian County Hospital of Traditional Chinese Medicine, Yulin , China; [2]Department of Respiratory and Critical Care Medicine, Yulin Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, Yulin , China; [3]Department of Allergy, Yulin Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, Yulin , China.

Correspondence: Wendong Hao. e-mail: hwdokgood@hotmail.com

ORCID ID: 0000-0002-8563-6512

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disproportionately large increases in resistance.[5]

Interleukin-6 (IL-6) is a multifunctional cytokine that plays an important role in regulating immune response, inflammation and haematopoiesis. It is produced by various cells in the body, especially including macrophages, T cells, B cells, fibroblasts and endothelial cells during inflammation.[6] IL-6 is known to contribute to the pathophysiology of asthma through its effects on airway inflammation and remodelling. Research has consistently demonstrated that elevated IL-6 levels correlate with decreased pulmonary function, particularly forced expiratory volume in 1 second (FEV1), in patients with severe asthma.[7-9]

While substantial research has focussed on the relationship between IL-6 and severe asthma, to our knowledge, there is limited literature examining this connection in patients with mild to moderate asthma, particularly concerning SAO. Small airway disease, characterised by obstruction in the smaller bronchi and bronchioles, can lead to respiratory symptoms and may not be fully captured by routine spirometry measures that primarily assess larger airways. The current study was planned to evaluate the correlation between various serum immunological biomarkers and SAO in children, and the prognostic value of the markers.

Patients and Methods

This study was conducted at the First Affiliated Hospital of Xi'an Jiaotong University, Yulin, China, from February 2023 to March 2024. After approval from the institutional ethics review committee, the participants were consecutively enrolled from the respiratory outpatient clinic of the hospital. Written informed consent was obtained in all cases. The subjects were divided into asthma group A and asthma+allergic rhinitis group B on the basis of differences observed with resoect to percentage of maximum mid-expiratory flow to the predicted value (MMEF25-75%pred), the percentage of flow rate and the predicted value at forced exhalation of 50% vital capacity (FEF50%pred), IL-6, C-reactive protein (CRP) and total immunoglobulin E (TIgE).

The sample size was determined by clinical availability and exceeded established methodological standards for diagnostic biomarker research as it satisfied the ≥100-subject minimum for robust receiver operating characteristic (ROC) curve analysis.[10] Besides, the 39:1 events-per-variable ratio (117 outcome events/3 biomarkers) surpassed the 10:1 threshold for stable multivariable modelling.[11] Finally, post-hoc power analysis confirmed >90% power (α=0.05) to detect significant discriminatory capacity (aura under the curve [AUC] >0.5) using established methods.[12]

The diagnosis of bronchial asthma was guided by Global Initiative for Asthma (GINA) guidelines, and the inclusion/exclusion criteria were designed to ensure a comprehensive evaluation of patients suspected of having asthma, taking into account clinical symptoms, functional tests and allergy assessments.[13] The following specific diagnostic criteria were used: recurrent clinical symptoms, positive bronchodilator test or bronchial provocation test, exclude obstructive pulmonary disease (COPD), vocal cord dysfunction, gastroesophageal reflux disease (GERD), heart failure, respiratory tract infections, respiratory failure, hepatic and renal impairment, interstitial lung disease, rheumatic diseases, and psychiatric disorders.

The requirement for the participants to have a positive result from either an allergen skin prick test (SPT) or a serum IgE test served as a critical criterion for inclusion in the study.

The diagnosis of allergic rhinitis is guided by the International Consensus Statement on Allergy and Rhinology (ICAR), as revised in 2023.[14] Symptoms included sneezing, runny nose and other symptoms lasting or accumulating for >1 hour a day, and could be accompanied by allergic conjunctivitis symptoms, such as itching and redness. The signs included pallor of the nasal mucosa, swelling and watery nasal discharge. The allergen test included at least 1 serum-specific IgE allergen and/or positive SPT, or a positive nasal provocation test.

The blood samples were centrifuged at 3000 rpm for 20 minutes using a refrigerated centrifuge. The resulting serum was stored in a -80°C freezer for further analyses. CRP was detected by immunotransmission turbidimetry. An automatic haematology analyser was employed to quantify eosinophil (EOS) counts in the blood samples. A fully automated fluorescence immunoassay analyser (Thermo Fisher Scientific, Waltham, MA, USA) was utilised to measure serum specific IgE levels and TIgE. Assessment of serum IL-6 levels was done using enzyme-linked immunosorbent assay (ELISA).

