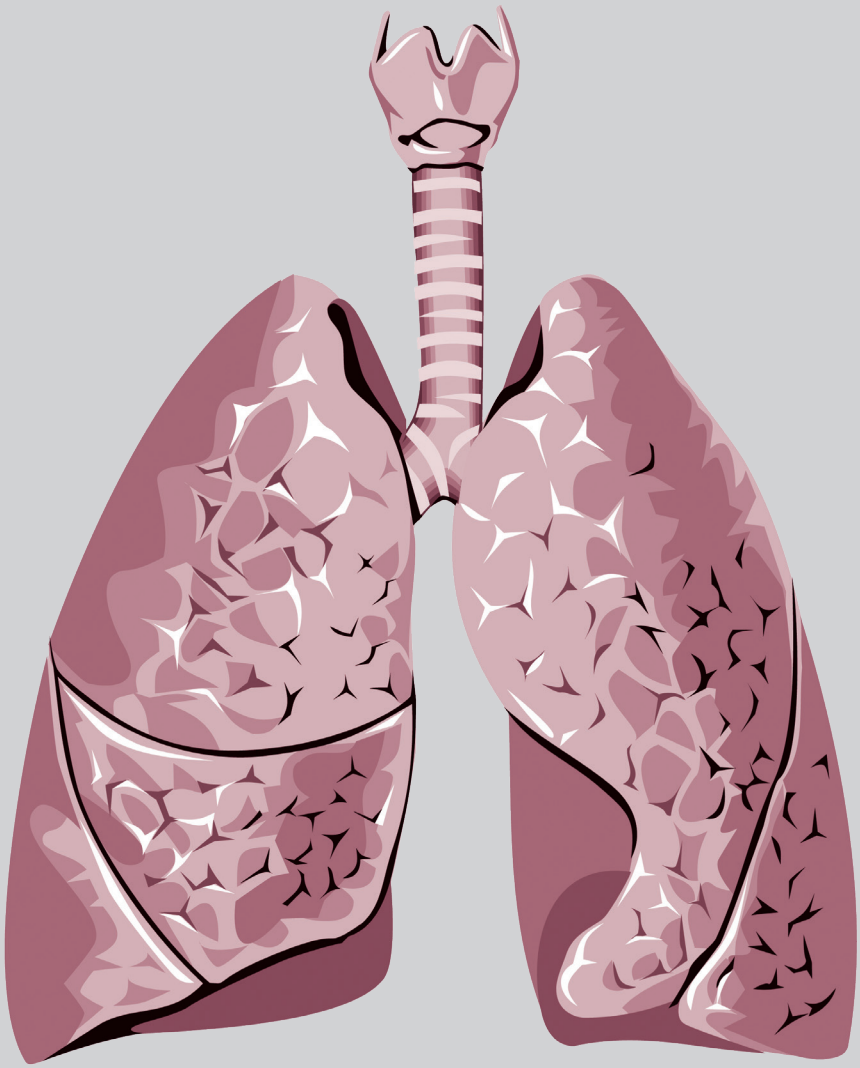
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Successful Weaning Predictive Model for Respiratory Care Center Patients

Tse-Yu Chen[1], Tsu-Hsuan Weng[2], Mei-Fen Lu[3], Chia-Hsin Liu[4], Chih-Hao Shen[4], Chen-Liang Tsai[4], Chung-Kan Peng[4], Ming-Tsung Chen[4]

Introduction: Mechanical ventilation (MV) is a critical support technique in intensive care medicine, and an appropriate weaning strategy is essential for patient outcomes. This study investigated key factors influencing successful weaning, using statistical analyses of demographic variables, clinical indicators, and nutritional status. Additionally, we developed a predictive model using logistic regression to support clinical decision-making.

Methods: This study employed a retrospective data analysis approach, using statistical tests to compare differences between weaning success and failure groups and applying multiple logistic regression to evaluate the impact of various factors. We analyzed data from patients who underwent MV for ≥14 days and were transferred to the respiratory care center (RCC) with endotracheal tube between January 1, 2023 and December 31, 2023. Data were collected from RCC-admitted patients and included variables such as age, sex, BMI, comorbidities, and other clinical parameters.

Results: A total of 100 patients on MV with an endotracheal tube were included in the study. Sixty-four successfully weaned patients had a lower APACHE II score, and higher albumin levels at RCC admission. In addition, unsuccessfully weaned patients had a longer duration of RCC stay and ventilator use. Factors associated with successful weaning included BMI, albumin levels, comorbidities, and the rapid shallow breathing index.

Conclusion: Patients admitted to the RCC remained critically ill and required comprehensive care. We found that BMI, albumin levels, comorbidities, and the rapid shallow breathing index at the RCC were important factors influencing ventilator weaning. Based on these predictors, we developed a predictive model to assist in extubation decisions. ***(Thorac Med 2026; 41: 143-152)***

Key words: Respiratory care center, mechanical ventilation, weaning

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Introduction

Mechanical ventilation (MV) plays a crucial role in the treatment of patients with acute or chronic respiratory failure. However, prolonged use of MV may lead to several adverse outcomes. Long-term ventilator dependence can result in disuse atrophy of respiratory muscles, thereby impairing spontaneous breathing ability and reducing the success rate of ventilator weaning [1-2]. Furthermore, MV entails significant use of healthcare resources, including personnel, equipment, and hospital stay, imposing a substantial financial burden on both the families and the healthcare system [3]. Therefore, successful weaning from MV has become a critical clinical objective.

To address the increasing demand for the care of long-term ventilator-dependent patients, Taiwan implemented the Integrated Delivery System under the National Health Insurance policy in 2000. Under this framework, patients who have received MV in the intensive care unit (ICU) for more than 21 days and meet transfer criteria may be transferred to a respiratory care center (RCC), where they receive up to 42 days of subacute care aimed at ventilator weaning. RCCs cater to clinically stable patients who remain dependent on MV, thereby reducing ICU occupancy and enhancing healthcare resource efficiency. Patients who do not achieve successful weaning are further transferred to a respiratory care ward (RCW) or a long-term care facility. This tiered care model serves as a critical component of Taiwan's strategy for managing chronic ventilator users. The Tri-Service General Hospital, a tertiary medical center in northern Taiwan, operates a 24-bed RCC staffed by a multidisciplinary team that provides weaning and supportive care for patients with prolonged MV (PMV).

Numerous studies have investigated clinical indicators and predictive factors related to ventilator weaning to facilitate the early identification of high-risk patients and optimize care strategies. Commonly reported predictors include physiological markers such as the rapid shallow breathing index (RSBI) and respiratory muscle load indices [4-5], nutritional indicators such as serum albumin levels and muscle strength [6-8], and severity or comorbidity scores including APACHE II and the Glasgow Coma Scale (GCS) [8]. Unlike previous studies, which have predominantly focused on ICU data to assess ventilator weaning outcomes [4-5, 7-8], this research centered on data from the RCC phase, offering insights into the subacute weaning process. This study aimed to investigate the clinical factors associated with successful weaning from MV in patients admitted to the RCC. By focusing on RCC data, this study addresses an important gap in the existing literature and provides a deeper understanding of weaning success during the subacute phase, extending beyond the ICU setting.

Methods

Study population

This study included all adult patients who received MV via an endotracheal tube for at least 14 days and were subsequently transferred to the RCC between January 1, 2023 and December 31, 2023. Successful weaning was defined as being free from MV for 5 or more consecutive days. The patients were divided into 2 groups depending on whether they were successfully weaned or not.

Data collection and clinical outcomes

The medical records of each patient were reviewed, and baseline characteristics were collected during their initial admission to the RCC. These characteristics included age, sex, BMI, APACHE II score, and albumin levels. Additionally, we recorded the underlying diseases and weaning parameters, such as RSBI and maximum inspiratory pressure (Pimax), before liberation from MV. Clinical outcomes included weaning rate and an analysis of the favorable weaning characteristics and indices of RCC patients who were successfully weaned from the ventilator. The completeness of all included variables, with no missing data, was guaranteed by the mandatory fields within the structured electronic medical records utilized for RCC admission and respiratory evaluation.

Statistical analysis

All data are presented as mean ± standard deviation (SD) or percentage. The Mann Whitney U test was used to analyze and compare continuous variables between the 2 groups, while Pearson's χ^2 test or Fisher's exact test was applied to categorical variables. Logistic regression was used to perform both univariate and multivariate analyses to identify variables associated with weaning success. A predictive model for successful weaning was then constructed using these factors, and model validation was carried out by generating a receiver operating characteristic (ROC) curve. All analyses were performed using SPSS software, version 26 (SPSS Inc., Chicago, IL, USA). A *p*-value < 0.05 was considered statistically significant for 2-sided tests. In addition, a post hoc power analysis was conducted using G*Power (version 3.1.9.7). Based on the observed odds ratio of 4.97 for serum albumin, with a weaning success probability of 64%, $\alpha = 0.05$, and an assumed R^2 of 0.2 among predictors, the calculated statistical power was 0.99, indicating sufficient power to detect large effect sizes.

Results

From January 1, 2023, to December 31, 2023, a total of 100 patients requiring endotracheal intubation and MV were transferred to our RCC and enrolled in this study. Of these, 64 (64%) were successfully weaned from MV and 36 (36%) experienced weaning failure. The average length of time in the RCC for these patients was 20.67 ± 11.89 days, and 24 (24%) patients had tracheostomy. The successful weaning rate was 64%. Patient characteristics, demographics, laboratory data, and physiological and clinical variables are shown in Table 1. The mean

Table 1. Characteristics of Study in the Baseline.

