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ORIGINAL RESEARCH

Non-Pharmaceutical Interventions May Attenuate Acute Exacerbations of Asthma: Experience During the COVID-19 Pandemic in Taiwan

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Background: Non-pharmaceutical interventions (NPIs) were widely used during the coronavirus disease 2019 (COVID-19) pandemic, however their impact on acute asthma exacerbations (AEs) is not well studied.

Methods: We had retrospectively collected patients with asthma AEs between 2019 and 2020 and retrieved data from the Chang Gung Research Database, including clinical manifestations, medications, pulmonary function, clinic and emergency department visits and hospitalizations.

Results: A total of 39,108 adult patients with asthma were enrolled, of whom 1502 were eligible for analysis. The prevalence of acute AEs significantly decreased throughout 2020 compared with 2019 after implementation of the NPI policy. The patients were categorized into four groups: Group 1, acute AEs in 2019 with influenza infection (n=692); Group 2: acute AEs in 2019 without influenza infection (n=328); Group 3: acute AEs in 2020 with influenza infection (n=268); Group 4: acute AEs in 2020 without influenza infection (n=214). The patients in group 4 were significantly older (73.3±29.1 vs 65.5±29.2, 69.7±26.2 years, $p<0.01$) and had significantly worse forced expiratory volume in one second/forced vital capacity ratio (70.5±13.9 vs 79.6±15.5, 72.9±18.0, $p<0.01$) than those in group 1 and 2, and the highest rate of oral corticosteroid prescriptions (17%, $p<0.01$). The patients in group 3 and 4 had significantly lower rates of oxygen therapy, ventilator use and mortality at 3 and 12 months of follow-up than those in group 1 and 2.

Conclusion: The use of NPIs during the COVID-19 pandemic in Taiwan may reduce the frequency and severity of asthma AEs. This may provide some cost-effective strategies to attenuate acute asthma AEs.

Keywords: non-pharmaceutical interventions, asthma, COVID-19

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global health crisis.[1–4] To prevent the spread of SARS-CoV-2 infection, non-pharmaceutical interventions (NPIs) were implemented worldwide, including public masking, regular hand hygiene and social distancing.[2,4] The infection control policy for people visiting hospitals in Taiwan was stricter than in the general population, including taking travel, occupation, contact, and cluster history. In addition, patients visiting the emergency department with fever were required to undergo a polymerase chain reaction (PCR) test for SARS-CoV-2, suspected cases were isolated, and alcohol sanitizers were placed at hospital entrances, elevators, and crowded areas.[3] These NPIs may not only have reduced SARS-CoV-2 infection, but also decreased exposure to other pathogens.

Environmental exposure to air pollutants (eg, tobacco smoke, NO_2 and diesel fuel), allergens, viruses, fungi and bacteria may aggravate the exacerbations of asthma,[5] and many respiratory viruses including seasonal influenza, respiratory syncytial virus, human rhinovirus, metapneumovirus, parainfluenza, and coronavirus, are major drivers of

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acute asthma exacerbations (AEs).[6–10] Pathogenic bacteria (*Streptococcus pneumoniae, Moraxella catarrhalis, and Haemophilus influenza*) are also associated with AEs,[5] and the influenza vaccine has been demonstrated to substantially reduce influenza-triggered asthma attacks.[11]

While protecting people from SARS-CoV-2, the NPIs employed during the COVID-19 pandemic in Taiwan may also have reduced environmental and pathogen exposure, and thereby alleviated AEs. Since few studies have investigated this issue, the aim of this study was to assess the impact of NPIs during the COVID-19 pandemic in Taiwan on acute AEs.

Methods

This research was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval no. CGMH 202001074B0). A waiver for written consent was obtained due to the retrospective nature of this study, along with no modifications in patient management. All personal information is encrypted in the hospital's database, and all accessed patient data were de-identified. There were no breaches of privacy.

