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ORIGINAL RESEARCH

# Bronchial Hyperreactivity in the COVID-19 Era: The Impact of SARS-CoV-2 Infection and COVID-19 Vaccination in Patients with Respiratory Symptoms

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**Introduction:** Persistent respiratory symptoms are commonly reported following coronavirus disease 2019 (COVID-19). Although COVID-19 vaccines are effective, concerns remain regarding their potential impact on airway hypersensitivity. The relationship between SARS-CoV-2 infection, vaccination, and bronchial hyperresponsiveness remains unclear.

**Materials and Methods:** This retrospective study included adults aged ≥18 years who underwent methacholine provocation testing. Participants were categorized into four groups according to their history of SARS-CoV-2 infection and COVID-19 vaccination: no infection/no vaccination (NI-NV), vaccination/no infection (V-NI), no vaccination/infection (NV–I), and vaccination/infection (V–I). Airway hypersensitivity was defined as a ≥20% reduction in forced expiratory volume in one second (FEV1) following methacholine challenge. Multivariable logistic regression analysis was performed to evaluate independent associations.

**Results:** A total of 340 participants were included (NI-NV: n=36; V-NI: n=163; NV-I: n=25; V-I: n=116). No significant differences were observed in methacholine positivity, pulmonary function parameters, or PC20 values across groups (all p>0.05). In multivariable analysis, neither prior infection (adjusted OR 0.99, 95% CI 0.63–1.55) nor vaccination (adjusted OR 1.06, 95% CI 0.60–1.88) was independently associated with bronchial hyperresponsiveness. Smoking was significantly associated with methacholine positivity (adjusted OR 3.33, 95% CI 1.43–7.77). Symptom severity differed among groups, with higher cough and sputum scores in the NI-NV group and greater dyspnea severity in the NV-I group.

**Conclusion:** Neither prior SARS-CoV-2 infection nor COVID-19 vaccination was associated with increased airway hypersensitivity after adjustment for confounders. Despite similar objective airway responsiveness, symptom severity varied across groups, suggesting a dissociation between subjective respiratory symptoms and measurable bronchial hyperresponsiveness.

**Keywords:** COVID-19 infection, vaccination, provocation test, airway hypersensitivity

## Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) viral infection, significantly impacts the respiratory system, with symptoms ranging from mild upper respiratory tract involvement to severe pneumonia and acute respiratory distress syndrome.[1] While most individuals recover within weeks, many experience lingering respiratory symptoms as part of post-COVID conditions or "long COVID".[2] Common persistent respiratory symptoms include shortness of breath, chronic cough, sputum, tightness of chest, and reduced exercise tolerance.[2] Pulmonary complications such as interstitial lung abnormalities, obstructive airway, and bronchial hyperresponsiveness have also been observed.[3] These prolonged respiratory issues can significantly affect quality of life and require careful evaluation and management.

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COVID-19 vaccines are widely recognized as effective against SARS-CoV-2 infection.[4] However, similar to any medical intervention, they may lead to short-term and, in rare cases, long-term side effects. Short-term symptoms typically include local reactions such as pain, redness, or swelling at the injection site, along with systemic symptoms such as fever, fatigue, headache, muscle pain, and chills.[5] Other symptoms, while uncommon, may involve prolonged fatigue, myocarditis, pericarditis, or other inflammatory conditions.[5] Rarely, adverse events such as Guillain–Barré syndrome or thrombosis with thrombocytopenia syndrome have been documented.[5] Some patients have reported increased shortness of breath following vaccination, and rare adverse events such as vaccine-associated pneumonitis have been documented, although a definitive link to vaccination has not been established in most cases.[6,7]

Airway hypersensitivity can lead to chronic respiratory issues, reduced quality of life, and increased healthcare burdens.[8] The provocation test is clinically important for diagnosing airway hypersensitivity, where airways exhibit an exaggerated response to stimuli.[9] By assessing bronchial reactivity, the test helps identify patients with airway inflammation, whether they exhibit prominent symptoms.[9] It also evaluates the severity of airway hyperresponsiveness, which can guide treatment decisions and determine the need for interventions, such as bronchodilators, inhaled corticosteroids, or biological agents.[10,11] Overall, this test is a valuable tool for managing and customizing treatment plans for patients with asthma and other reactive airway diseases.[9]

Although the peak of the COVID-19 pandemic has subsided, SARS-CoV-2 continues to circulate, and persistent respiratory symptoms remain common in clinical practice.[12] Many patients with prior infection or vaccination present with dyspnea, cough, or chest tightness, raising concerns about possible airway hyperresponsiveness.[13] Respiratory symptoms are frequently reported in individuals with a history of SARS-CoV-2 infection or a history of COVID-19 vaccination, with some patients experiencing persistent airway-related manifestations.[2,6,7] However, the relationship between COVID-19 infection or vaccination and the development or exacerbation of airway hypersensitivity remains unclear. Given the global prevalence of COVID-19 infection and the widespread implementation of vaccination programs, understanding its potential effects is of significant clinical importance. This study aimed to address this critical gap by analyzing the impact of COVID-19 infection and vaccination on airway hypersensitivity.