	Overall		Weaning success		Weaning failure		*p-value*
	n	%	n	%	n	%	
Total	100		64	64.00	36	36.00	
Age	70.82 ± 14.84		69.52 ± 14.27		73.15 ± 15.75		0.139
Sex							0.831
Male	61	61.00	40	62.5	21	58.3	
Female	39	39.00	24	37.5	15	41.7	

Height		162.10 ± 9.61		162.62 ± 9.58		161.17 ± 9.73		0.555
Weight		62.91 ± 16.97		61.86 ± 15.71		64.77 ± 19.12		0.672
BMI		23.76 ± 5.26		23.25 ± 4.97		24.68 ± 5.70		0.293
APACHE II score at RCC admission		19.96 ± 4.98		19.23 ± 4.98		21.25 ± 4.78		0.030
Glasgow Coma Scale at RCC admission		8.46 ± 2.10		8.70 ± 1.93		8.03 ± 2.34		0.123
Albumin at RCC admission		3.22 ± 0.48		3.33 ± 0.49		3.03 ± 0.40		0.002
Ventilator period before RCC (day)		25.56 ± 22.06		22.64 ± 19.03		30.75 ± 26.10		0.001
Ventilator period RCC (day)		17.27 ± 12.19		13.56 ± 9.85		23.86 ± 13.27		< 0.001
Total days on mechanical ventilation		42.83 ± 27.21		36.20 ± 23.46		54.61 ± 29.68		< 0.001
RCC length of stay (day)		20.67 ± 11.89		18.88 ± 10.74		23.86 ± 13.27		0.040
Tracheostomy								0.626
	without	76	76.00	50	78.10	26	72.20	
	with	24	24.00	14	21.90	10	27.80	
Comorbidities								
Chronic lung diseases								0.161
	without	85	89.47	60	93.40	30	82.40	
	with	10	10.53	4	6.60	6	17.60	
Hypertension								0.297
	without	54	56.84	33	50.80	14	38.20	
	with	41	43.16	31	49.20	22	61.80	
Coronary artery disease								0.775
	without	80	84.21	55	85.90	30	83.30	
	with	15	15.79	9	14.10	6	16.70	
Stroke								0.999
	without	73	76.84	49	77.00	28	76.50	
	with	22	23.16	15	23.00	8	23.50	
Chronic kidney disease								0.138
	without	74	77.89	53	82.00	25	70.60	
	with	21	22.11	11	18.00	11	29.40	
Cancer								0.626
	without	71	74.74	50	81.20	26	72.20	
	with	24	25.26	14	18.80	10	27.80	
Diabetes Mellitus								0.522
	without	58	61.05	41	63.90	20	55.90	
	with	37	38.95	23	36.10	16	44.10	
Weaning profile								
Pimax		-29.26 ± 10.00		-30.25 ± 9.51		-27.41 ± 10.77		0.324
RSBI		87.65 ± 68.94		73.45 ± 37.41		113.55 ± 100.12		0.159

BMI: body mass index; RCC: respiratory care center; Pimax: maximum inspiratory pressure; RSBI: rapid shallow breathing index

age of the study population was 70.82 ± 14.84 years. Patients in the successful weaning group had a slightly lower mean age (69.52 ± 14.27 years) than the failed weaning group (73.15 ± 15.75 years), although the difference was not statistically significant (p = 0.139). Gender distribution showed no significant difference between the 2 groups (p = 0.831). BMI was similar between the 2 groups, with a mean BMI of 23.25 ± 4.97 in the success group and 24.68 ± 5.70 in the failure group. We found that the successful weaning group at the time of RCC admission had a lower APACHE II score (19.23 ± 4.98 vs. 21.25 ± 4.78, p = 0.003), higher GCS scores (8.70 ± 1.93 vs. 8.03 ± 2.34, p = 0.123), and a higher albumin level (3.33 ± 0.49 vs. 3.03 ± 0.40, p = 0.002). The failed weaning group had a higher comorbidity rate, including chronic lung disease, hypertension, coronary artery disease, stroke, chronic kidney disease, cancer, and diabetes mellitus, compared to the successful group; however, no significant statistical differences were observed.

The results of both univariate and multivariate stepwise logistic regression analyses, highlighting the factors associated with weaning success, can be seen in Table 2. We found that the predictive factors included BMI, albumin, RSBI, and comorbidities such as chronic lung disease and chronic kidney disease (p < 0.05 for all). Based on these findings, we constructed the following formula for predicting successful weaning by incorporating various predictors in the logistic regression analysis:

$$\log\left[\frac{\text{Probability of successful weaning}}{1-\text{Probability of successful weaning}}\right] = \left[\begin{array}{c}0.191 + (-0.109 * \text{BMI}) + (1.463 * \text{Albumin}) + (-1.627 * \text{Chronic lung diseases}) \\ +(-0.860 * \text{CKD}) + (-0.013 * \text{RSBI})\end{array}\right]$$

The predictive value of this model was assessed using the ROC curve, which showed an area under the curve (AUC) of 0.791 (p < 0.001), indicating good discriminative ability. The optimal cut-off value for predicting weaning success was 0.580, yielding a sensitivity of 0.790 and a specificity of 0.676 (Fig. 1). Further analysis based on the duration of MV showed that as the ventilation time increased, the proportion of successful weaning decreased (Fig. 2).

Discussion

In this study, we examined key clinical indicators associated with weaning outcomes among patients admitted to the RCC for prolonged MV. A total of 100 patients were included, of whom 64 (64%) were successfully weaned and 36 (36%) experienced weaning failure. Comparative analysis between the 2 groups identified BMI, serum albumin levels, RSBI, and the presence of comorbidities such as chronic lung disease and chronic kidney disease as significant predictors of successful weaning.

Prolonged exposure to MV is known to result in a progressive decline in respiratory muscle strength, particularly affecting diaphragmatic function, which significantly hampers the weaning process [6, 9]. To systematically evaluate a patient's readiness for ventilator discontinuation, clinicians often rely on a set of indicators commonly referred to as the weaning profile. Among these, Pimax assesses inspirato-

Table 2. Factors of Weaning Success by Using Logistic Regression.

	Crude OR	95% CI	95% CI	*P*	Adjusted OR	95% CI	95% CI	*P*
Age	0.978	0.95	1.008	0.147	1.003	0.957	1.051	0.890
Sex								
Male	1.19	0.517	2.74	0.682	0.970	0.317	2.969	0.957
Female	Reference				Reference			
BMI	0.95	0.879	1.027	0.197	0.892	0.806	0.987	0.026
APACHE II score at RCC admission	0.92	0.845	1.003	0.057	0.992	0.880	1.118	0.889
Glasgow Coma Scale at RCC admission	1.162	0.958	1.41	0.127	1.222	0.915	1.631	0.174
Albumin at RCC admission	4.312	1.6	11.622	0.004	4.974	1.153	21.460	0.031
Tracheostomy								
without	Reference				Reference			
with	0.728	0.284	1.863	0.508	0.867	0.258	2.915	0.818
Comorbidities								
Chronic lung diseases								
without	Reference				Reference			
with	0.333	0.087	1.272	0.108	0.163	0.028	0.945	0.043
Hypertension								
without	Reference				Reference			
with	0.598	0.261	1.371	0.225	0.947	0.290	3.089	0.928
Coronary artery disease								
without	Reference				Reference			
with	0.818	0.266	2.519	0.727	1.968	0.431	8.984	0.382
Stroke								
without	Reference				Reference			
with	1.071	0.404	2.842	0.890	1.138	0.294	4.402	0.852
Chronic kidney disease								
without	Reference				Reference			
with	0.472	0.18	1.234	0.126	0.196	0.041	0.945	0.042
Cancer								
without	Reference				Reference			
with	0.728	0.284	1.863	0.508	0.704	0.190	2.610	0.600
Diabetes Mellitus								
without	Reference				Reference			
with	0.701	0.305	1.612	0.403	1.228	0.380	3.965	0.731
Weaning profile								
Pimax	0.971	0.929	1.014	0.184	0.970	0.911	1.032	0.337
RSBI	0.991	0.983	0.998	0.018	0.987	0.977	0.998	0.015

OR: odds ratio; BMI: body mass index; RCC: respiratory care center; Pimax: maximum inspiratory pressure; RSBI: rapid shallow breathing index

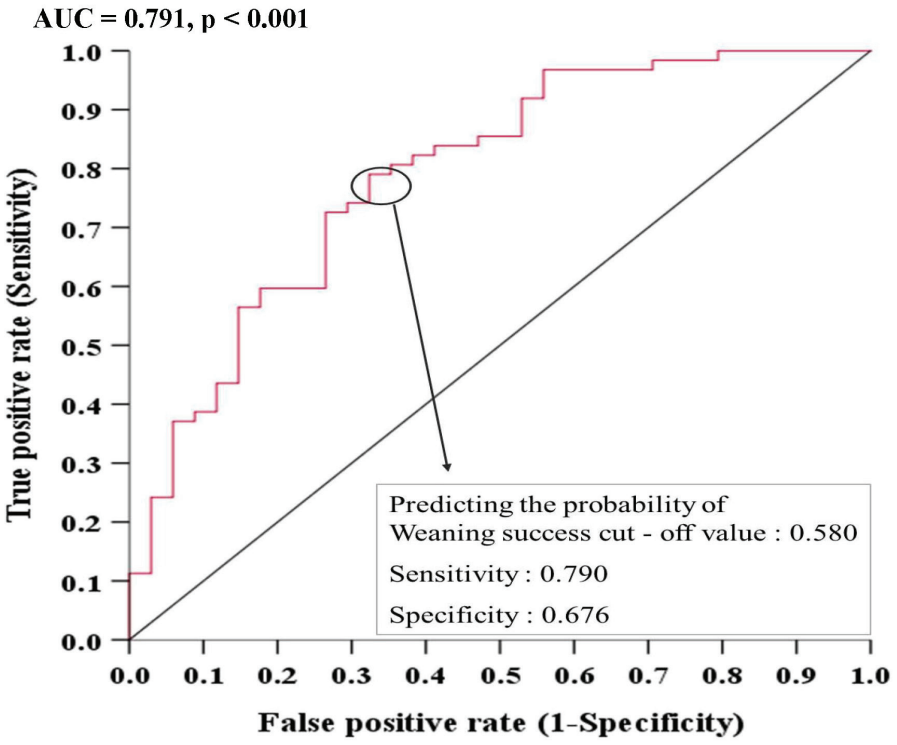


Fig. 1. Receiver operating characteristic curve for the prediction of weaning success.