NPIs During the COVID-19 Pandemic in Taiwan

COVID-19 was first identified in Wuhan, China, in December 2019, and was declared a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020.[1] The Taiwanese Government implemented an NPI policy in January 2020, which included wearing a mask in public, social distancing, and hand and surface hygiene. In addition, strict hospital visitor restrictions were put in place, including the use of outdoor triage tents, travel, occupation, contact, and cluster history, PCR for SARS-CoV-2 tests for those with a fever, and isolation of suspected cases.[3,4]

Data Source

The Chang Gung Research Database (CGRD) is the electronic medical records database of the Chang Gung Medical Foundation, which is the largest hospital system in Taiwan, comprising three medical centers and four regional hospitals located around Taiwan (http://www.chang-gung.com/en/index.aspx). We used the CGRD to obtain data on patients with asthma from January 1, 2019 to December 31, 2020.

Adult AE Cohort

Data of patients with an asthma diagnosis according to the International Classification of Diseases (ICD-10) code were retrieved from the CGRD. Patients aged ≥20 years with at least two primary asthma diagnoses on different dates during outpatient visits or one diagnosis during hospitalization (at least 12 months follow-up) were included in the asthma cohort. Among these patients, those who had unscheduled outpatient clinic visits with short-term prescriptions (< 7 days) for systemic steroids, and those who visited the emergency department or were hospitalized with a main diagnosis of AE were included in this study. The exclusion criteria were patients who: (1) were not followed in the pulmonary subspecialty clinic for asthma, (2) were not tested for influenza infection (influenza A, B RNA reverse transcription (RT)-PCR), (3) had incomplete medical records, and (4) missed follow-up visits. Data on age, sex, body mass index (BMI), medication history, and comorbidities were obtained from the CGRD, along with laboratory data including serum IgE test results, eosinophil cationic protein levels, and blood eosinophil count during exacerbations. Spirometric parameters and Asthma Control Test (ACT) scores were recorded. Asthma severity was assessed using the Global Initiative for Asthma (GINA) 2020 guidelines.

Diagnosis of Influenza Infection

Respiratory specimens were collected by physicians using nasopharyngeal swabs and sent to the laboratory within 30 minutes of sampling, where they were processed by trained technicians according to manufacturers' instructions. All patients were tested with the QuickVue influenza A + B test (Quindal, San Diego, CA), a commercially available lateral-flow immunoassay. For RT-PCR, viral RNA was extracted using a MagNA PURE Autoextractor with MagNA Pure LC Total Nucleic Acid Isolation Kit (Roche Diagnostics, Mannheim, Germany). Extracted nucleic acid was amplified using

an ABI 7000/7900 instrument with a commercial kit, TaqMan one-step RT-PCR mix reagent (Applied Biosystems, Foster City, CA). Detailed methods have been previously described.[12,13]

Definitions of Severity and Exacerbation

The severity of asthma was defined according to the GINA 2020 criteria. An acute AE was defined as an event that was clinically diagnosed by a physician and required a systemic steroid prescription for the acute onset of an increasing cough, worsening dyspnea, and chest tightness (www.ginasthma.com). We recorded acute AE events, along with emergency department visits, hospitalizations, respiratory failure events due to acute AEs, and all-cause mortality. Each patient was followed for 1 year.

Statistical Analysis

Categorical variables were described as count (percentage), and parametric data were expressed as mean ± standard deviation. We used analysis of variance and the Student's *t*-test to compare numerical data, and the chi-square test to compare independent categorical data. We compared the risks of requiring ventilation and all-cause mortality between groups using a Cox proportional hazards regression model. A p value < 0.05 was considered statistically significant. Data processing and analyses were performed using SAS Enterprise Guide version 7.1 (SAS Institute, Inc).