# Materials and Methods

## Study Design and Participant Selection

This retrospective study was conducted at the Pulmonary Medicine outpatient clinic of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan. All patients who underwent methacholine provocation testing between 1 May 2022 and 30 December 2022 were screened for eligibility.

Inclusion and Exclusion Criteria: Eligible participants were adults aged ≥18 years who presented with persistent respiratory symptoms (eg, cough, wheezing, chest tightness, or dyspnea) and were referred for methacholine provocation testing during the study period. To minimize treatment-related confounding, only patients who had not used inhaled or systemic corticosteroids or bronchodilators prior to testing were included. Patients were excluded if they had active COVID-19, COVID-19–related interstitial lung disease or significant structural lung abnormalities on imaging, inability to perform the methacholine challenge test, or refusal to participate.

## Classification of Study Groups

Participants were categorized into four groups based on their documented history of SARS-CoV-2 infection and COVID-19 vaccination. A history of SARS-CoV-2 infection was defined as a confirmed diagnosis documented in the medical record based on a positive reverse transcription polymerase chain reaction test or rapid antigen test. A history of COVID-19 vaccination was defined as receipt of at least one dose of a COVID-19 vaccine prior to the provocation test. Accordingly, participants were categorized into four groups: Group 1 (NI-NV: no infection, no vaccination), Group 2 (V-NI: vaccination, no infection), Group 3 (NV–I: no vaccination, infection), and Group 4 (V–I: vaccination and infection), where NI denotes no prior SARS-CoV-2 infection, NV denotes no COVID-19 vaccination, I denotes prior infection, and V denotes vaccination.

The study included 340 participants who underwent an evaluation that encompassed demographic data collection, symptom assessment, and a provocation test. The research protocol was approved by the Ethics Committee of Taipei Tzu

Chi Hospital (IRB Number: 13-IRB012), and informed consent was obtained from all participants. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

## Demographic Variables

Demographic factors, including age, sex, body weight, height, smoking habits, and allergy history, were assessed. Additionally, family and medical histories of systemic diseases were documented.

## Evaluation of Respiratory Symptoms

Respiratory symptoms were evaluated by chest physicians, and patients reported their subjective symptoms and severity during outpatient visits. Symptom severity was classified into five levels: none (score 0), mild (score 1), moderate (score 2), severe (score 3), and very severe (score 4). This symptom severity classification reflected the intensity of respiratory symptoms at the time of clinical evaluation and was independent of COVID-19 disease severity.

## Provocation Tests

### Baseline Pulmonary Function Tests Before Methacholine Challenge

Baseline pulmonary function tests (PFTs) prior to the methacholine challenge were conducted using a spirometer in compliance with established American Thoracic Society guidelines.[14] The tests were performed in a negative pressure room to minimize the risk of airborne transmission of respiratory viruses, including SARS-CoV-2.[15] The testing environment was thoroughly disinfected after each session to ensure the safety of participants and staff.

### PFTs During Methacholine Challenge

Provocation test was conducted using a methacholine solution prepared in phosphate-buffered saline.[15] PFTs were performed at baseline and after inhalation of methacholine concentrations ranging from 0.0625 mg/mL to 16.0 mg/mL.[15] Methacholine was delivered using a five-breath deep-breathing technique with nasal occlusion, utilizing a breath-actuated nebulizer (Trudell Medicinal International, Ontario, Canada).[16] PFTs following methacholine administration were conducted 3 min after each inhalation. Percentage changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and maximum mid-expiratory flow (MMEF) were calculated by comparing the differences between post-provocation and baseline values relative to baseline values. A provocation test was considered positive if FEV1 or FVC decreased by >20%.[15] The provocative concentration (PC20) was defined as the methacholine concentration that caused a 20% reduction in FEV1. If a reduction of more than 20% in FEV1 was not achieved at the highest methacholine concentration of 16.0 mg/mL, the test was interpreted as negative.[15] The differences in terms of changes in forced vital capacity (dFVC), forced expiratory volume in one second (dFEV1), and maximum mid-expiratory flow (dMMEF) were calculated by comparing the differences between post-challenge and baseline values, relative to the baseline values.

### PFT After Bronchodilator Spirometry

A post-bronchodilator PFT was conducted following methacholine challenge. A bronchodilator was administered at a dose of 200 μg using a pressurized metered-dose inhaler. PFTs were performed 15 min after bronchodilator administration. dFVC, dFEV1, and dMMEF were calculated by comparing the post-bronchodilator and post-challenge values relative to the post-challenge values.