Jaeger MasterScreen (CareFusion Corporation, San Diego, CA, USA) pulmonary function test (PFT) system[15] was used to measure various pulmonary parameters, ensuring high-quality and reliable results. The parameters included MMEF25-75%pred and FEF50%pred). At least 3 acceptable tests were done to ensure accuracy. The difference between the best and suboptimal values for forced vital capacity (FVC) and FEV1 was maintained below 0.15L. Overlapping patterns of the flow-volume (F-V) and time-volume (T-V) curves was confirmed to demonstrate good test repeatability.

Data was analysed using SPSS 19. for general statistical analyses and GraphPad Prism 5 for graphical representation and specific statistical tests. The correlation of MMEF25-75%pred and FEF50%pred with inflammatory mediators was analysed by Pearson correlation analysis. The chi-square test was employed specifically for analysing count data to assess the association between categorical variables. P<0.05 indicated a statistically significant association between the variables.

Diagnostic performance of serum TIgE, CRP, IL-6, and their combined panel was evaluated using ROC curve analysis. Sensitivity (true positive [TP] rate=TP/(TP+false negative [FN]) and specificity (true negative [TN] rate = TN/(TN+false positive [FP]) were calculated across all decision thresholds. The area under the ROC curve (AUC-ROC) quantified overall discriminatory power for detecting allergic rhinitis-asthma comorbidity, with optimal cut-off points determined using the Youden Index.[16]

Results

Of the 295 patients, 178(60.3%) were in group A; 105(59%) girls and 73(41%) boys with mean age 8.5±1.8 years. The other 117(39.7%) patients were in group B; 72(61.5%) girls and 45(38.5%) boys with mean age 8.9±2.2 years. The two groups showed no significant differences in age, gender, maximum symptom days, controller medication use, allergic sensitisation, or asthma symptom days in the preceding 2 weeks (p>0.05). There were significant intergroup differences in MMEF25-75%pred, FEF50%pred, IL-6, CRP and TIgE (p<0.05) (Table 1).

Table-1: Demographic and clinical characteristics of the participants.

Variable	Asthma (n=178)	Asthma+AR (n=117)	*p*-value
Demographics			
Male	73 (41.01%)	45 (38.46%)	0.5092
Female	105 (58.99%)	72 (61.54%)	0.7155
Mean Age (years)	8.5±1.8	8.9±2.2	0.0579
Clinical Characteristics			
Maximum Symptom Days (14 days), mean±SD	1.6±2.9	1.9±3.1	0.0547
Controller Medication Use, n (%)	114 (64.04%)	72(61.54%)	0.6520
Allergic Sensitization 1 Allergen, n (%)	112 (62.92%)	67 (57.26%)	0.2193
Asthma symptom days in past 2 weeks, mean (CI)	1.6±0.7, 3.9	1.9±0.8, 4.7	0.0643
Spirometry Outcome Measures			
MMEF25-75 (% predicted), mean (CI)	74.8±65.7, 85.9	63.7±56.5, 79.4)	0.0411
FEF50% (% predicted), mean (CI)	77.2±73.4, 87.6	61.4±53.5, 78.6	<0.01
FEV1/FVC, mean (CI)	87.4±82.8, 91.7	86.1±81.2, 90.3	0.4787
FEV1 (% predicted), mean (CI)	96.5±88.3, 105.2	91.2±83.4, 95.8	0.7814
Biomarkers			
Interleukin 6, (pg/mL), mean (CI)	20.5±15.6, 25.7	38.0±31.4, 54.3	<0.01
C-reactive protein, (mg/L), mean (CI)	11.5 (5.4, 16.8)	25.2±18.4, 31.5	<0.01
Total immunoglobulin E, (IU/mL), mean (CI)	320.9±221.6, 407.3)	363.5±277.4, 449.6	<0.05

Days and age are presented as mean (range). Continuous and count outcomes are presented as least-squares means with 95% confidence intervals. Categorical variables are represented as number (%). NS: Not significant. AR: Allergic rhinitis, FEV1: Forced expiratory volume in first second, FVC: Forced vital capacity, FEV1/FVC: Ratio of FEV1 to FVC, MMEF25-75: Average flow velocity in the exhalation interval 25-75% of FVC, FEF50%: Forced expiratory flow at 50% of FVC.