Results

Study Population

In total, 39,108 patients with at least two outpatient visits or one inpatient record between 2019 and 2020 in the CGRD were included in our asthma cohort. After applying the aforementioned exclusion criteria, a total of 1502 patients were included for analysis (Figure 1). After implementation of the NPI policy in Taiwan, the rates of acute AEs, outpatient clinic visits, emergency department visits, and inpatient admissions all significantly decreased throughout 2020 compared with 2019 (Figure 2). Asthmatics experienced AE with influenza test in 2019 was 1020 and was 482 in 2020. Total asthma exacerbation in 2019 was 14055, and was 8885 in 202. Influenza test done in 2019 was 7.26% and was 5.42% in 2020 for all asthma subjects. The patients were further categorized based on the year and presence of influenza infection into four groups: Group 1, acute AEs in 2019 with influenza infection (n=692); Group 2: acute AEs in 2019 without influenza infection (n=328); Group 3: acute AEs in 2020 with influenza infection (n=268); and Group 4: acute AEs in 2020 without influenza infection (n=214) (Figure 1). None of them had COVID-19 infection.

Clinical Characteristics

The patients' characteristics are summarized in Table 1. Despite the decrease in acute AEs, the patients in group 4 were significantly older than those in group 1 and 2 (73.3±29.1 vs 65.5±29.2, 69.7±26.2 years, $p < 0.01$). More male patients had acute AEs in 2020 ($p < 0.01$). The patients in group 4 had significantly worse forced expiratory volume in one second/forced vital capacity (FEV1/FVC) ratio than those in group 1 and 2 (70.5±13.9 vs 79.6±15.5, 72.9±18.0, $p < 0.01$). The patients in group 2 had a significantly higher eosinophil count during acute AEs than group 1 and group 3 (78.3±173 vs 39.0±124.8 and 52.5±168.0, $p < 0.01$). The patients in group 1 and 2 had significantly higher rates of allergic rhinitis than those in group 4 (50% and 55% vs 39%, $p < 0.01$). The patients in group 3 and 4 had significantly higher rates of montelukast prescriptions than those in group 1 and 2 (25% and 22% vs 15% and 10%, $p < 0.01$). The patients in group 4 had the highest rate of long term (> 6 months) oral corticosteroid (OCS) prescriptions (17%, $p < 0.01$), while the patients in group 1 had the lowest rate of long-acting muscarinic agonist prescriptions (6%, $p < 0.01$). There were no significant differences in GINA stepwise therapy, ACT score, the use of biologic agents (omalizumab, mepolizumab) and clarithromycin among the four groups.