## Statistical Analysis

All statistical analyses were conducted using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA). Chi-square tests were used to analyze categorical variables across the four groups. These data are reported as sample size (n) and percentage (%). Continuous variables were analyzed using the analysis of variance (ANOVA) to determine significant differences in means among the four groups, with post-hoc comparisons performed using the Least Significant Difference method to identify differences between specific groups. Continuous data are presented as mean ± standard deviation, and statistical significance was defined as $p<0.05$. Multivariable logistic regression analysis was performed to evaluate the independent

associations between prior SARS-CoV-2 infection, COVID-19 vaccination, and bronchial hyperresponsiveness. Covariates included age, sex, body mass index, and smoking status. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test, and model explanatory power was estimated using the Nagelkerke $R^2$ statistic. Post-hoc detectable effect size estimation was performed based on the observed sample size and event rate.

# Results

A total of 340 patients were included in the analysis, comprising Group 1 (n = 36), Group 2 (n = 163), Group 3 (n = 25), and Group 4 (n = 116).

## Baseline Characteristics of Participants in the Four Groups

Table 1 shows the baseline characteristics of participants in the four groups. There were no significant differences in age, height, weight, BMI, sex distribution, smoking status, or tobacco consumption between the groups (all p>0.05).

## Allergic and Systemic Diseases Among Participants in the Four Groups

Table 2 presents the prevalence of allergic and systemic diseases among participants in the four groups. No significant differences were observed in the prevalence of food allergies, drug allergies, family history of asthma, allergic rhinitis, tuberculosis, chronic obstructive pulmonary disease (COPD), bronchiectasis, idiopathic pulmonary fibrosis (IPF), hypertension, congestive heart failure (CHF), coronary artery disease (CAD), renal disease, liver disease, diabetes mellitus (DM), or cancer between the groups (all p>0.05). A family history of asthma was more common in Group 1 (NI-NV) with 41.7%, compared to 24.5% in Group 2 (V-NI), 28.0% in Group, 3 (NV–I), and 22.4% in Group 4 (V-I); however, this difference was not statistically significant (p=0.132).

## Prevalence and Severity of Symptoms Among Participants in the Four Groups

Table 3 shows the prevalence and severity of symptoms among participants in the four groups. There were no significant differences in the prevalence of wheezing, cough, chest tightness, or dyspnea between groups (all p>0.05). However, the severity scores for cough, sputum production, dyspnea, and wheezing were significantly different (p<0.05). Group 1 (NI-NV) had the highest severity of cough and sputum production, with mean scores of 2.3±1.1 and 1.9±1.2, respectively, compared to the other groups (p<0.05). Group 3 (NV-I) reported the highest severity of dyspnea (1.3±1.1, p=0.002). Wheezing severity was significantly higher in Group 4 (0.4±0.9) compared to Group 2 (0.1±0.5, p=0.033).

**Table 1** Baseline Characteristics of Participants in the Four Groups

| | **Group 1 (NI-NV) (n=36)** | **Group 2 (V-NI) (n=163)** | **Group 3 (NV-I) (n=25)** | **Group 4 (V-I) (n=116)** | **P value** |
|---|---|---|---|---|---|
| Age (years) | 50.8±17.4 | 52.9±15.8 | 48.5±16.2 | 48.5±16.2 | 0.049 |
| BH (cm) | 163.7±8.7 | 162.2±9.1 | 160.2±7.9 | 161.5±9.4 | 0.417 |
| BW (kg) | 65.6±17.4 | 63.4±12.9 | 60.3±11.0 | 61.9±13.4 | 0.349 |
| BMI (kg/m$^2$) | 24.3±5.4 | 24.0±4.1 | 23.6±4.3 | 23.6±4.1 | 0.787 |
| Male/Female | 13/23 (36.1%/63.9%) | 61/102 (37.4%/62.6%) | 7/18 (28.0%/72.0%) | 32/84 (27.6%/72.4%) | 0.334 |
| Current smoker/never smoking | 2/34 (5.6%/94.4%) | 17/146 (10.4%/89.6%) | 1/24 (4.0%/96.0%) | 8/108 (6.9%/93.1%) | 0.522 |
| Tobacco consumption (pack-year) | 0.5±2.5 | 2.0±9.6 | 0.8±4.0 | 0.9±4.7 | 0.484 |

**Abbreviations**: NI-NV, no infection, no vaccination; V-NI, vaccination, no infection; NV-I, no vaccination, infection; V-I, vaccination and infection; BH, body height; BW, body weight; BMI, body mass index.