Table-2: Correlation of inflammatory mediators with lung function indicators.

Pulmonary function metrics	TIgE	EOS	CRP	IL-6
MMEF25-75%pred	r=-0.445, p<0.05	r=-0.216, p=0.517	r=-0.416, p<0.05	r=-0.564, p<0.05
FEF50%pred	r=-0.420, p<0.05	r=-0.187, p=0.650	r=-0.384, p=0.129	r=-0.521, p<0.05
FEV1%pred	r=-0.377, p=0.217	r=-0.194, p=0.592	r=-0.361, p=0.254	r=-0.401, p=0.078

CRP: C-reactive protein, IL-6: Interleukin-6, TIgE: Total immunoglobulin E, EOS: Eosinophil. MMEF25-75: Average flow velocity in the exhalation interval 25-75% of forced vital capacity, FEF50%: Forced expiratory flow at 50% of forced vital capacity, FEV1%pred: The percentage of predicted forced expiratory volume in one second. Relationship between inflammatory mediators and lung function parameters was statistically processed by Pearson correlation analysis.

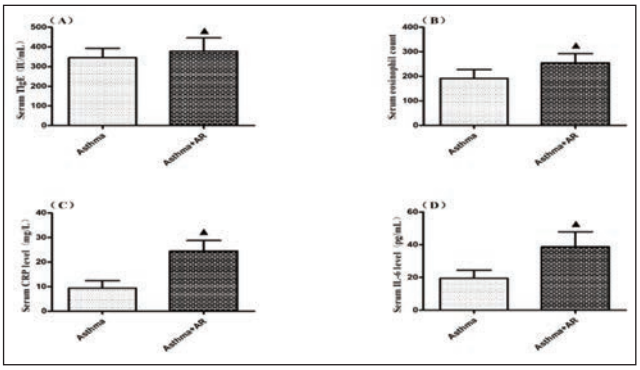

Figure-1: Intergroup comparison of serum biomarkers.

Serum TIgE levels in group B were significantly inversely associated with MMEF25-75%pred (r=-0.445, p<0.05) and FEF50%pred (r=-0.420, p<0.05), and serum IL-6 levels in group B were significantly inversely associated with MMEF25-75%pred (r=-0.564, p<0.05) and FEF50%pred (r=-0.521, p<0.05). CRP levels were significantly negatively correlated with MMEF25-75%pred in group B (r=-0.416, p<0.05). FEV1%pred was not significantly correlated with serum TIgE, EOS, CRP and IL-6 (Table 2).

TIgE, EOS, CRP and IL-6 exhibited significantly increased levels in group B compared to group A (p<0.05) (Figure 1).

Compared to group A, MMEF25-75%pred and FEF50%pred values in group B were significantly lower (p<0.05)(Figure 2).

The cut-off values for IgE, CRP and IL-6 were 337.80IU/mL (AUC=0.816, 95% confidence interval [CI]: 0.749~0.894; sensitivity 64.31%, specificity 87.61%), 24.51mg/L (AUC=0.848, 95%CI: 0.779~0.922; sensitivity 75.73%, specificity 81.44%) and 38.75pg/mL (AUC=0.748, 95%CI: 0.661~0.826; sensitivity 62.95%, specificity 82.06%), respectively. The AUC, sensitivity and specificity of the combined diagnosis of IgE, CRP and IL-6 were 0.885, 78.51%

Table-3: Performance of biomarkers for the diagnosis of asthma patients with allergic rhinitis.

Biomarkers	AUC(95%CI)	Cutoff value	Sensitivity (%)(95%CI)	Specificity(%)(95%CI)	*z*- score	*p*- value
TIgE	0.816(0.749~0.894)	>337.80IU/mL	64.31 (56.78-71.25)	87.61 (81.54–91.57)	9.411	<0.01
CRP	0.848(0.779~0.922)	>24.51mg/L	75.73 (72.35-83.15)	81.44 (75.12-86.79)	10.289	<0.01
IL-6	0.748(0.661~0.826)	>38.75pg/mL	62.95 (55.49-71.13)	82.06 (74.45-85.28)	6.863	<0.01
Combined	0.885(0.817~0.925)	—	78.51 (77.63-84.60)	89.26 (83.17-93.15)	11.965	<0.01

TIgE: Total immunoglobulin E, CRP: C-reactive protein, IL-6: Interleukin-6, AUC: Area under the curve, CI: Confidence interval.