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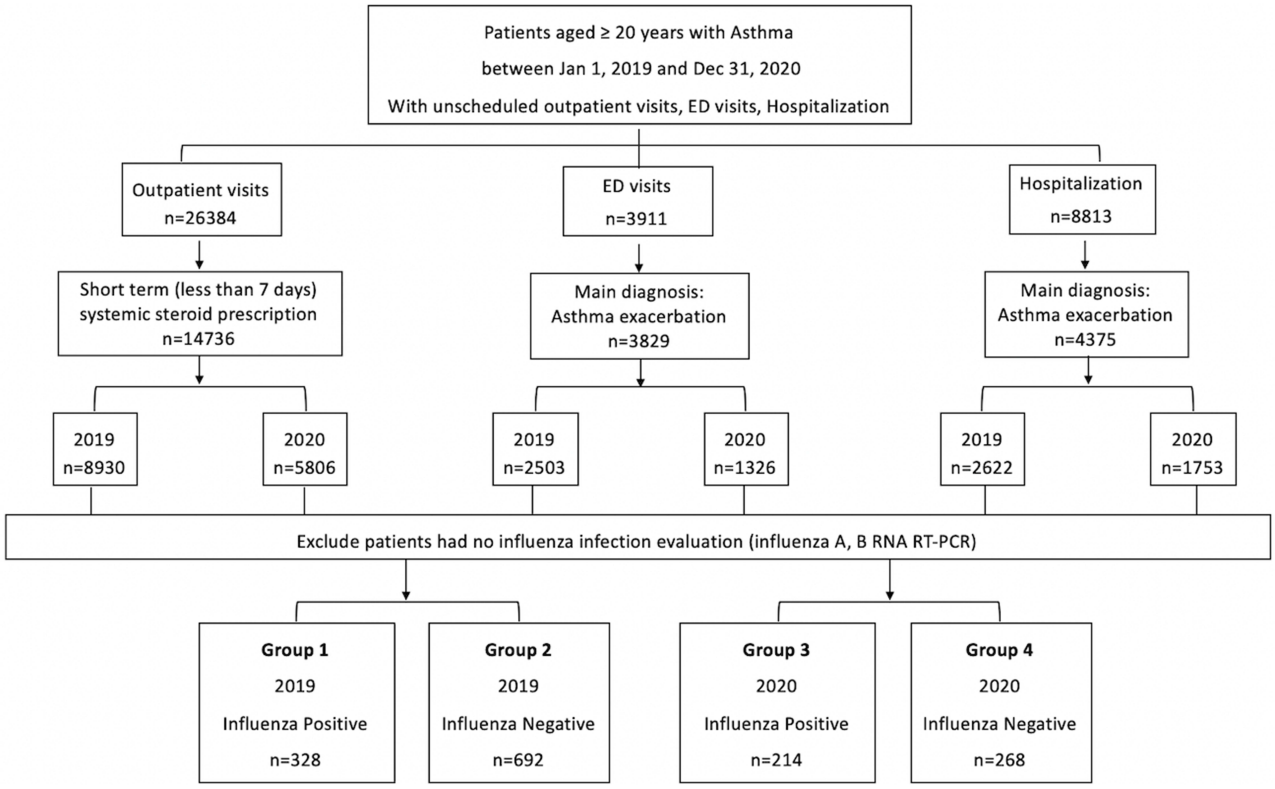

Figure 1 Flow chart of participant enrollment.
Notes: Group 1, acute AEs in 2019 with influenza infection (n=692); Group 2: acute AEs in 2019 without influenza infection (n=328); Group 3: acute AEs in 2020 with influenza infection (n=268); Group 4: acute AEs in 2020 without influenza infection (n=214).
Abbreviations: AE, asthma exacerbation.

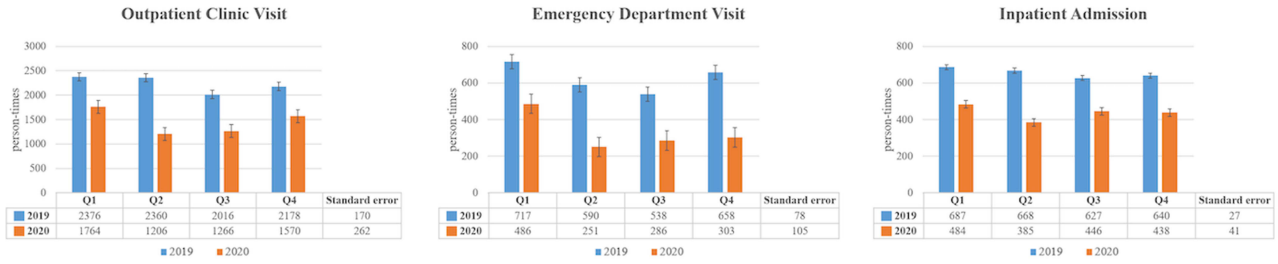

Figure 2 Comparison of acute asthma exacerbation rates by season in 2019 and 2020.
Notes: Q1: January to March; Q2: April to June; Q3: July to September; Q4: October to December.