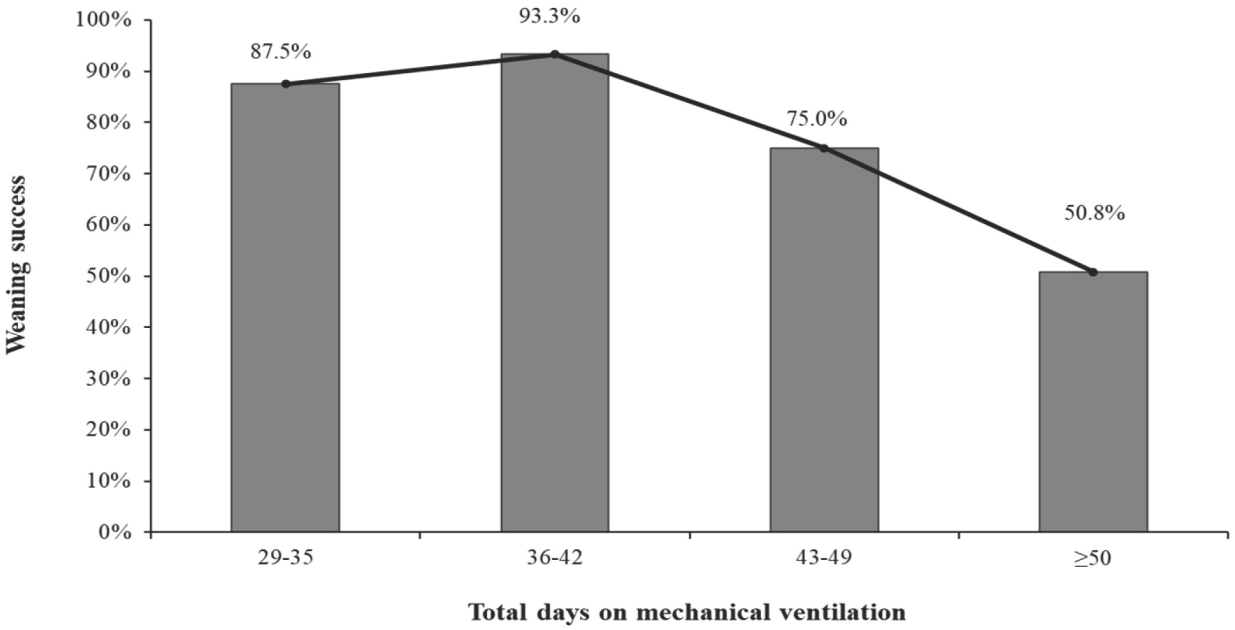


Fig. 2. Distribution of weaning success across different durations of mechanical ventilation.

ry muscle strength, especially of the diaphragm, while RSBI, calculated by dividing respiratory rate by tidal volume, reflects ventilation efficiency and respiratory fatigue [10]. However, both clinical experience and existing literature suggest that these conventional indices alone may be insufficient in predicting weaning outcomes, especially in patients requiring prolonged mechanical ventilation (PMV). As a result, there is growing interest in incorporating broader clinical parameters, including nutritional status, systemic physiology, and comorbid conditions [11-12]. Previous studies have identified a variety of prognostic indicators, such as age, APACHE II score, blood urea nitrogen (BUN) levels, neurological status (e.g., GCS), and the presence of neuromuscular or chronic pulmonary disorders [8, 13-14].

The International Consensus Conference described the pathophysiological mechanisms leading to the need for MV and provided recommendations for assessing patient readiness for ventilator liberation following critical illness. These guidelines emphasize the resolution of respiratory and hemodynamic instability as key prerequisites for weaning. The most common barriers to successful weaning include respiratory diseases, chronic heart failure, neuromuscular disorders, critical illness-associated neuromuscular abnormalities, and metabolic disturbances. Effective clinical management of these conditions can significantly enhance the likelihood of successful ventilator liberation [15]. Previous studies have shown that approximately 15% of intubated patients require MV for more than 7 days, and about 4.6% continue to require support beyond 60 days. By the 1980s, the growing prevalence of PMV led to the establishment of specialized weaning units (SWUs), either integrated within hospitals or operated as standalone facilities [16]. A population-based cohort study in Canada demonstrated that MV extending beyond 21 days is associated with elevated overall mortality—both in-hospital and post-discharge—as well as increased healthcare utilization [17]. Additionally, Ghiani *et al*. identified several independent predictors of prolonged weaning failure, including female sex, obesity, chronic obstructive pulmonary disease (COPD), elevated $PaCO_2$ levels during MV, and failure of the initial spontaneous breathing trial upon admission to the weaning center [18].

In this study, we observed that, in addition to traditional indices such as RSBI, several other parameters—including BMI, serum albumin levels, and the presence of chronic lung disease or chronic kidney disease—were independently associated with weaning success. One study demonstrated that BMI is closely related to pulmonary function, showing a negative correlation with both forced expiratory volume in one second (FEV1) and the FEV1/FVC ratio [19]. Moreover, BMI has been associated with respiratory symptoms such as cough, shortness of breath, and dyspnea, with higher BMI in particular linked to a greater prevalence of these symptoms [20]. Hypoalbuminemia, commonly seen in critically ill patients, has been associated with systemic inflammation, impaired recovery, and reduced diaphragmatic strength [5, 21]. Chronic lung diseases, such as COPD, may worsen ventilatory mechanics due to air trapping and increased breathing workload, thereby reducing the likelihood of successful weaning [22]. Similarly, patients with chronic kidney disease may experience additional weaning challenges owing to fluid overload, acid–base imbalances, and uremia-related muscle weakness [23].

Taiwan's RCC system, a unique step-down care model from the ICU, was specifically developed to manage patients requiring PMV. Several local studies have explored factors associated with ventilator weaning outcomes within this system. In our study, the weaning rate was 64%, which is consistent with findings from previous research. Reported weaning rates in RCC settings generally range from 48.2% to 69.2% [4-5, 7-8]. A retrospective observational study conducted at Chang Gung Memorial Hospital found that a longer duration of RCC stay, elevated BUN levels and APACHE II scores, as well as lower serum albumin levels and Pimax, were associated with unsuccessful ventilator weaning [8]. Similarly, a study from the RCC at Kaohsiung Medical University Hospital reported neuromuscular disease as a common cause of respiratory failure at the time of RCC admission. This study also found that the presence of neuromuscular disease, along with lower APACHE II scores and BUN levels at admission, were significant predictors of successful ventilator weaning [7]. Tracheostomy, commonly performed in patients with PMV, provides a stable airway, facilitates pulmonary hygiene and weaning, reduces laryngeal injury, and enhances patient comfort and daily functioning [24]. A study from Taipei Veterans General Hospital found that tracheostomy improves the weaning success rate in patients with a low GCS score (<7T) [25]. In contrast, our study demonstrated that the presence of a tracheostomy did not significantly affect the weaning rate, highlighting the importance of personalized interventions for specific patient subgroups.

Despite these valuable insights, our study has several limitations. First, it was a single-center, retrospective analysis, which may limit the generalizability of the findings to other institutions with different care models. Second, the relatively small sample size restricts the power of subgroup analyses and the robustness of multivariate modeling. Third, while key physiological parameters were included, other potentially important variables—such as sedative use, functional status, and nutrition therapy—were not available. Lastly all measurements were taken at single time points; serial or trend-based variables such as RSBI or albumin changes were not evaluated, even though prior studies suggest such data may offer better prognostic value.

Conclusion

In summary, this RCC-based study confirms that BMI, serum albumin levels, comorbidities, and RSBI may be useful indicators in assessing weaning readiness among patients with prolonged MV. Our predictive model, based on simple clinical variables, provides an accessible and effective tool for clinicians to identify patients who are likely to succeed in weaning, demonstrating reasonable discriminative performance for routine RCC practice.

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Lung Function Outcomes and Predictive Factors in Severe Asthma Patients Treated With Anti-IL-5 Therapy: A Real-world Cohort Study

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Introduction: Anti–interleukin-5 (anti–IL-5) therapies have emerged as effective treatments for severe eosinophilic asthma, with demonstrated benefits in reducing exacerbations and oral corticosteroid use. However, real-world evidence of their effects on pulmonary function and predictors of treatment response remains limited. This study aimed to evaluate the real-world effectiveness of anti–IL-5 therapy on pulmonary function and identify clinical predictors of significant FEV_1 improvement.

Methods: A retrospective cohort study was conducted from July 2015 to May 2024 with patients with severe asthma receiving anti–IL-5 therapy. Lung function parameters were assessed at baseline and after 12 months of treatment. Patients achieving an FEV_1 increase of >100 mL were identified, and univariate and multivariate logistic regression analyses were performed to explore potential predictors.

Results: A total 86 patients with severe asthma receiving anti–IL-5 therapy were enrolled, including 42 on mepolizumab and 44 on benralizumab. Anti–IL-5 therapy significantly improved the FEV_1 percentage predicted and PEFR, with the greatest improvement observed in the benralizumab group. In this group, FEV_1 volume (1.46 ± 0.57 L vs. 1.58 ± 0.66 L, p = 0.050), FEV_1 percentage (61.48% ± 19.88 vs. 67.00% ± 22.53, p = 0.024), and PEFR (214.72 ± 86.67 vs. 237.50 ± 113.10, p = 0.042) significantly increased after 12 months. Multivariate analysis confirmed body weight as a significant predictor (OR = 1.16, 95% CI: 1.02–1.31, p = 0.02).

Conclusion: Anti–IL-5 therapy improves lung function in patients with severe asthma, particularly with benralizumab. Body weight was found to be a significant predictor of meaningful FEV_1 improvement. Further studies are needed to explore the relationship between body weight and lung function response, as well as the potential mechanisms. ***(Thorac Med 2026; 41: 153-161)***

Key words: severe asthma, anti-IL-5 therapy, lung function outcome, predictive factor

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Introduction

Asthma is a heterogeneous respiratory disease typically characterized by chronic airway inflammation, airway smooth muscle hyperresponsiveness, and airway remodeling, with symptoms that vary in intensity and over time [1]. Although most patients achieve adequate disease control with inhaled corticosteroids and bronchodilators, approximately 5–10% experience severe asthma, remaining symptomatic despite maximal pharmacologic therapy [2]. These patients are at an increased risk of frequent exacerbations, reduced quality of life, and progressive decline in lung function.

Eosinophilic inflammation plays a central role in the pathogenesis of severe asthma. Interleukin-5 (IL-5), a cytokine critical for the growth, differentiation, recruitment, and survival of eosinophils, has emerged as a key therapeutic target [3-5]. Biologic agents targeting IL-5 or its receptor—including mepolizumab, reslizumab, and benralizumab—have demonstrated clinical efficacy not only in reducing exacerbation frequency and systemic corticosteroid use, but also in producing modest yet statistically significant improvements in lung function, particularly in forced expiratory volume in 1 second (FEV_1) and peak expiratory flow rate (PEFR), in patients with eosinophilic asthma [6-8]. However, the magnitude of lung function improvement varies among individuals, highlighting the need to identify predictive factors that may optimize patient selection and therapeutic outcomes.

This study aimed to evaluate the effects of anti-IL-5 treatment on lung function in patients with severe asthma and to investigate potential predictive factors associated with lung function improvement.

Methods

Study Design and Patient Recruitment

In this retrospective study, patients with asthma who were enrolled in a pay-for-performance program were consecutively recruited at the Linkou branch of Chang Gung Memorial Hospital, Taiwan, from July 2015 to May 2024. Adult patients (aged ≥18 years) diagnosed with severe asthma in accordance with the Global Initiative for Asthma (GINA) guidelines were included. Eligible patients were identified using the International Classification of Diseases, 10th Revision (ICD-10) code J45. Patients who initiated biologic therapy (mepolizumab or benralizumab) during the study period were selected. Those with insufficient data for complete analysis were excluded. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital (no. 202401221B0).