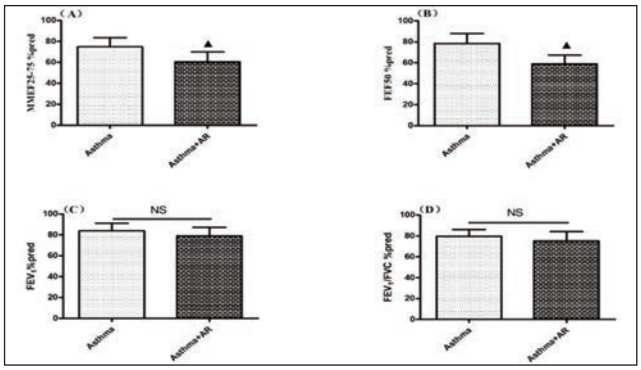

Figure-2: Intergroup comparison of pulmonary function parameters.

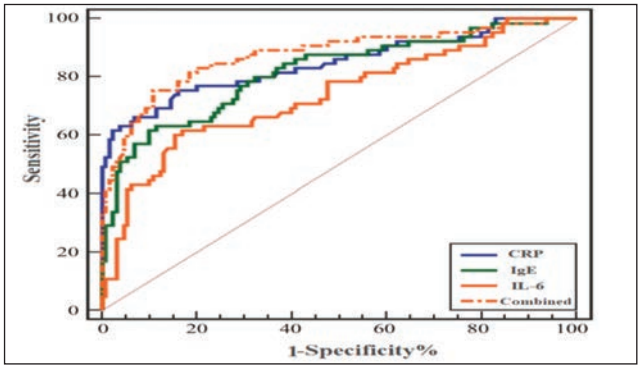

Figure-3: ROC curves of CRP, TIgE, IL-6 and their combination in distinguishing patients with asthma and allergic rhinitis from asthma patients.

ROC: Receiver operating characteristic, CRP: C-reactive protein, IL-6: Interleukin-6, TIgE: Total immunoglobulin E.

and 89.26%, respectively (Table 3, Figure 3).

Discussion

The current study investigated the characteristics of airway inflammation in children diagnosed with mild-to-moderate asthma and allergic rhinitis, and evaluated the association between these inflammatory cytokines and SAO. The data suggested that several laboratory variables, including specific inflammatory markers, showed significant association with SAO in paediatric population.

There were significantly higher levels of TIgE, EOS, CRP and IL-6 biomarkers in asthma+allergic rhinitis group compared to the asthma group, which was consistent with earlier results.[17-21] Furthermore, compared to the asthma group, the SAO parameters MMEF25-75 %pred and FEF50%pred in asthma+allergic rhinitis group were significantly lower (p<0.05). Circulating levels of IL-6, TIgE and CRP in asthma+allergic rhinitis group were significantly inversely associated with SAO indexes MMEF25-75%pred and FEF%50pred. These findings indicated a clear association between the degree of airway inflammation and the extent of SAO in the paediatric population.

However, the current study showed that SAO parameters MMEF25-75%pred and FEF50%pred were significantly correlated with serum TIgE, EOS and CRP in these patients, but, that was not the case with FEV1%pred. IgE is a crucial antibody in the immune system, particularly recognised for its involvement in allergic diseases. Serum IgE serves as a crucial biomarker in the diagnosis and management of allergic airway symptoms. Its measurement aids healthcare providers in making informed decisions about patient care, offering a tailored approach to allergy management that includes diagnostic assessments, environmental control strategies, and specific therapeutic options.[22-24] The crosslinking of IgE bound to mast cells is a critical event in the allergic response.[25] In the bronchial mucosa, the release of highly sensitive inflammatory mediators, such as histamine, prostaglandins and leukotrienes, plays a critical role in the pathophysiology of respiratory conditions, like asthma and allergic rhinitis.[23] Research[23] has highlighted an important relationship between IgE levels and lung function, specifically measured as FEV1, in patients with asthma. The observation of an inverse correlation between serum IgE levels and predicted FEV1 percentages, as reported by Elias JA et al., contrasts with the current findings.[23] In addition, the current study indicated that MMEF25-75%pred and FEF50%pred, not FEV1%pred were considerably correlated with EOS and CRP in children. It is universally acknowledged that small airway refers to an airway with a diameter <2mm. In the early stages of chronic airway diseases, SAO may not substantially impact overall airway resistance, so it is easy to be ignored. The reason why inflammatory mediators of IgE, EOS and CRP are related to MMEF25-75%pred and FEF50%pred rather than FEV1%pred may be that the severity of asthma disease is different, that is, subjects with asthma included in the study were all patients with mild to moderate asthma, while the previous study[23] included participants with moderate to severe asthma.