Severity of Asthma AEs

Age (every 5 year-old) was an independent risk factor for oxygen therapy, ventilator use and mortality at 3 and 12 months of follow-up (hazard ratio (HR): 1.03 and 1.07, $p < 0.01$; hazard ratio (HR): 1.02 and 1.03, $p < 0.01$; hazard ratio (HR): 1.02 and 1.03, $p < 0.01$, Tables 2–4). The patients in group 3 and 4 had significantly lower rates of oxygen therapy (month 3: HR: 0.04, $p < 0.01$ and HR: 0.07, $p < 0.01$; month 12: HR: 0.17, $p < 0.01$ and HR: 0.19, $p < 0.01$, respectively), ventilator use (month 3: HR: 0.01, $p < 0.01$ and HR: 0.02, $p < 0.01$; month 12: HR: 0.06, $p < 0.01$ and HR: 0.09, $p < 0.01$, respectively) and mortality (month 3: HR: 0.01, $p < 0.01$ and HR: 0.01, $p < 0.01$; month 12: HR: 0.03, $p < 0.01$ and HR: 0.05, $p < 0.01$, respectively) at 3 and 12 months of follow-up (Tables 2-4). The patients with OCS prescriptions were correlated with an increased risk of oxygen therapy at 12 months (HR: 1.30, $p = 0.01$), while those with long-acting muscarinic agonist prescriptions had a higher risk of requiring ventilation at 12 months (HR: 1.23, $p = 0.02$).

Table 1 Clinical Characteristics of the Study Groups

Characteristic	Group 1 (n=328)	Group 2 (n=692)	Group 3 (n=214)	Group 4 (n=268)	P value
Age, year	65.5±29.2	69.7±26.2	68.3±31.2	73.3±29.1	<0.01
Male, n (%)	105 (32)	256 (37)	98 (46)	109 (41)	<0.01
BMI, kg/m^2	25.9±6.2	25.2±6.6	25.6±6.6	25.3±5.8	0.51
Smoking history, n (%)	32 (14)	84 (14)	36 (21)	36 (15)	0.13
FEV1, % of predict	69.3±26.6	63.0±28.0	68.5±26.0	63.0±31.8	0.14
FVC, % of predict	75.0±34.4	68.0±27.5	68.3±28.5	68.0±24.0	0.26
FEV1/FVC (%)	79.6±15.5	72.9±18.0	76.5±14.2	70.5±13.9	<0.01
IgE, IU/mL	79.0±261.6	87.0±276.0	129.0±361.7	115.0±419.6	0.13
ECP, μg/L	8.4±12.2	9.09±15.6	7.7±10.7	10.6±20.9	0.60
ACT	22±5	23±4	24±6.5	22±4.5	0.50
EOS in AE, counts/μL	39.0±124.8	78.3±173	52.5±168.0	71.7±181.8	<0.01
Allergic rhinitis, n (%)	164 (50)	314 (45)	117 (55)	104 (39)	<0.01
GERD, n (%)	117 (36)	230 (33)	84 (39)	104 (39)	0.25
GINA step					0.10
Step 1–3, n (%)	257 (78.4)	511 (73.8)	149 (69.6)	191 (71.3)	
Step 4–5, n (%)	71 (21.7)	181 (26.2)	65 (30.4)	77 (28.7)	
Medication					
Montelukast, n (%)	49 (15)	72 (10)	54 (25)	59 (22)	<0.01
High dose ICS, n (%)	56 (17)	159 (23)	44 (21)	52 (19)	0.17
Long-term OCS, n (%)	27 (8)	73 (11)	24 (11)	45 (17)	<0.01
LAMA, n (%)	20 (6)	85 (12)	31 (14)	42 (16)	<0.01
Omalizumab, n (%)	5 (2)	8 (1)	5 (2)	2 (1)	0.44
Mepolizumab, n (%)	0 (0.00)	1 (0.1)	1 (0.5)	3 (1.1)	0.08
Clarithromycin, n (%)	7 (2.1)	16 (2.3)	8 (3.7)	7 (2.6)	0.66

Notes: Group 1: AE in 2019 with influenza infection; Group 2: AE in 2019 without influenza infection; Group 3: AE in 2020 with influenza infection; Group 4: AE in 2020 without influenza infection.
Abbreviations: AE: acute exacerbation; BMI: body mass index; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity; ECP, Eosinophil Cationic Protein; IgE, Immunoglobulin E; EOS, eosinophil; ACT, asthma control test; GERD, Gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, Long-acting β2 Sympathomimetic Agonists; OCS, Oral corticosteroids; LAMA, Long-acting muscarinic agonist.