**Table 2** Allergic and Systemic Diseases Among Participants in the Four Groups

| | Group 1 (NI-NV) (n=36) | Group 2 (V-NI) (n=163) | Group 3 (NV-I) (n=25) | Group 4 (V-I) (n=116) | P value |
|---|---|---|---|---|---|
| Food allergy | 3 (8.3%) | 12 (7.4%) | 2 (8.0%) | 6 (5.2%) | 0.859 |
| Drug allergy | 8 (22.2%) | 25 (15.3%) | 4 (16.0%) | 18 (15.5%) | 0.779 |
| FHx of asthma | 15 (41.7%) | 40 (24.5%) | 7 (28.0%) | 25 (22.4%) | 0.132 |
| Allergic rhinitis | 19 (52.8%) | 95 (58.3%) | 15 (60.0%) | 68 (58.6%) | 0.926 |
| Asthma | 6 (16.7%) | 21 (12.9%) | 2 (8.0%) | 13 (11.2%) | 0.744 |
| TB | 1 (2.8%) | 2 (1.2%) | 0 (0.0%) | 1 (0.9%) | 0.754 |
| COPD | 4 (11.1%) | 18 (11.0%) | 2 (8.0%) | 12 (10.3%) | 0.973 |
| Bronchiectasis | 0 (0.0%) | 7 (4.3%) | 0 (0.0%) | 0 (0.0%) | 0.333 |
| IPF | 1 (2.8%) | 1 (0.6%) | 0 (0.0%) | 0 (0.0%) | 0.285 |
| HTN | 4 (11.1%) | 36 (22.1%) | 5 (20.0%) | 19 (16.4%) | 0.390 |
| CHF | 1 (2.8%) | 4 (2.5%) | 0 (0.0%) | 6 (5.2%) | 0.463 |
| CAD | 2 (5.6%) | 10 (6.1%) | 1 (4.0%) | 4 (3.4%) | 0.778 |
| Renal disease | 2 (5.6%) | 1 (0.6%) | 0 (0.0%) | 2 (1.7%) | 0.145 |
| Liver disease | 1 (2.8%) | 7 (4.3%) | 2 (8.0%) | 3 (2.6%) | 0.599 |
| DM | 2 (5.6%) | 13 (8.0%) | 5 (20.0%) | 8 (6.9%) | 0.157 |
| Cancer | 0 (0.0%) | 3 (1.8%) | 0 (0.0%) | 6 (5.2%) | 0.176 |

**Abbreviations**: NI-NV, no infection, no vaccination; V-NI, vaccination, no infection; NV-I, no vaccination or infection; V-I, vaccination and infection; FHx, family history; TB, tuberculosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; HTN, hypertension; CHF, congestive heart failure; CAD, coronary artery disease; DM, diabetes mellitus.

**Table 3** Prevalence and Severity of Symptoms Among Participants in the Four Groups

| | Group 1 (NI-NV) (n=36) | Group 2 (V-NI) (n=163) | Group 3 (NV-I) (n=25) | Group 4 (V-I) (n=116) | P value |
|---|---|---|---|---|---|
| **Prevalence of symptoms** | | | | | |
| Wheezing | 13 (36.1%) | 36 (22.1%) | 5 (20.0%) | 33 (28.4%) | 0.256 |
| Cough | 26 (72.2%) | 105 (64.4%) | 15 (60.0%) | 75 (64.7%) | 0.770 |
| Chest tightness | 21 (58.3%) | 73 (44.8%) | 9 (36.0%) | 63 (54.3%) | 0.144 |
| Dyspnea | 12 (33.3%) | 57 (35.0%) | 10 (40.0%) | 39 (33.6%) | 0.939 |
| **Severity of symptoms** | | | | | |
| Cough | 2.3±1.1$^{\dagger\S\#}$ | 1.6±1.0$^{*\S}$ | 1.8±1.0$^{*\dagger\#}$ | 1.5±1.0$^{*\S}$ | 0.001 |
| Sputum | 1.9±1.2$^{\dagger\S\#}$ | 1.2±1.1* | 1.3±1.1* | 1.0±1.1* | <0.001 |
| Dyspnea | 0.8±1.2$^{\S}$ | 0.6±0.9$^{\S}$ | 1.3±1.1$^{*\dagger\#}$ | 0.8±0.9$^{\S}$ | 0.002 |
| Chest tightness | 1.0±1.4 | 0.8±0.9 | 1.1±1.2 | 0.9±1.0 | 0.208 |
| Wheezing | 0.1±0.6 | 0.1±0.5$^{\#}$ | 0.3±0.8 | 0.4±0.9$^{\dagger}$ | 0.033 |

**Notes**: *p<0.05, compared to Group 1; $^{\dagger}$p<0.05, compared to Group 2; $^{\S}$p<0.05, compared to Group 3; $^{\#}$p<0.05, compared to Group 4.
**Abbreviations**: NI-NV, no infection, no vaccination; V-NI, vaccination, no infection; NV-I, no vaccination, infection; V-I, vaccination and infection.