Patient Data

The following data were collected through questionnaires and medical records: age, sex, body mass index (BMI), smoking status, comorbidities, number of exacerbations in the previous year (including oral corticosteroid [OCS] use, emergency department visits, or hospitalizations), pulmonary function during exacerbations, and T2 inflammation biomarkers (including eosinophil count, eosinophil cation protein, total immunoglobulin E [IgE] level, and specific IgE, measured using ImmunoCAP [Phadia, Uppsala, Sweden]). The degree of asthma control was evaluated using the Asthma Control Test (ACT), which consists of 5 questions scored from 1 to 5, and lower total scores indicate poorer asthma control.

Outcome Measurement

The pulmonary function test was assessed before and after 12 months' use of anti-IL-5 agents. Clinical remission was defined on the basis of a composite of 3 criteria outlined in the consensus statement: the absence of exacerbation that required emergency room visits or hospitalization in the preceding 12 months, the absence of OCS use for asthma maintenance, and the absence of significant asthma symptoms [9].

An additional definition of remission (4-component definition) included an improvement in FEV_1 of >100 mL as the fourth criterion. This expanded definition was used to further analyze potential predictive factors.

Statistical analysis

Categorical and continuous variables are presented as count (percentage) and median [interquartile range], respectively. Two-way categorical variables were compared using the chi-square test. The Mann–Whitney U test was used to compare continuous variables with non-normal distributions, considering the small sample sizes in subgroups. Paired t-tests were conducted to compare baseline and 12-month values. Univariate and multivariate logistic regression analyses were performed to identify predictive factors associated with independent variables. Results are presented as odds ratios (ORs) with corresponding p-values. A *p*-value <0.05 was considered statistically significant. Data processing and analysis were performed using SPSS software, version 26 (IBM Corporation, Armonk, NY, USA).

Results

A total of 97 patients receiving anti-IL-5 therapy for severe asthma were enrolled in the study, among whom, 4 were excluded for missing regular asthma clinic visits, 3 for missing spirometry measurements, and 4 for receiving less than 12 months of anti-IL-5 treatment. The remaining 86 patients were considered eligible for analysis. Fig. 1 provides the patient selection flowchart. Of the 86 patients, 42 received mepolizumab and 44 received benralizumab, with 8 patients switching from mepolizumab to benralizumab during the study period. Baseline demographic and clinical characteristics are summarized in Table 1. Significant differ-

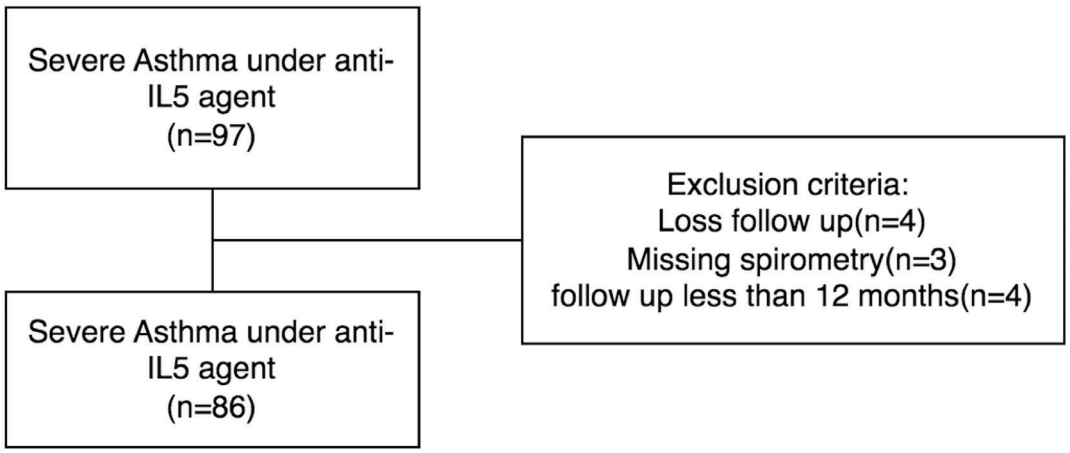


Fig. 1. Patient inclusion flowchart.

Table 1. Demographic and Clinical Characteristics of Patients with Severe Asthma Treated with anti-IL-5 Biologics.

	Total cohort N=86	Mepolizumab N=42	Benralizumab N=44	*p* value
Age, years, mean (SD)	62.3±14.1	64.0±12.4	61.1±15.6	0.34
Male, n (%)	48 (56%)	26 (62%)	22 (50%)	0.27
Body mass index, kg/m2	25.6±5.0	26.2±5.6	25.0±4.2	0.255
Never smoker, n (%)	57 (66%)	28 (67%)	29 (66%)	0.941
Active smoker, n (%)	10 (12%)	6 (14%)	4 (9%)	0.453
Former smoker, n (%)	18 (21%)	8 (19%)	10 (23%)	0.675
Asthma Control Test, mean (SD)	19.6±4.7	20.5±5.1	19.4±5.6	0.522
Comorbidities				
Gastroesophageal reflux, n (%)	50 (58%)	26 (62%)	24 (55%)	0.489
Allergic rhinitis, n (%)	73 (85%)	37 (88%)	36 (82%)	0.417
Rhinosinusitis with or without polyp, n (%)	22 (26%)	13 (31%)	9 (20%)	0.265
Aspirin sensitivity, n (%)	0 (0%)	0 (0%)	0 (0%)	
Anxiety or depression, n (%)	8 (9%)	4 (10%)	4 (9%)	0.945
Obstructive sleep apnea, n (%)	8 (9%)	4 (10%)	4 (9%)	0.945
Malignancy, n (%)	10 (12%)	2 (5%)	8 (18%)	0.052
Type 2 diabetes mellitus, n (%)	10 (12%)	4 (10%)	6 (14%)	0.552
Old tuberculosis, n (%)	4 (5%)	3 (7%)	1 (2%)	0.284
Laboratory examination				
WBC, /μL	9161.8±3022.6	9260.8±3072.2	9070.0±3011.0	0.781
Eosinophil, (%)	5.5±7.4	5.2±9.1	5.7±5.6	0.785
Eosinophil count, cells/μL	528.4±1142.7	594.7±1566.7	462.0±425.1	0.602
IgE level, KU/L, mean (SD)	674.5±1005.6	566.3±843.3	779.1±1145.4	0.413
ECP level, μg/L, mean (SD)	20.1±22.1	15.3±11.7	25.9±29.5	0.145
Any specific IgE (%)	36 (42%)	20 (67%)	16 (64%)	0.836
Pulmonary function				
FVC, liter	2.1±0.7	2.1±0.7	2.1±0.7	0.828
FVC, % of pred.	70.3±16.1	69.8±17.2	70.8±15.2	0.769
FEV1, liter	1.4±0.5	1.3±0.5	1.5±0.6	0.22
FEV1, % of pred.	59.1±20.0	56.6±19.8	61.5±19.9	0.253
FEV1/FVC (%)	66.6±14.2	64.8±13.9	68.3±14.4	0.254
PEFR, liter/min	219.6±82.6	222.1±78.8	217.3±86.9	0.809
Treatment				
ICS+LABA, n (%)	60 (70%)	33 (79%)	27 (61%)	0.082
LAMA, n (%)	43 (50%)	22 (52%)	21 (48%)	0.666
Triple therapy, n (%)	25 (29%)	8 (19%)	17 (39%)	0.046
Acute exacerbation				
Exacerbation in past 1 year	78 (91%)	38 (90%)	40 (91%)	0.945
Any systemic corticosteroid burst	65 (76%)	31 (74%)	34 (77%)	0.709
Any emergency department visit	22 (26%)	6 (14%)	16 (36%)	0.019
Any hospitalization	18 (21%)	5 (12%)	13 (30%)	0.044

WBC: white blood cells, IgE: immunoglobulin E, ECP: eosinophil cationic protein, ICS: inhaled corticosteroid, LABA: long-acting beta 2 agonist, LAMA: long-acting muscarinic antagonist

ences were observed between the mepolizumab and benralizumab groups in the use of single-inhaler triple therapy (SITT) (19% vs. 39%, p = 0.046), emergency department visits (14% vs. 36%, p = 0.019), and hospital admissions due to exacerbations (12% vs. 30%, p = 0.044). Other characteristics showed no significant differences between groups.

Lung function results at baseline and after 12 months of anti–IL-5 therapy are presented in Table 2. Anti-IL-5 therapy was associated with significant improvements in FEV_1 and PEFR. In subgroup analysis, the benralizumab group demonstrated significant increases in FEV_1 volume (1.46 ± 0.57 L vs. 1.58 ± 0.66 L, p = 0.050), FEV_1 percentage predicted (61.48% ± 19.88 vs. 67.00% ± 22.53, p = 0.024), and PEFR (214.72 ± 86.67 vs. 237.50 ± 113.10, p = 0.042).

Table 2. Lung Function Outcome at Baseline and After 12 Months of anti-IL-5 Treatment.

	Baseline	12 months	*P* value
FVC (L)			
Anti-IL-5	2.07±0.67	2.16±0.75	0.109
Mepolizumab	2.06±0.70	2.11±0.69	0.460
Benralizumab	2.09±0.65	2.20±0.80	0.135
FVC (%)			
Anti-IL-5	70.31±16.12	73.67±17.11	0.057
Mepolizumab	69.79±17.19	71.95±15.38	0.375
Benralizumab	70.82±15.22	75.32±18.65	0.081
FEV1 (L)			
Anti-IL-5	1.39±0.54	1.47±0.62	0.056
Mepolizumab	1.32±0.50	1.36±0.55	0.484
Benralizumab	1.46±0.57	1.58±0.66	0.050
FEV1 (%)			
Anti-IL-5	59.07±19.90	62.86±21.36	0.027
Mepolizumab	56.55±19.84	58.52±19.38	0.412
Benralizumab	61.48±19.88	67.00±22.53	0.024
FEV1/FVC			
Anti-IL-5	66.57±14.18	67.85±14.63	0.153
Mepolizumab	64.78±13.93	65.00±14.58	0.858
Benralizumab	68.29±14.36	70.56±14.31	0.078
FEV1 change (%)			
Anti-IL-5	11.61±13.45	10.38±12.33	0.487
Mepolizumab	12.95±13.78	12.04±12.98	0.729
Benralizumab	10.40±13.19	8.88±11.66	0.532
PEFR			
Anti-IL-5	221.64±81.29	236.57±99.28	0.049
Mepolizumab	229.68±75.17	235.48±82.21	0.563
Benralizumab	214.72±86.67	237.50±113.10	0.042

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, PEFR: peak expiratory flow rate

An increase in FEV_1 of over 100 mL was observed in 31 patients after 12 months of therapy, of whom 14 received mepolizumab and 17 received benralizumab. Univariate analysis identified age as negatively associated with achieving FEV_1 improvement >100 mL (OR: 0.97; 95% CI: 0.93–1.00; $p = 0.04$), whereas body weight was positively associated (OR: 1.04; 95% CI: 1.01–1.09; $p = 0.03$). BMI, absolute eosinophil count, and FEV_1 value before treatment were not significant predictors. In multivariate analysis, only body weight remained a significant predictor (OR = 1.16, 95% CI: 1.02–1.31, $p = 0.02$) (Table 3).