Table 2 Multivariate Analysis of 3-month and 12-month Oxygen Therapy Use

	3m HR (95% CI)	p-value	12m HR (95% CI)	p-value
Age (5 year-old)	1.03 (1.01–1.05)	<0.01	1.07 (1.06–1.09)	<0.01
Gender	1.03 (0.91–1.16)	0.69	0.97 (0.85–1.1)	0.60
EOS counts	1.00 (1.00–1.00)	0.33	1.00 (1.00–1.00)	0.88
Group 1	1.00		1.00	
Group 2	0.88 (0.75–1.02)	0.08	0.97 (0.83–1.13)	0.69
Group 3	0.04 (0.03–0.06)	<0.01	0.17 (0.14–0.21)	<0.01
Group 4	0.07 (0.05–0.09)	<0.01	0.19 (0.15–0.25)	<0.01
Montelukast	0.85 (0.71–1.01)	0.06	0.88 (0.74–1.05)	0.17
Long-term OCS	1.02 (0.83–1.24)	0.86	1.30 (1.06–1.59)	0.01
LAMA	1.06 (0.87–1.29)	0.60	1.20 (0.98–1.47)	0.07

Notes: Group 1: AE in 2019 with influenza infection; Group 2: AE in 2019 without influenza infection; Group 3: AE in 2020 with influenza infection; Group 4: AE in 2020 without influenza infection.
Abbreviations: EOS, eosinophil; OCS, Oral corticosteroids; LAMA, Long-acting muscarinic agonist.

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Table 3 Multivariate Analysis of 3-month and 12-month Ventilator Use

	3m HR (95% CI)	p-value	12m HR (95% CI)	p-value
Age (5 year-old)	1.02 (1.00–1.03)	0.02	1.03 (1.02–1.05)	<0.01
Gender	1.04 (0.92–1.16)	0.54	1.00 (0.90–1.12)	0.96
EOS counts	1.00 (1.00–1.00)	0.23	1.00 (1.00–1.00)	0.45
Group 1	1.00		1.00	
Group 2	0.95 (0.82–1.10)	0.49	0.99 (0.86–1.14)	0.90
Group 3	0.01 (0.01–0.02)	<0.01	0.06 (0.05–0.08)	<0.01
Group 4	0.02 (0.01–0.03)	<0.01	0.09 (0.07–0.12)	<0.01
Montelukast	0.90 (0.76–1.05)	0.18	0.92 (0.78–1.07)	0.28
Long-term OCS	0.93 (0.78–1.11)	0.41	1.06 (0.89–1.26)	0.53
LAMA	1.11 (0.93–1.32)	0.26	1.23 (1.03–1.46)	0.02

Notes: Group 1: AE in 2019 with influenza infection; Group 2: AE in 2019 without influenza infection; Group 3: AE in 2020 with influenza infection; Group 4: AE in 2020 without influenza infection.
Abbreviations: EOS, eosinophil; OCS, Oral corticosteroids; LAMA, Long-acting muscarinic agonist.

Table 4 Multivariate Analysis of 3-month and 12-month Mortality

	3m HR (95% CI)	p-value	12m HR (95% CI)	p-value
Age (5 year-old)	1.02 (1.00–1.03)	0.04	1.03 (1.01–1.04)	<0.01
Gender	1.02 (0.91–1.14)	0.78	1.02 (0.91–1.13)	0.79
EOS counts	1.00 (1.00–1.00)	0.17	1.00 (1.00–1.00)	0.36
Group 1	1.00		1.00	
Group 2	0.92 (0.80–1.06)	0.25	0.96 (0.83–1.10)	0.52
Group 3	0.01 (0.01–0.01)	<0.01	0.03 (0.02–0.05)	<0.01
Group 4	0.01 (0.01–0.02)	<0.01	0.05 (0.04–0.07)	<0.01
Montelukast	0.88 (0.75–1.02)	0.09	0.86 (0.74–1.01)	0.06
Long-term OCS	0.88 (0.74–1.05)	0.15	0.94 (0.79–1.11)	0.45
LAMA	1.08 (0.91–1.27)	0.39	1.13 (0.96–1.34)	0.14