## Provocative and Post-Bronchodilator Pulmonary Function Parameters Among Participants in the Four Groups

Table 4 presents the PFT parameters of participants in the four groups. At baseline, there were no significant differences in FVC, FEV1, FEV1/FVC ratio, or MMEF across the groups ($p>0.05$). After provocation, no significant differences were observed in FVC, FEV1, or MMEF between groups ($p>0.05$). Post-bronchodilator measurements showed that FVC

**Table 4** Provocative and Post-Bronchodilator Pulmonary Function Parameters Among Participants in the Four Groups

| | Group 1 (NI-NV) (n=36) | Group 2 (V-NI) (n=163) | Group 3 (NV-I) (n=25) | Group 4 (V-I) (n=116) | P value |
|---|---|---|---|---|---|
| **Baseline** | | | | | |
| FVC (L) | 3.1±1.0 | 3.1±1.0 | 3.0±1.0 | 3.0±0.9 | 0.815 |
| FVC (% predicted) | 87.6±15.3 | 92.4±15.1 | 93.5±15.2 | 89.0±12.2 | 0.080 |
| FEV1 (L) | 2.5±0.8 | 2.5±0.8 | 2.5±0.9 | 2.5±0.8 | 0.992 |
| FEV1 (% predicted) | 86.0±15.0 | 91.2±16.8 | 94.4±16.3 | 89.2±13.6 | 0.135 |
| FEV1/FVC (%) | 81.1±6.8 | 80.9±7.3 | 82.4±6.2 | 83.0±7.3 | 0.108 |
| MMEF (L/sec) | 2.5±1.1 | 2.6±1.2 | 2.6±1.1 | 2.7±1.2 | 0.779 |
| MMEF (% predicted) | 79.2±24.5 | 84.5±27.4 | 91.2±29.0 | 85.9±25.8 | 0.185 |
| **Post-MCT** | | | | | |
| FVC (L) | 2.8±0.9 | 2.8±1.0 | 2.7±1.1 | 2.7±0.9 | 0.840 |
| FVC (% predicted) | 77.6±16.2 | 82.5±16.7 | 84.6±17.8 | 29.0±15.3 | 0.119 |
| FEV1 (L) | 2.1±0.7 | 2.1±0.8 | 2.1±0.9 | 2.1±0.8 | 0.932 |
| FEV1 (% predicted) | 70.9±15.7 | 76.8±16.6 | 80.1±16.6 | 73.3±17.3 | 0.083 |
| FEV1/FVC (%) | 75.7±8.0 | 76.0±7.5 | 77.5±6.9 | 76.5±8.5 | 0.785 |
| MMEF (L/sec) | 1.3±0.7 | 1.5±1.0 | 1.5±0.9 | 1.6±1.2 | 0.537 |
| MMEF (% predicted) | 41.9±25.4 | 46.8±26.7 | 50.1±24.0 | 48.2±30.2 | 0.640 |
| dFVC (%) | −11.7±8.2 | −10.9±8.3 | −9.8±8.6 | −11.6±9.1 | 0.769 |
| dFEV1 (%) | −17.6±8.9 | −16.2±9.5 | −15.4±7.0 | −18.3±11.0 | 0.280 |
| dMMEF (%) | −51.3±20.6 | −44.7±33.1 | −47.9±7.0 | −47.2±22.1 | 0.596 |
| **Post-BD** | | | | | |
| FVC (L) | 3.0±0.9 | 3.0±1.0 | 2.9±1.1 | 2.9±0.9 | 0.742 |
| FVC (% predicted) | 84.3±14.4[†] | 90.2±15.1[*#] | 91.2±16.1 | 86.1±12.9[†] | 0.027 |
| FEV1 (L) | 2.4±0.8 | 2.4±0.8 | 2.4±0.9 | 2.4±0.8 | 0.998 |
| FEV1 (% predicted) | 83.3±13.1 | 88.2±16.3 | 91.2±15.3 | 85.5±13.6 | 0.099 |
| FEV1/FVC (%) | 81.7±6.1 | 79.8±8.4[#] | 89.9±5.4 | 82.3±7.1[†] | 0.052 |
| MMEF (L/sec) | 2.3±1.0 | 2.3±1.1 | 2.3±1.0 | 2.3±1.2 | 0.980 |
| MMEF (% predicted) | 71.8±23.9 | 74.7±27.0 | 80.4±26.8 | 73.7±26.8 | 0.630 |

(*Continued*)

**Table 4** (Continued).

| | Group 1 (NI-NV) (n=36) | Group 2 (V-NI) (n=163) | Group 3 (NV-I) (n=25) | Group 4 (V-I) (n=116) | P value |
|---|---|---|---|---|---|
| dFVC (%) | 10.2±10.4 | 10.5±11.1 | 8.9±10.6 | 10.4±11.4 | 0.925 |
| dFEV1 (%) | 19.5±13.5 | 16.5±15.5 | 15.5±12.0 | 19.7±19.5 | 0.364 |
| dMMEF (%) | 129.0±116.2 | 104.9±115.3 | 83.0±70.1 | 92.5±86.0 | 0.245 |

**Notes**: *p<0.05, compared to Group 1; †p<0.05, compared to Group 2; #p<0.05, compared to Group 4.
**Abbreviations**: NI-NV, no infection, no vaccination; V-NI, vaccination, no infection; NV-I, no vaccination, infection; V-I, vaccination and infection; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; MMEF, maximum mid-expiratory flow; MCT, methacholine challenge test; BD, bronchodilator; dFVC, change in forced vital capacity; dFEV1, change in forced expiratory volume in one second; dMMEF, change in maximum mid-expiratory flow.