Table 3. Predictive Factors for FEV1 Improvement Over 100 ml.

	Univariate analysis		Multivariate analysis	
Variable	OR (95%CI)	*P* value	OR (95% CI)	*P* value
Age	0.97 (0.93-1.00)	0.04	0.96 (0.91-1.01)	0.10
Body weight	1.04 (1.01-1.09)	0.03	1.16 (1.02-1.31)	0.02
BMI	1.07 (0.98-1.18)	0.14		
Eosinophil count	1.00 (1.00-1.00)	0.18		
FEV1 before treatment	0.57 (0.24-1.37)	0.21		

Discussion

Our study demonstrated that anti–IL-5 therapy significantly improved pulmonary function parameters, particularly FEV_1 and PEFR, with the greatest effects observed in patients treated with benralizumab. Additionally, body weight emerged as a predictive factor for FEV_1 improvement >100 mL after 12 months of treatment.

Previous randomized-controlled trials about anti-IL-5 therapy have shown similar findings. The MUSCA trial reported a mean FEV_1 increase of 120 mL after 24 weeks of mepolizumab treatment [10], while the MENSA trial found improvements of 146 mL and 138 mL for intravenous and subcutaneous formulations, respectively, at 32 weeks, with the finding of significant improvements in morning PEFR [6]. Similarly, the SIROCCO and CALIMA trials for benralizumab reported FEV_1 improvements of 231 mL and 165 mL, respectively, after 48 weeks of treatment [8, 11]. Real-world evidence from a systemic review also supports FEV_1 improvements of 170 mL and 210 mL in patients treated with mepolizumab and benralizumab, respectively [12].

Consistent with these studies, our data confirm pulmonary function improvement in the overall cohort, with particularly notable changes in the benralizumab group. Although FEV_1 improvement did not reach statistical significance in the mepolizumab group, this aligns with real-world variability, where some studies report stable FEV_1 or low rates of patients achieving >100 mL improvement [13-14]. A 12-year longitudinal study found an average FEV_1 increase of only 20 mL per year in the mepolizumab group, compared to approximately 40 mL in our cohort [15]. Furthermore, studies in specific

subgroups, such as patients with eosinophilic granulomatosis with polyangiitis or nasal polyps, have reported limited FEV_1 improvement after mepolizumab treatment [16-17], Our study didn't evaluate this specific group, which may have influenced our result.

Obesity is a common asthma comorbidity and may worsen disease control. Leptin, an adipokine elevated in obese individuals, enhances the IL-5 pathway and may exacerbate asthma symptoms [18]. IL-5 plays not only a central role in eosinophil activation, contributing to the pathogenesis of eosinophilic asthma [4] but also presents at an elevated level in obese patients, as an inflammatory marker [19]. Prior studies have suggested that obesity is associated with reduced clinical remission rates across various biologics [20-22], which were less focused on an FEV_1 improvement predictor within the 4-components definition of clinical remission criteria. In addition, fewer studies have discussed pulmonary outcome in obese patients. A previous study evaluated biologic therapy in an asthma-obese phenotype and found no significant change in FEV_11, FVC or FEV_1 ratio, compared with obese and non-obese groups [23], while Albers *et al*. found an increased FEV_1 volume in all body weight groups, except in those over 90 kg and also in all BMI groups after mepolizumab treatment [24].

Reductions in body weight following anti-IL-5 treatment have been noted in some studies, and this was potentially due to decreased OCS doses; however, the studies were based on small sample sizes [25-26]. Edith Visser, *et al*. found that women receiving biologic therapy exhibited a decrease in their body fat mass index along with an improvement in FEV_1 percentage. In contrast, men showed only a slight, borderline-significant increase in their fat-free mass index [27]. These findings suggest that BMI may not be a reliable predictor of pulmonary function improvement under anti-IL-5 therapy. Our study found that body weight, rather than BMI, emerged as a predictive factor for an increased FEV_1 over 100 ml with a modest but statistically significant increase in probability (OR = 1.16). However, we did not assess changes in body weight or body composition over time, limiting our ability to investigate potential underlying mechanisms. Given that only a few prior studies have explored body weight changes in response to biologic or anti-IL-5 therapies, and even fewer have examined their relationship with pulmonary outcomes, further research is warranted. In addition, a direct anti-inflammatory effect of these therapies on body composition may also contribute to treatment response [26, 28]. Future studies are needed to elucidate potential mechanisms and their clinical implications.

Limitations

This study has several limitations. Its retrospective design introduces inherent risks of data collection bias and unmeasured confounding factors. We did not assess changes in body weight, body composition, or OCS dose over time, limiting our ability to investigate potential mechanisms underlying treatment response. Additionally, the small sample size may have reduced the statistical power of subgroup analyses. The absence of fractional exhaled nitric oxide data also limits the assessment of T2 inflammation status. Despite these limitations, the study provides valuable real-world insights into predictors of pulmonary function improvement following anti-IL-5 therapy in patients with severe asthma. Notably, body weight—rather than

BMI—was identified as a significant predictor of FEV_1 improvement. The identification of such predictive factors may help guide treatment strategies, enabling earlier intervention and more personalized asthma management.

Conclusion

In conclusion, anti–IL-5 therapy for severe asthma resulted in significant improvements in FEV_1 and PEFR after 12 months of treatment. Body weight, rather than BMI, was identified as a predictive factor for FEV_1 improvement of over 100 mL. Future studies are needed to investigate the association between changes in body weight or body composition and pulmonary function improvement, as well as to explore the underlying biological mechanisms of this relationship.

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Predicting Post-COVID Symptoms Based on Initial Presentation

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Introduction: Post-Coronavirus disease 2019 (COVID-19) can have a substantial, multisystem effect. Post-COVID symptoms involve the neuropsychiatric, cardiopulmonary, gastrointestinal, and dermatological systems. We analyzed the initial and post-COVID symptoms to determine how initial clinical presentation relate to the risk of post-COVID symptoms.

Methods: This study was conducted using an online questionnaire administered between July 1 and July 29, 2022, to patients diagnosed with COVID-19. The questionnaire assessed both initial and post-COVID symptoms.

Results: Of the 717 patients included in this analysis, 98.6% had a mild illness and 1.4% had a critical illness. Of 412 patients (57%) with acute infection symptoms, the most common were sore throat (35%), cough (35%), fever (30%), and fatigue (30%). Of 623 patients (87%) with post-COVID-19 symptoms, the most common were fatigue (66%), cough (53%), and difficulty thinking (25%). Critical illness was associated with a higher risk of post-COVID general symptoms, such as fever or general soreness. Initial neuropsychiatric symptoms, dyspnea, and critical illness were associated with higher post-COVID neuropsychiatric symptoms. Initial chest pain, dyspnea, and insomnia were associated with higher post-COVID cardiopulmonary symptoms, while initial gastrointestinal symptoms and critical illness were associated with higher post-COVID gastrointestinal symptoms. An initial rash was associated with a higher incidence of post-COVID rash.

Conclusion: COVID-19 survivors frequently experienced post-COVID symptoms affecting multiple organ systems. Certain initial symptoms and critical illnesses were associated with a higher risk of post-COVID symptoms. ***(Thorac Med 2026; 41: 162-177)***

Key words: COVID-19; post-COVID; questionnaire; SARS-CoV-2; system assessment

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Introduction

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has a great impact worldwide and is therefore a global health crisis.[1] Besides causing morbidities and mortalities in participants with acute COVID, post-COVID also significantly impacts participants after acute infection. The effects of post-COVID can affect multiple organ systems. [2] Residual effects of SARS-CoV-2 infection cause symptoms in neuropsychiatric, cardiopulmonary, gastrointestinal (GI), and dermatological systems, and lead to reduced health-related quality of life in COVID-19 survivors. [2] One previous telephone survey study showed that 32.6% of 488 participants reported persistent symptoms, including 18.9% with new or worsened symptoms.[3] Exertional dyspnea (22.9%) was most commonly reported, with cough (15.4%) and persistent altered taste or smell (13.1%). [3] In another post-COVID survey, 87% of 143 COVID-19 survivors reported persistent symptoms, with fatigue (53.1%), dyspnea (43.4%), arthralgia (27.3%), and chest pain (21.7%) being the most common, and 55% of participants experienced three or more symptoms.[4] Other cohorts have found persistence of symptoms in 66% of 150 non-critical illness survivors at 60 days, [5] and, in a prospective study, at least one symptom in 76% of 1,733 participants 2 months after infection. [6] Fatigue was the most common symptom (63%), followed by insomnia (26%) and anxiety/depression (23%). [6] Greater severity of acute SARS-CoV-2 infection was significantly associated with the persistence of symptoms, pulmonary dysfunction, and reduced health-related quality of life. [2]

Potential mechanisms contributing to the pathophysiology of post-COVID symptoms include virus-related changes, inflammatory damage in response to acute infection, and sequelae of post-critical illness. [2] Cellular damage, a robust innate immune response with inflammatory cytokine production, and a procoagulant state induced by SARS-CoV-2 infection may contribute to these post-COVID sequelae. [2] Because SARS-CoV-2 infection can damage multiple organ systems, a systematic investigation of post-COVID sequelae and the establishment of a multidisciplinary care models for affected patients are essential. A comprehensive understanding of these symptoms beyond the acute stage will help develop strategies for COVID-19 survivors. Identifying participants for post-COVID syndrome can help healthcare providers determine their care priorities.

The aim of this study was to evaluate acute COVID-19 symptoms in relation to post-COVID-19 sequelae and to identify the possible risk factors for developing post-COVID symptoms.

Methods

Study design and population

The policy for the diagnosis and treatment of COVID-19 followed Taiwan Centers for Disease Control guidelines. The diagnosis of COVID-19 was based on positive real-time reverse transcriptase-polymerase chain reaction results or rapid screening for SARS-CoV-2 using nasopharyngeal swabs. Once diagnosed with COVID-19, participants were required to be isolated at home or in hospitals for 7 days. Participants with mild symptoms received treatment at a video clinic. Patients with severe symptoms visited the emergency department and were hospitalized for treatment. Those with unstable vital signs or respiratory distress were defined as critically ill

and were placed in an intensive care unit (ICU). Acute symptoms were observed within 7 days of diagnosis.