Notes: Group 1: AE in 2019 with influenza infection; Group 2: AE in 2019 without influenza infection; Group 3: AE in 2020 with influenza infection; Group 4: AE in 2020 without influenza infection.
Abbreviations: EOS, eosinophil; OCS, Oral corticosteroids; LAMA, Long-acting muscarinic agonist.

Discussion

To the best of our knowledge, this multi-institution observational study is the first to investigate the impact of NPIs on asthma AEs during the COVID-19 pandemic in Taiwan. The prevalence of acute AEs reduced throughout 2020 after the NPI policy had been widely implemented compared to 2019. The patients who had acute AEs in 2020 were significantly older, predominantly male, and had a higher rate of montelukast prescriptions. Moreover, the severity of acute AEs was significantly attenuated in 2020 after implementation of the NPI, as evidenced by the lower risks of short-term and long-term oxygen therapy, ventilator use and mortality.

NPIs were widely implemented worldwide during the COVID-19 pandemic to slow transmission of the SARS-CoV-2 virus.[14] The use of NPIs has been associated with attenuation in other respiratory pathogens and infectious diseases by blocking the transmission route, including influenza, bacterial pneumonia, and even airway pneumococcal carriage.[14–17] In China, the NPI policy had different intensity levels, from initially stringent restrictions on human movement to the reopening of schools, businesses and resumption of recreational activities.[16] Geng et al reported that the incidence of respiratory diseases was still relatively low compared to gastrointestinal and enteroviral diseases after the NPIs had become less stringent.[16] Both indoor and outdoor air pollution had impacts in asthmatics, including impaired pulmonary function and exacerbation.[18] For patients with asthma, these NPIs may not only have attenuated airway pathogen-related infections, but also decreased environmental air pollution and exposure to allergens, thereby further reducing the risk of acute AEs.[5] Our findings are consistent with this hypothesis. After implementation of the NPI policy in Taiwan (public masking, regular hand hygiene and social distancing), the prevalence of acute AEs significantly decreased throughout

2020 compared with 2019. This decrease in the prevalence of acute AEs was also associated with a lower severity of acute AEs, as evidenced by significant decreases in the rates of oxygen therapy, respiratory failure, and even mortality. The precise mechanism between the reduction in acute AEs and implementation of NPIs is unclear. Stringent NPIs may have greatly reduced the prevalence of infectious diseases, but may also have had a significantly negative socioeconomic impact. Less stringent NPIs, such as public masking, regular hand hygiene in Taiwan and Phase IV in China,[16] may have provided adequate protection from exposure to respiratory pathogens in patients with asthma.