IL-6 is a pro-inflammatory cytokine that plays a significant

role in the pathophysiology of asthma. It is produced by various cell types, including macrophages, T cells, and airway epithelial cells, in response to inflammatory stimuli.[26] The current research revealed significantly higher serum levels of IL-6 in children. The finding is consistent with the results of previous studies.[27,28] Akar-Ghibril N et al. showed that serum IL-6 concentrations in paediatric asthma patients were inversely correlated with the pulmonary function parameter FEV1.[29] This finding suggested that higher levels of IL-6 are associated with poorer lung function, as measured by FEV1. However, the current study indicated that serum IL-6 levels in paediatric patients were not significantly correlated with FEV1, but were negatively correlated with SAO parameters, specifically MMEF25-75%pred and FEF50%pred. Small airway dysfunction refers to pathological changes occurring in the smaller airways of the lungs, which can precede and contribute to the progression of asthma.[30] The current findings diverge from earlier studies[29] that may have targetted different patient populations, such as those with more severe asthma or varying stages of airway remodelling. The inconsistency across studies regarding IL-6 levels and their correlation with FEV1 in asthma patients likely reflects the complexity of the disease, including variations in patient demographics, disease severity, and study methodologies. Further research is needed to account for these factors and to better understand how IL-6 and other inflammatory mediators relate to asthma pathophysiology and clinical outcomes in diverse patient populations. This understanding will ultimately lead to more effective diagnosis and treatment strategies tailored to individual patient needs.

The current study indicated that children with mild-to-moderate asthma and allergic rhinitis exhibit significant increases in immunological markers CRP, IgE and IL-6. The findings are directly in line with previous findings.[18-20] The significant performance of CRP for the diagnosis was observed in participants whose CRP values were equal to or higher than 24.51mg/L, followed by IgE values equal to or higher than 337.80IU/mL, and IL-6 value equal to or higher than 38.75pg/mL. The AUC and 95% CI of CRP, IgE and IL-6 were 0.848 (0.779~0.922), 0.816 (0.749~0.894) and 0.748 (0.661~0.826), respectively. The AUC and 95% CI of the combined diagnosis of these three biomarkers was 0.885 (0.817~0.925). The findings suggest there is a strong diagnostic ability among children patients, particularly when considering the combined use of the three immunological markers.

The current study has several limitations. Firstly, the sample size is relatively small. The sample size was estimated on the basis of similar studies[31] rather than formal power calculations, which may have limited the ability to detect smaller but clinically meaningful effects. A larger sample size would provide more robust data and strengthen the conclusions drawn from the study. Secondly, the levels of inflammatory markers in different biological samples, such as serum, sputum and bronchoalveolar lavage fluid, and their correlation with lung function parameters were not compared. Such comparisons could offer valuable insights into how these biomarkers relate to asthma severity and control, potentially identifying key indicators of airway inflammation and responsiveness to treatment. Thirdly, this is a single-centre study, which may have introduced biases related to the specific population being studied and the methods used for data collection. If data on asthma patients could be gathered from multiple centres, it would enhance the external validity of the results and allow for a more comprehensive understanding of the inflammatory profiles in diverse patient populations. Also, in children doing a forced oscillation technique (FOT) or impulse oscillometry (IOS) would be more useful marker of SAO in children.

Conclusions

In children with mild-to-moderate asthma combined with allergic rhinitis, serum TIgE, CRP and IL-6 levels were associated with SAO, and the combination of the three biomarkers had a high diagnostic power for the diagnosis of asthma with allergic rhinitis patients.

Disclaimer: None.

Conflict of Interest: None.

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Author Contribution:
JX: Data analysis, validation and final approval.
XL: Data analysis and final approval.
CB: Formal analysis and final approval.
YZ: Validation and final approval.
WH: Writing and final approval.