This study was conducted using an online questionnaire from July 1 to 29, 2022. Inclusion criteria were patients diagnosed with COVID-19. Participants unwilling to complete the questionnaire were excluded. The questionnaire was designed to assess the initial symptoms and post-COVID symptoms and was distributed electronically via mobile phones or computers in the form of a message, and responses were completed on these devices. All methods were performed in accordance with the relevant guidelines and regulations. This study was approved by the Research Ethics Committee of the Taipei Tzu Chi Hospital (11-XD-125). Informed consent was obtained verbally and recorded. For minors, the questionnaire was explained to their parents or guardians, from whom consent was obtained.

Statistical analysis

We analyzed the relationships between related categories and symptoms of acute infection and post-COVID. For continuous variables, we used the Student's t-test to analyze the mean difference between patients with and without post-COVID symptoms. The parameters are presented as the mean ± standard deviation. For categorical variables, we analyzed the differences in the proportion of related variables between participants with and without post-COVID symptoms using the chi-squared test. We used multiple logistic regression model to identify characteristics associated with affect post-COVID symptoms, adjusting for variables that showed significant effect. Statistical significance was set at $p < 0.05$. The statistical software used in this study was R (version 4.1.3, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical characteristics

The baseline characteristics of the patients are shown in Table 1. Of the 717 participants included in this analysis, 98.6% had mild illness and 1.4% had critical illness. The mean infection duration in these participants was 43.4 ± 30.6 days.

A total of 412 patients (57%) showed symptoms at the initial diagnosis of COVID-19. Among patients with acute infection, the most common initial symptoms were sore throat (35%), cough (35%), fever (30%), fatigue (30%), headache (22%), general soreness (17%), dizziness (16%), dyspnea (15%), diarrhea (12%), and chest pain (11%). Only 17 participants (4%) had symptoms in a single system, while most had symptoms involving multiple systems (Figure 1A).

There were 623 participants (87%) with post-COVID-19 symptoms. The common post-COVID symptoms were fatigue (66%), cough (53%), difficulty thinking (25%), general pain (23%), dyspnea (22%), headache (22%), sleep disturbance (22%), dizziness (19%), diarrhea (17%), fever (15%), depression (12%), palpitation (12%) and chest pain (11%). Sixty-five participants (10%) had symptoms in a single system, and most participants had symptoms involving multiple systems (Figure 1B).

- **Chi-squared test of initial and post-COVID symptoms**

  Chi-squared analyses examining the associations between initial symptoms and post-COVID manifestations are summarized in Figure 2, with detailed results provided in

Table 1. Clinical Characteristics.

		n	%
Initial symptoms	Yes/No	412/305	57.46% /42.54%
	Fever	215	29.99%
	Fatigue	215	29.99%
	Dizziness	116	16.18%
	Headache	157	21.90%
	Poor sleep	66	9.21%
	Rhinorrhea	198	27.62%
	Sore throat	253	35.29%
	Cough	254	35.43%
	Dyspnea	112	15.62%
	Chest pain	79	11.02%
	Abdominal pain	33	4.60%
	Diarrhea	86	11.99%
	General soreness	122	17.02%
	Skin rash	23	3.21%
	Critical illness	10	1.39%
Post-COVID symptoms	Yes/No	623/94	86.89% /13.11%
General symptoms	Fever	105	14.64%
	General soreness	169	23.57%
Neuropsychiatric symptoms	Fatigue	474	66.11%
	Difficulty thinking	180	25.10%
	Insomnia	161	22.45%
	Headache	158	22.04%
	Dizziness	138	19.25%
	Depression	87	12.13%
	Altered smell or taste	54	7.53%
	Tingling	43	6.00%
Cardiopulmonary symptoms	Dyspnea	161	22.45%
	Cough	380	53.00%
	Chest pain	81	11.30%
	Palpitation	84	11.72%
Digestive symptoms	Diarrhea	125	17.43%
	Abdominal pain	55	7.67%
Dermal symptom	Skin rash	68	9.48%

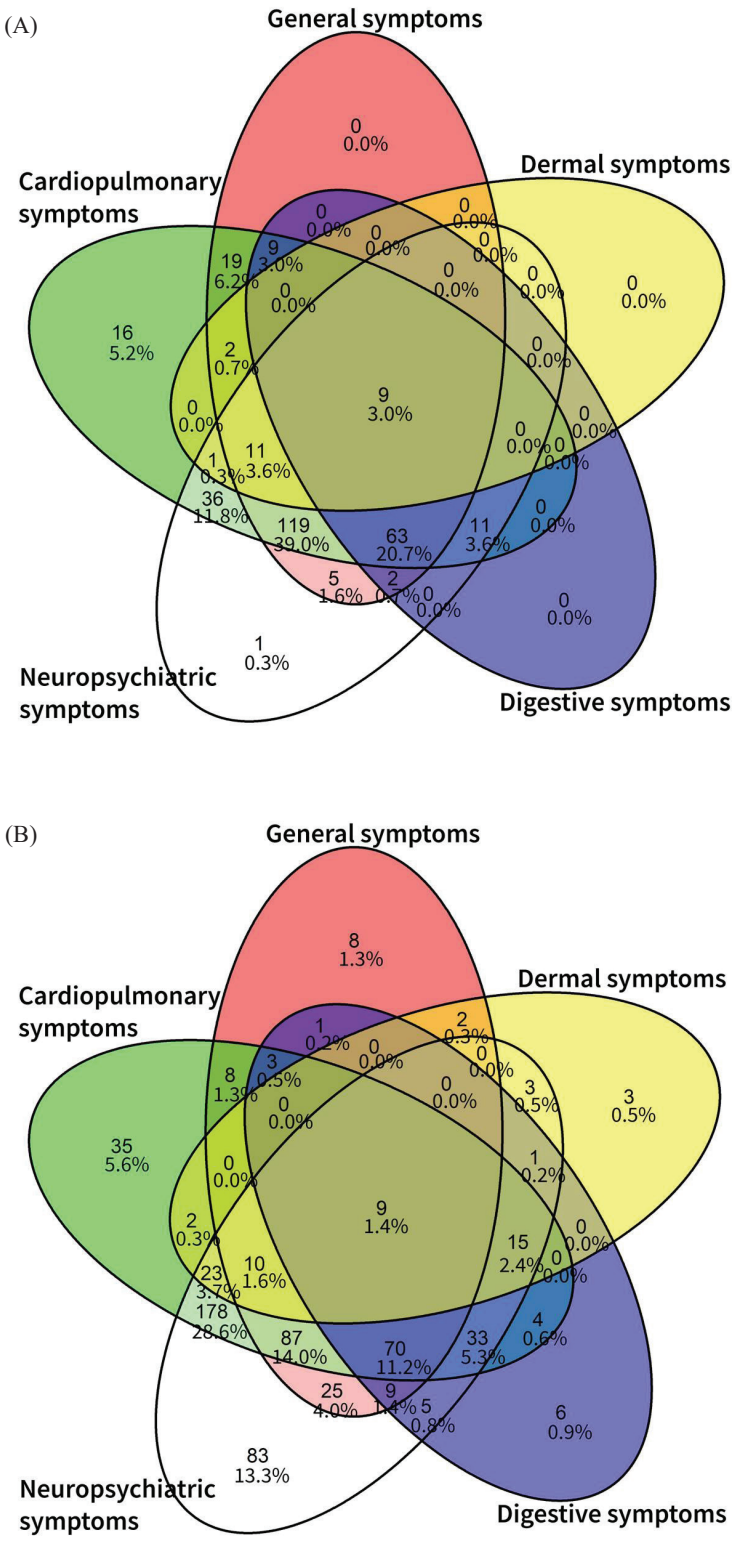


Fig. 1. Proportion of Initial and Post-COVID Symptoms in Different Systems.

(A) There were 412 participants (57%) with symptoms at the initial diagnosis of COVID-19. Only 17 participants (4%) had symptoms in the sole system, and most participants had symptoms involving more than one organ system.

(B) There were 623 participants (87%) with post-COVID-19 symptoms. Sixty-five participants (10%) had symptoms in the sole system, and most participants had symptoms involving more than one organ system (Figure 1B).

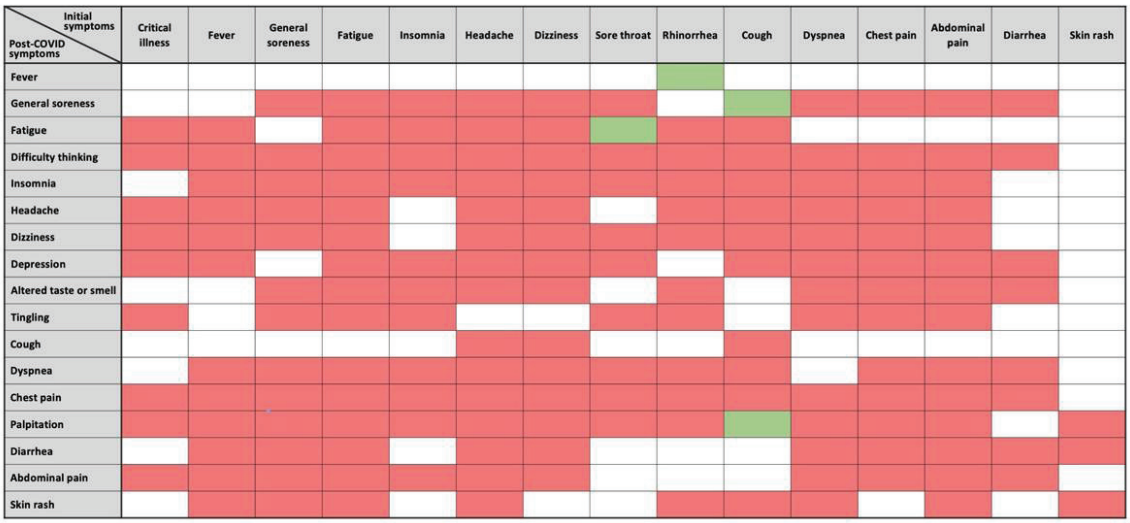


Fig. 2. Results of Chi-Squared Test of Initial and Post-COVID Symptoms.

the online Supplementary Material.