Acute AEs have a strong negative impact in terms of increased health care costs, impaired quality of life, greater loss of lung function, acute care visits and hospitalizations.[19] Many factors can trigger acute AEs, including sex, age, lung function, smoking history, and exposure to respiratory viruses.[20] Whether these factors contribute to frequent AEs is unclear. Viral infections in the upper airway trigger the majority of AEs.[5,20,21] Theoretically, asthmatics with Th2-predominant inflammation would be more susceptible to viral infection, and those with increased Th1 responses have been associated with mild colds and rapid clearance of viruses.[7,9] However, the clinical association between exacerbation-prone asthma and viral infection remains unknown. Peters et al recently prospectively analyzed 3 years of AE data, and found that patients with exacerbation-prone asthma were characterized by lower FEV1 and significantly higher plasma IL-6 levels, but no correlation was found with blood eosinophil count.[7] In contrast, Denlinger et al found that the frequency of acute AEs was associated with blood eosinophil count, BMI, bronchodilator responsiveness, chronic sinusitis and gastroesophageal reflux.[20,22] In the current study, after the NPIs had probably attenuated the effect of airway pathogen-related infections, the older patients, those with worse FEV1/FVC, and those with OCS prescriptions still had acute AEs even without influenza infection. Although blood eosinophil levels were different between our patient groups, the levels were much lower than in previous reports,[7,20] and this may have affected correlations. This may be due to the retrospective nature of our study and may represent selection bias. Nevertheless, smoking status, BMI, serum IgE levels, ACT scores, GINA stepwise therapy, and gastroesophageal reflux were not different between groups. These finding suggest that the NPIs may have attenuated acute AEs by reducing exposure to environmental air pollutants, allergens and airway pathogens. However, the benefits of NPIs may not be significant in older asthmatics with worse lung function and those dependent on OCS therapy.

The prevention of acute AEs remains a major unmet need in asthma management. Better understanding of the pathogenesis of acute AEs will likely lead to precise prevention strategies, such as influenza vaccination to protect asthmatics from seasonal influenza.[10,11] Acute AEs occur more frequently in patients with severe asthma, and an increasing number of studies are investigating preventative strategies with biologics such as anti-IgE and anti-IL-5.[19,23] During the COVID-19 pandemic, NPIs such as wearing face masks and frequent hand hygiene may have attenuated exposure and transmission of airway pathogens, allergens, and air pollutants. Our findings demonstrate that the NPI policy in Taiwan may have been a cost-effective strategy in mitigating SARS-CoV-2 infection, and may attenuating both the frequency and severity of acute AEs.

Some limitations to this study should be acknowledged. First, data were obtained from 2019 and 2020 during the COVID-19 pandemic, and hence there may be uncertainty in health service utilization. Some patients with less severe symptoms of acute AEs may hesitate or not have visited the clinic for medications. This may have led to overestimation in our results. Moreover, the rate of influenza PCR test were relatively low, and the flu detection rate may have varied according to the virus detection methodology and sampling skill of the physician. Thus, the prevalence of influenza infection may not be accurate. However, in addition to the significant reduction in the prevalence of acute AEs, the incidence of serious and life-threatening acute AEs was also greatly reduced, including oxygen therapy, ventilator use and even mortality. This suggests that NPIs may at least have had a clinical benefit in the patients with severe acute AEs. Second, patients were identified using ICD coding, and some patients may have been missed if their ICD coding was incorrect. Third, this was a retrospective study, and information on some parameters was lacking or incomplete in the CGRD. However, data in the CGRD are derived from patients registered at Chang Gung Memorial Hospital, the largest hospital system comprising medical centers and regional hospitals across Taiwan, and hence the database contains comprehensive data on a relatively large number of patients. The strength of this study is that it is the first and largest study focusing on the clinical benefits of NPIs in Taiwan in patients with acute AEs. Over time, the NPIs became less

stringent, and the benefit on acute AEs is unknown after 2020. Further studies are warranted to validate our results and investigate whether the NPIs continued to have a beneficial effect on acute AEs after this date.

In summary, NPIs during the COVID-19 pandemic in Taiwan may attenuated both the prevalence and severity of acute AEs. Although this benefit was not significant in older patients, those with worse lung function, and those dependent on OCS therapy, NPIs may provide some cost-effective strategies to attenuate asthma AE.

Abbreviations

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; CGRD, Chang Gung Research Database; ICD, International Classification of Diseases; GINA, Global Initiative for Asthma; AE, asthma exacerbation; ACT, Asthma Control Test; OCS, oral corticosteroid; BMI, body mass index.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Review Committee of Chang Gung Medical Foundation (IRB number: 202001074B0). The Chang Gung Research Database has granted access to the database. Written informed consent for participation was not required for this study in accordance with national legislation and the institutional requirements.

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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

The authors declare that they have no competing interests in this work.

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