(% predicted) was the lowest in Group 1 (p=0.027). However, there were no significant differences in the percentage changes (dFVC, dFEV1, or dMMEF) post-bronchodilator across the groups.

## Comparison of Provocation Test Outcomes and Airway Obstruction Among Participants Across Four Groups

The provocation test outcomes and airway obstruction in the participants are summarized in Table 5. The provocation positive rate and mean PC20 showed no significant differences between the groups (p>0.05). Airway obstruction at baseline (FEV1/FVC<70%) was infrequent, ranging from 1.7% to 7.4% across the groups, with no significant difference (p=0.203). Following provocation, the airway obstruction rates increased, ranging from 4.0% to 25.0%; however, the differences were not statistically significant (p=0.195). Post-bronchodilator airway obstruction rates decreased from 0.0% to 8.0%, with no significant differences (p=0.093).

## Multivariable Logistic Regression Analysis of Factors Associated with Bronchial Hyperresponsiveness

Multivariable logistic regression analysis (Table 6) demonstrated that neither COVID-19 vaccination (adjusted OR 1.06, 95% CI 0.60–1.88, p = 0.838) nor prior SARS-CoV-2 infection (adjusted OR 0.99, 95% CI 0.63–1.55, p = 0.963) was independently associated with methacholine positivity. Smoking was significantly associated with bronchial hyperresponsiveness (adjusted OR 3.33, 95% CI 1.43–7.77, p = 0.005). No significant associations were observed for age, sex, or body mass index. The model demonstrated acceptable calibration (Hosmer–Lemeshow p = 0.717).

**Table 5** Comparison of Provocation Test Outcomes and Airway Obstruction Among Participants Across Four Groups

| | Group 1 (NI-NV) (n=36) | Group 2 (V-NI) (n=163) | Group 3 (NV-I) (n=25) | Group 4 (V-I) (n=116) | P value |
|---|---|---|---|---|---|
| Provocation positive rate (n, %) | 18 (50.0%) | 68 (41.7%) | 7 (28.0%) | 54 (36.7%) | 0.295 |
| PC20 (mg/mL) | 4.4±3.6 | 4.9±3.5 | 4.6±3.3 | 4.0±3.0 | 0.686 |
| Airway obstruction* at Baseline (n, %) | 2 (5.6%) | 12 (7.4%) | 1 (4.0%) | 2 (1.7%) | 0.203 |
| Airway obstruction after provocation (n, %) | 9 (25.0%) | 28 (17.2%) | 1 (4.0%) | 19 (16.4%) | 0.195 |
| Airway obstruction after BD (n, %) | 0 (0.0%) | 13 (8.0%) | 1 (4.0%) | 3 (2.8%) | 0.093 |

**Note**: *Airway obstruction was defined as an FEV1/FVC ratio of less than 70%.
**Abbreviations**: NI-NV, no infection, no vaccination; V-NI, vaccination, no infection; NV-I, no vaccination, infection; V-I, vaccination and infection; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PC20, provocative concentration of methacholine causing a 20% decline in FEV1; BD, bronchodilator.

**Table 6** Multivariable Logistic Regression Analysis of Factors Associated with Bronchial Hyperresponsiveness

| Variable | Adjusted OR (95% CI) | p value |
|---|---|---|
| COVID-19 vaccination | 1.06 (0.60–1.88) | 0.838 |
| Prior SARS-CoV-2 infection | 0.99 (0.63–1.55) | 0.963 |
| Male sex | 1.52 (0.92–2.49) | 0.101 |
| Age (per year) | 1.00 (0.98–1.01) | 0.544 |
| Body mass index | 1.00 (0.95–1.05) | 0.952 |
| Smoking | 3.33 (1.43–7.77) | 0.005 |

**Notes**: Model fit statistics: Hosmer–Lemeshow goodness-of-fit test p = 0.717; Nagelkerke $R^2$ = 0.041.
**Abbreviations**: OR, odds ratio; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Based on post-hoc detectable effect size estimation, the present sample size was sufficient to detect moderate associations (odds ratio approximately ≥1.7). Although small effect sizes cannot be excluded, the absence of significant associations suggests that large or clinically substantial increases in bronchial hyperresponsiveness related to prior infection or vaccination are unlikely.

## Discussion

This study provides real-world clinical evidence by directly evaluating airway hypersensitivity using objective methacholine provocation testing in symptomatic adults with differing histories of SARS-CoV-2 infection and COVID-19 vaccination. In multivariable logistic regression analysis, neither prior infection nor vaccination was independently associated with increased bronchial hyperresponsiveness, whereas smoking emerged as a significant predictor of methacholine positivity. Despite comparable objective airway responsiveness and pulmonary function across groups, symptom severity demonstrated distinct patterns: cough and sputum production were more pronounced in individuals without prior infection or vaccination, dyspnea was greater in those with infection but no vaccination, and wheezing severity was higher in patients with both infection and vaccination. These findings suggest a dissociation between subjective respiratory symptom burden and measurable airway hyperreactivity, providing insight into the evaluation of post-COVID respiratory complaints.