- **General symptoms:**
  Participants with post-COVID fever showed a lower prevalence of initial rhinorrhea ($p < 0.05$) and a shorter infection duration than those without post-COVID fever (34.7 ± 18.2 vs. 44.9 ± 32.0 days, $p < 0.05$). Post-COVID general soreness was associated with multiple initial systemic symptoms but was less common among participants with an initial cough ($p < 0.05$).
- **Neuropsychiatric symptoms:**
  Post-COVID neuropsychiatric manifestations, including fatigue, difficulty thinking, insomnia, headache, dizziness, depression, altered smell or taste, and tingling, were consistently associated with a wide range of initial symptoms, particularly general soreness, fatigue, dizziness, headache, insomnia, dyspnea, chest pain, abdominal pain, and diarrhea (all $p < 0.05$). Critically ill participants had significantly higher proportions of post-COVID fatigue, difficulty thinking, headache, dizziness, depression, and tingling (all $p < 0.05$). In addition, a longer infection duration was observed in participants with post-COVID insomnia and depression (both $p < 0.05$).
- **Pulmonary symptoms:**
  Participants with post-COVID cough had higher rates of initial dizziness, headache, and cough ($p < 0.05$) and shorter infection duration (40.9 ± 28.5 vs. 46.3 ± 32.5 days, $p < 0.05$). Post-COVID dyspnea was associated with a broad spectrum of initial systemic and respiratory symptoms and was linked to a longer infection duration (49.9 ± 35.3 vs. 41.6 ± 28.9 days, $p < 0.05$).
- **Cardiovascular symptoms:**
  Post-COVID chest pain and palpitations were associated with multiple initial systemic, respiratory, and gastrointestinal symptoms (all $p < 0.05$). Notably, post-COVID palpitations were less frequent among participants with an initial cough ($p < 0.05$) but more common in critically ill participants and those with a longer infection duration (both $p < 0.05$).

- **GI and dermatologic symptoms:**
  Post-COVID diarrhea and abdominal pain were significantly associated with initial systemic symptoms and corresponding gastrointestinal complaints (all $p < 0.05$). Critically ill participants had a higher proportion of post-COVID abdominal pain ($p < 0.05$) and a longer infection duration. Post-COVID skin rash was associated with initial systemic symptoms and the presence of an initial skin rash ($p < 0.05$).

Multiple logistic regression model

The results of the multivariable logistic regression analyses identifying the initial presentations predictive of post-COVID symptoms are summarized in Tables 2–6.

- **General symptoms:**
  As shown in Table 2, initial rhinorrhea was associated with a lower risk of post-COVID fever (OR 0.57, 95% confidence interval [CI] 0.33–0.94), and a longer duration after infection was inversely associated with post-COVID fever (OR per day 0.98, 95% CI 0.97–0.98). In contrast, post-COVID general soreness was more likely among participants with initial general soreness (OR 4.13, 95% CI 2.19–7.99) and critical illness (OR 7.59, 95% CI 1.45–60.24), and less likely in those with initial cough (OR 0.37, 95% CI 0.17–0.77).
- **Neuropsychiatric symptoms:**
  Distinct associations were observed between initial symptoms and post-COVID neuropsychiatric outcomes (Table 3). Post-COVID fatigue was associated with initial fatigue (OR 1.93, 95% CI 1.05–3.58) and headache (OR 1.92, 95% CI 1.01–3.72), while initial sore throat was inversely associated (OR 0.50, 95% CI 0.25–0.97). Post-COVID difficulty thinking was associated with initial dizziness (OR 2.79, 95% CI 1.59–4.97), dyspnea (OR 2.08, 95% CI 1.16–3.71), and critical illness (OR 6.72, 95% CI 1.32–52.90). Post-COVID insomnia showed a strong association with initial insomnia (OR 9.58, 95% CI 4.96–19.24) and dyspnea (OR 2.56, 95% CI 1.34–4.92). In addition, post-COVID headache was associated with initial dizziness (OR 1.84,

Table 2. Initial Predictors of Post-COVID General Symptoms.

Initial predictor \ Post-COVID	Fever	General soreness
Duration of infection (per day)	0.98 (0.97–0.98)*	–
Rhinorrhea	0.57 (0.33–0.94)*	–
Cough	–	0.37 (0.17–0.77)*
General soreness	–	4.13 (2.19–7.99)*
Critical illness	–	7.59 (1.45–60.24)*

Presented as odds ratio (OR) with 95% confidence interval (CI).
* $p < 0.05$.
Cells marked "–" indicate non-significant associations ($p \geq 0.05$).

Table 3. Initial Predictors of Post-COVID Neuropsychiatric Symptoms.

Initial predictor \ Post-COVID	Fatigue	Difficulty thinking	Insomnia	Headache	Dizziness	Depression
Fatigue	1.93 (1.05–3.58)*	–	–	–	–	–
Dizziness	–	2.79 (1.59–4.97)*	–	1.84 (1.02–3.33)*	10.88 (5.50–22.75)*	–
Headache	1.92 (1.01–3.72)*	–	–	3.63 (1.91–7.10)*	–	–
Insomnia	–	–	9.58 (4.96–19.24)*	–	–	3.06 (1.50–6.21)*
Dyspnea	–	2.08 (1.16–3.71)*	2.56 (1.34–4.92)*	–	–	–
Sore throat	0.50 (0.25–0.97)*	–	–	–	–	–
Critical illness	–	6.72 (1.32–52.90)*	–	–	–	–

Presented as odds ratio (OR) with 95% confidence interval (CI).
* $p < 0.05$.
Cells marked "–" indicate non-significant associations ($p \geq 0.05$).

95% CI 1.02–3.33) and headache (OR 3.63, 95% CI 1.91–7.10), while post-COVID dizziness was strongly associated with initial dizziness (OR 10.88, 95% CI 5.50–22.75). Post-COVID depression was associated with initial insomnia (OR 3.06, 95% CI 1.50–6.21). No significant predictors were identified for post-COVID tingling or altered smell or taste.

- **Pulmonary symptoms:**

As shown in Table 4, a longer duration after infection was associated with a lower risk of post-COVID cough (OR per day 0.99, 95% CI 0.99–1.00), but a higher risk of post-COVID dyspnea (OR per day 1.01, 95% CI 1.00–1.01). Post-COVID dyspnea was independently associated with initial insomnia (OR 2.83, 95% CI 1.41–5.73), dyspnea (OR 7.33, 95% CI 3.97–13.97), and chest pain (OR 3.64, 95% CI 1.83–

Table 4. Initial Predictors of Post-COVID Pulmonary Symptoms.

Initial predictor \ Post-COVID	Cough	Dyspnea
Duration of infection (per day)	0.99 (0.99–1.00)*	1.01 (1.00–1.01)*
Insomnia	–	2.83 (1.41–5.73)*
Dyspnea	–	7.33 (3.97–13.97)*
Chest pain	–	3.64 (1.83–7.33)*

Presented as odds ratio (OR) with 95% confidence interval (CI).
* $p < 0.05$.
Cells marked "–" indicate non-significant associations ($p \geq 0.05$).

7.33).

- **Cardiovascular symptoms:**
  As shown in Table 5, post-COVID chest pain was associated with initial dizziness (OR 3.10, 95% CI 1.40–7.04) and chest pain (OR 11.83, 95% CI 5.03–30.07). Post-COVID palpitations were associated with initial insomnia (OR 4.73, 95% CI 2.24–10.19), dyspnea (OR 2.30, 95% CI 1.10–4.81), and chest pain (OR 3.99, 95% CI 1.86–8.72), whereas initial cough was inversely associated with palpitations (OR 0.24, 95% CI 0.09–0.62).
- **GI symptoms:**
  As shown in Table 6, initial diarrhea was associated with a higher risk of post-COVID diarrhea (OR 3.79, 95% CI 2.04–7.10). Post-COVID abdominal pain was associated with initial abdominal pain (OR 3.84, 95% CI 1.38–10.58) and critical illness (OR 5.76, 95% CI 1.16–28.18).
- **Dermatologic symptoms:**
  Participants with an initial skin rash (OR 104.24, 95% CI 30.05–506.40, $p < 0.001$) had a higher risk of post-COVID skin rash. Figure 3 shows the associated risk factors

Table 5. Initial Predictors of Post-COVID Cardiovascular Symptoms.

Post-COVID / Initial predictor	Chest pain	Palpitation
Dizziness	3.10 (1.40–7.04)*	–
Insomnia	–	4.73 (2.24–10.19)*
Dyspnea	–	2.30 (1.10–4.81)*
Chest pain	11.83 (5.03–30.07)*	3.99 (1.86–8.72)*
Cough	–	0.24 (0.09–0.62)*

Presented as odds ratio (OR) with 95% confidence interval (CI).
* $p < 0.05$.
Cells marked "–" indicate non-significant associations ($p \geq 0.05$).

Table 6. Initial Predictors of Post-COVID Gastrointestinal Symptoms.

Post-COVID / Initial predictor	Diarrhea	Abdominal pain
Diarrhea	3.79 (2.04–7.10)*	–
Abdominal pain	–	3.84 (1.38–10.58)*
Critical illness	–	5.76 (1.16–28.18)*

Presented as odds ratio (OR) with 95% confidence interval (CI).
* $p < 0.05$.
Cells marked "–" indicate non-significant associations ($p \geq 0.05$).

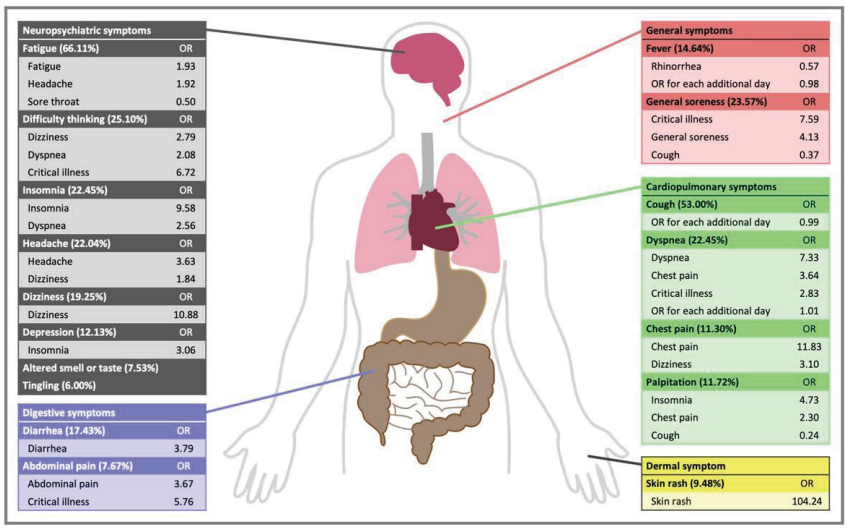


Fig. 3. Associated Risk Factors of Post-COVID Symptoms.
Abbreviation: OR, odds ratio

of post-COVID symptoms across neuropsychiatric, general, cardiopulmonary, digestive, and dermal systems, presented as ORs.

Discussion

Although most participants had mild disease, 57% had acute symptoms, with sore throat (35%), cough (35%), fever (30%), and fatigue (30%) being the most common. However, 87% of the participants had post-COVID symptoms, and the most common were fatigue (66%), cough (53%), cognitive difficulty (25%), and general pain (23%). The proportion and pattern of post-COVID symptoms differed from those in the acute phase. Multiple logistic regression analysis showed that initial symptoms, critical illness, and infection duration predicted post-COVID symptoms.