A high proportion of patients with post-COVID-19 report ongoing respiratory symptoms.[12] Among this type of subjects, previous analyses have found that around 40% of these patients with persistent respiratory symptoms test positive for airway hypersensitivity.[13,17] COVID-19 infection has a complex impact on airway inflammation. SARS-CoV-2 contributes to a hyper-proinflammatory immune response in the airways of patients with COVID-19.[18] The exact mechanisms behind the proinflammatory phenotype in the COVID-19 airway remain to be fully understood.[18] Research has shown that the SARS-CoV-2 spike protein enhances small airway inflammatory response.[18] Airway inflammation is known to lead to an increased responsiveness of the airways to various stimuli, contributing to symptoms such as wheezing, coughing, and shortness of breath.[19,20] In some cases, this heightened airway sensitivity and airway remodeling may persist even after recovery, contributing to ongoing respiratory symptoms.[21,22] Symptoms of worsening airway allergies can be very similar to those of COVID-19.[20] Patients and clinicians may often mistake these respiratory symptoms as a simple post-COVID condition, overlooking the potential for underlying airway hypersensitivity. This highlights the critical need for comprehensive evaluation when managing patients with post-COVID-19 respiratory symptoms. Both personal history and environmental factors must be thoroughly considered to differentiate between the long-term COVID effects and other potential causes, such as airway hypersensitivity, to ensure appropriate treatment and management.

A previous study revealed that, regardless of history of COVID-19 vaccination, children with a history of COVID-19 infection had a higher incidence of newly diagnosed asthma compared to non-infected children.[23] This study analyzed asthma rates in a broad pediatric population, including both symptomatic and asymptomatic individuals, after vaccination or infection, concluding that COVID-19 infection significantly increased the likelihood of asthma diagnosis.[23] In contrast, our study specifically examined adults seeking medical attention for persistent respiratory symptoms, analyzing

airway hypersensitivity rates across four groups with varying vaccination and infection histories. Our findings revealed no significant increase in the rate of airway hypersensitivity in patients with COVID-19 infection or those who were vaccinated. The difference in the results between the two studies may be attributed to several factors. A previous study focused on children,[23] whose immune systems and respiratory responses may differ from those of adults. Children and adults may have different levels of exposure to environmental triggers or access to early medical interventions, further influencing the observed outcomes.[24] Second, the pediatric analysis included both symptomatic and asymptomatic children,[23] whereas our research exclusively focused on symptomatic adults, highlighting a substantial difference in study populations. The clinical significance of these two studies lies in their distinct focuses and implications for managing respiratory conditions in different populations. The pediatric study emphasizes the newly diagnosed asthma development in children following COVID-19 infection.[23] Our study underscores the necessity of evaluating airway hypersensitivity in adults presenting with persistent respiratory symptoms after COVID-19 infection or vaccination.

While some studies have suggested that COVID-19 vaccination may reduce the severity and symptoms of the infection, others have raised concerns regarding potential post-vaccination respiratory issues in certain individuals. However, the relationship between COVID-19 vaccination and airway hypersensitivity remains unclear. Several studies have explored the association between COVID-19 vaccinations and other pulmonary diseases such as ILD. Initially, concerns were raised about the potential for COVID-19 vaccination to increase the risk of ILD.[25,26] However, one recent study showed a lower incidence of ILD in vaccinated individuals, contradicting earlier concerns about a strong link between COVID-19 vaccination and ILD.[7] These results indicate that the risk of vaccination-related ILD is not as high as initially feared.[7] Studies on the relationship between COVID-19 vaccination and airway hypersensitivity are lacking, and there are two case reports describing eosinophilic pneumonitis following COVID-19 vaccination.[6] However, the causal link between eosinophilic pneumonia and COVID-19 vaccination remains unclear. In the current study, there was no associated increase in the prevalence of airway hypersensitivity in patients with or without COVID-19 vaccination.

Interestingly, group-specific variations in symptom severity were observed, despite a similar prevalence of airway hypersensitivity across the groups. To date, no published studies have addressed the differences in symptom severity among asthma phenotypes. The differences in symptom severity may be attributed to several factors, including underlying genetic predispositions, environmental factors, and the impact of COVID-19-related immune responses.[27,28] One observation was that patients in Group 1 (NI-NV) had a higher prevalence (41%) of a family history of asthma. Patients with a family history of asthma share similar genetic and environmental factors with their relatives, which may include genes predisposed to asthma and exposure to similar environments.[29] These environmental exposures, often accumulated over time, can lead to chronic, gradual airway inflammation. As a result, individuals may develop a certain level of tolerance for breathlessness without being fully aware of it. In contrast, patients in Groups 3 (NV-I) and 4 (V-I), who had a history of COVID-19 infection, often experienced acute or subacute airway inflammation triggered by viral infections,[18] making them more likely to experience symptoms such as dyspnea and wheezing. This could explain the varying severity of symptoms across different patient groups. Further research is required to elucidate the mechanisms underlying these differences.

It is noteworthy that smoking was identified as a significant predictor of methacholine positivity in our multivariable analysis, further supporting the association between tobacco exposure and bronchial hyperresponsiveness.[30,31] This finding is biologically plausible, as chronic cigarette smoking has been shown to induce airway inflammation, epithelial injury, neural sensitization, and enhanced reflex bronchoconstriction, all of which may increase airway reactivity.[30,31] Experimental and translational evidence demonstrates that chronic smoking promotes airway inflammatory responses and hypersensitivity through both structural and neurogenic mechanisms.[30,31] These pathophysiological effects provide mechanistic support for our observation that smoking, rather than infection or vaccination status, was independently associated with methacholine positivity.

Although the primary findings of this study were largely negative, they carry important clinical implications. In this real-world cohort of symptomatic adults undergoing objective methacholine provocation testing, neither prior SARS-CoV-2 infection nor COVID-19 vaccination was associated with an increased prevalence of airway hypersensitivity. This suggests that persistent respiratory symptoms following infection or vaccination do not necessarily reflect measurable bronchial hyperresponsiveness and may help prevent overdiagnosis of reactive airway disease and unnecessary escalation

of inhalation therapy. Our findings are consistent with previous reports indicating that post-COVID respiratory complaints do not uniformly correlate with objective airway hyperreactivity. A recent provocation study found variable bronchial responsiveness among symptomatic post-COVID adults despite frequent respiratory complaints, highlighting that measurable airway hyperreactivity is not universally present in all symptomatic individuals.[13] Moreover, broader clinical observations of post-COVID respiratory sequelae suggest that persistent symptoms such as dyspnea and cough may arise from multifactorial mechanisms—including deconditioning, dysfunctional breathing, or other physiological changes—rather than classic bronchial hyperreactivity alone.[32] Together, these findings reinforce the importance of objective physiological assessment rather than symptom-based diagnosis in patients presenting with post-COVID respiratory complaints.

## Clinical Implication

The findings of this study have important clinical implications for the management of respiratory symptoms in COVID-19 infection and vaccination. Although COVID-19 infection and vaccination did not significantly affect airway hypersensitivity, the overall prevalence of airway hypersensitivity was approximately 43% in the patients with respiratory symptoms. This underscores the importance of provocation testing for evaluating airway reactivity in patients with persistent respiratory symptoms. Furthermore, the observed group-specific variations in symptom severity emphasized the need for individualized symptom management strategies to effectively address the unique clinical profiles of different patient groups. Additionally, the lower post-bronchodilator FVC in the participants suggests that subtle impairments in lung function may exist, warranting careful pulmonary function monitoring.

## Limitations of the Study

This study has several limitations that should be considered when interpreting its findings. First, the sample sizes of certain groups, particularly Groups 1 (NV-NI) and 3 (NV-I), were relatively small, which may limit the statistical power and generalizability of the results. Because most individuals have been vaccinated or infected, the number of participants in these groups continues to decrease. Additionally, this was a single-center study, which may have introduced potential bias and limited the broader applicability of the results. Furthermore, although the results were predominantly negative, they should be interpreted within the context of the study design. The retrospective nature of the study, unequal group sizes, relatively small sample sizes in certain subgroups, and the potential for residual confounding may have reduced the ability to detect subtle associations. Future prospective multicenter studies with larger cohorts and more comprehensive statistical adjustment would help further validate and refine these observations. Although this study has some limitations, it provides valuable real-world insights into the effects of COVID-19 infection and vaccination on airway hypersensitivity, contributing to a better understanding of respiratory symptoms in this context.

# Conclusions

This study provides real-world clinical evidence regarding the effects of a history of SARS-CoV-2 infection and a history of COVID-19 vaccination on airway hypersensitivity in adults presenting with respiratory symptoms. The findings demonstrated that neither prior infection nor prior vaccination was associated with increased airway hypersensitivity, whereas smoking was identified as a significant predictor of methacholine positivity. Despite similar objective airway responsiveness, distinct group-specific variations in symptom severity were observed. Cough and sputum production were most pronounced in individuals without prior infection or vaccination, dyspnea was most severe in those with infection but no vaccination, and wheezing severity was greater in patients with both infection and vaccination. These findings suggest a dissociation between subjective symptom burden and objective airway hyperresponsiveness, underscoring the importance of comprehensive physiological evaluation in symptomatic patients.

# Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The research protocol was approved by the Ethics Committee of Taipei Tzu Chi Hospital (IRB Number: 13-IRB012), and informed consent was obtained from all participants.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

No potential conflicts of interest are reported by the authors.

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