The pathophysiology of the acute symptoms of COVID-19 involves viral toxicity, immunological dysregulation, microvascular damage, and hypercoagulation. [2] Although the World Health Organization initially reported that the time from onset to recovery was approximately 2 weeks for mild cases and 3–6 weeks for severe cases, [5] later studies reported that more than half of the participants remained unwell, sometimes felling worse than at onset. [5-6] Huang *et al*. reported that 76% of participants reported at least one symptom after the infection. [6] A long-term follow-up study of SARS survivors in 2003 showed that 40% of the participants continued to experience chronic symptoms for 41.3 months after infection. [7] Therefore, it is important to monitor the post-infection status of patients with COVID-19. Identifying initial presentation patterns and factors associated with post-COVID symptoms can inform their clinical management.

We reported that neuropsychiatric sequelae were the most common components of the post-COVID-19 syndrome, similar to previous reports. [2, 8] Montani *et al*. reported that, within 6 months post-infection, 40–70% had fatigue, 54% had insomnia, 31% had anxiety, 22% had

depression, and 14% had post-traumatic stress disorder. [8] Nalbandian *et al*. also reported that, at 6 months follow-up, 38% had headache, 30–40% had depression and anxiety, and 10% had altered taste and smell. [2] Persistent fatigue after 6 months has been reported in both severely and non-severely ill patients and is associated with poor quality of life, persistent dyspnea, and cognitive impairment. [8] The mechanisms of the neuropsychiatric sequelae of COVID-19 include direct viral infection, neuroinflammation, dysautonomia, neurodegeneration, systemic inflammation, and microvascular thrombosis.[2] Besides neurological injury, social and media environments trigger anxiety and depression.[8] Screening tools, including history-taking, imaging evaluation, or referral to a neurologist, are recommended to identify participants with neuropsychiatric sequelae. In this study, initial fatigue, dizziness, headache, insomnia, and depression were associated with higher post-COVID neuropsychiatric sequelae. Ghosn *et al*. similarly suggested that multiple initial symptoms were associated with post-COVID neuropsychiatric sequelae, [9] and Montani *et al*. suggested that cognitive impairment was associated with headache and anosmia during acute infection. [8] These findings indicate that patients with such initial symptoms warrant closer follow-up.

Cough is one of the most common post-COVID pulmonary symptoms. Song *et al*. reported that cough can persist for weeks or months after SARS-CoV-2 infection and is often accompanied by chronic fatigue, cognitive impairment, dyspnea, or pain. [10] Post-COVID cough has been hypothesized to result from neuroinflammation and neurostimulation of vagal sensory nerves, leading to a cough hypersensitivity state. [8, 10] In the current study, 53% of participants had a post-acute cough, and initial cough was strongly associated with post-COVID cough. We also found that a longer the duration after infection was associated with lower risk of developing a post-COVID cough. Montani *et al*. reported that cough is a highly prevalent symptom, affecting 42% of participants after COVID-19. [8] The other common post-COVID pulmonary symptoms are dyspnea. In the current study, 22% of the participants had post-COVID dyspnea, and initial dyspnea, insomnia, and chest pain were associated with a higher risk of developing post-COVID dyspnea. Previous studies have shown that the prevalence of dyspnea ranges from 5% to 81% of hospitalized and 14% of non-hospitalized participants. [8] Nalbandian *et al*. reported that dyspnea and exercise intolerance are common post-COVID symptoms. [2] The mechanisms of dyspnea after COVID-19 include lung parenchymal sequelae, respiratory and cardiovascular dysfunction, pulmonary emboli, muscle deconditioning, anxiety, and psychological trauma. [8, 11] Pulmonary function tests showed that 22–56% of COVID-19 survivors had abnormal lung diffusion after 6 months of infection. [6] Anxiety, depression, and post-traumatic stress symptoms have been associated with concomitant dyspnea in the months following infection. [8] In our study, a longer duration after infection was associated with a higher risk of developing dyspnea, indicating dyspnea may worsen over time in some patients. Therefore, aggressive assessment and treatment of dyspnea are important. For participants with dyspnea and exercise intolerance, pulse oximetry, chest radiography, D-dimer, pulmonary function test, 6 minute walk distance, echocardiogram, or computed tomography (CT) scan may be considered. [2] Management of dyspnea includes breathing ex-

ercises, airway clearance, pulmonary rehabilitation, and psychological interventions. [8]

Palpitations and chest pain are the most common post-COVID cardiovascular symptoms. [2, 6] Previous studies reported that persistent symptoms of cardiovascular sequelae, such as chest pain, were reported in 20% of COVID-19 survivors at 2 months. In a Chinese study, palpitations and chest pain were reported in 9% and 5% of COVID-19 survivors, respectively, at 6 months. [6] Mechanisms contributing to post-COVID cardiovascular sequelae include viral invasion of cardiomyocytes, immunological damage to cardiac tissues and the conduction system, vascular thrombosis, myocardial ischemia due to coronary plaques, hypoxemia, and stress cardiopathy. [2, 8] In a cohort with mild or asymptomatic COVID-19, cardiac magnetic resonance imaging (MRI) performed 11–28 days after infection revealed myocarditis in 15% and myocardial injury in 30%. [12] Another study reported myocardial inflammation on post-COVID cardiac MRI in 60% of survivors 2 months post-infection. [13] COVID-19-associated arrhythmias were also described and were suspected to result from elevated catecholaminergic tone, myocardial injury with reentrant arrhythmias, and postural orthostatic tachycardia syndrome. [2] Participants with cardiovascular symptoms should be monitored using serial clinical judgment, echocardiography, and electrocardiogram follow-up. In this study, initial chest pain and dizziness were associated with a higher incidence of post-COVID chest pain, whereas initial chest pain and insomnia are associated with a higher incidence of post-COVID palpitation.

Interestingly, an initial cough was associated with a lower incidence of post-COVID palpitations in our cohort. One possible explanation is autonomic modulation through Valsalva-like mechanism. A previous Cochrane analysis demonstrated that the Valsalva maneuver, a simple noninvasive intervention, can terminate certain arrhythmias, with reported reversion success rates of 19.4% to 54.3%.[14] Consistent with this concept, a recent study demonstrated that the Valsalva maneuver is effective for cardioversion of atrioventricular nodal reentrant tachycardia, highlighting the clinical relevance of vagal modulation in arrhythmia control.[15] Coughing transiently increases intrathoracic pressure and stimulates vagal tone, producing physiological effects analogous to the Valsalva maneuver.[16] Based on this mechanism, we propose that cough-induced autonomic modulation during acute COVID-19 may reduce susceptibility to post-infectious palpitations by altering cardiac conduction and autonomic balance. This hypothesis remains speculative and should be interpreted with caution, but provides a plausible physiological framework linking the respiratory symptoms and cardiovascular sequelae in post-COVID syndrome. Further prospective studies incorporating autonomic function assessments and rhythm monitoring are warranted to validate this observation and elucidate the underlying mechanisms.

Owing to the expression of angiotensin-converting enzyme 2 in the GI mucosa, acute SARS-CoV-2 infection is associated with GI symptoms such as nausea, vomiting, diarrhea, and abdominal pain. [17] In patients with post-COVID, GI-related symptoms may persist. [17] In a study of 749 COVID-19 survivors, 29% reported GI symptoms, including heartburn (16%), constipation (11%), diarrhea (10%), abdominal pain (9%), and nausea (7%), at 6 months after infection. [18] Another study involving 73,435 survivors showed GI symptoms after COV-

ID-19, including constipation, diarrhea, dysphagia, and abdominal pain. [19] Possible mechanisms underlying post-COVID GI symptoms include viral persistence, microbial dysbiosis, intestinal immune activation, and neuroimmune maladaptation. [17, 20] Prolonged viral fecal shedding has been reported in participants with post-COVID, with viral RNA detectable at an average of 28 days after the onset of infection. [2] In addition, SARS-CoV-2 may alter the gut microbiota, enrich opportunistic infectious organisms, and deplete beneficial symbionts. [2] Post-infectious neuro-immune maladaptation can also causes motility disorders and related GI symptoms. [17] In the current study, diarrhea and abdominal pain persisted during the post-COVID period, and critical illness, initial diarrhea, and abdominal pain were associated with a higher risk of post-COVID GI symptoms. Therefore, aggressive management of the initial GI symptoms is recommended. [20]

Initial dermatological manifestations help to identify and treat SARS-CoV-2 infections. Most skin lesions (88%) occurred after or were concurrent with other COVID-19 symptoms, whereas a minority occurred before the onset of other symptoms.[21] An international study of 716 participants from 31 countries showed that the most common morphologies during the initial SARS-CoV-2 infection were morbilliform (22%), pernio-like (18%), urticaria (16%), macular erythema (13%), vesicular (11%), papulosquamous (9.9%), and retiform purpura (6.4%). [21] Among these lesions, pernio-like lesions were common in participants with mild disease, and retiform purpura was common in hospitalized participants. [21] One meta-analysis reported that the most common skin lesions in early SARS-CoV-2 infection were pernio-like lesions (51.5%), erythematous maculopapular rashes (13.3%), and viral exanthems (7.7%). [22] Average latency from the time of respiratory symptoms to cutaneous lesions was 1.5 days in children and 7.9 days in adults. [22] Studies on dermatological manifestations post-COVID are relatively limited. McMahon *et al*. used an international registry spanning 41 countries and reported a median duration of COVID-19–related dermatologic signs and symptoms of 13 days. [23] In the current study, 9.5% of the patients had a post-COVID skin rash, and the only factor associated with post-COVID rash was an initial rash.

In this study, critical illness was associated with a higher risk of post-COVID general soreness (OR 7.59), difficulty in thinking (OR 6.72), and abdominal pain (OR 5.42). Chronic pain is a common symptom following COVID-19, and previous studies suggests that survivors of critical illness are at high risk of developing chronic pain. [24] Fiala *et al*. reported that chronic pain is of particular concern for patients with COVID-19 admitted to hospitals, particularly to the intensive care units (ICUs). [25] Factors associated with the development of chronic general soreness after critical illness due to COVID-19 include multiple morbidities and old age. [24-25] Overall physical conditions may predispose COVID-19 surviviors to chronic pain [25] There are many causes of chronic pain among the survivors of COVID-19. SARS-CoV-2 can invade multiple tissues, leading to diffuse pain manisfestations. [26] Myalgia, a symptom of muscle discomfort typically related to systemic or local infections or inflammation, may occur when cytokines stimulate prostaglandin E2 production, activating peripheral pain receptors. [26] Additional contributors to chronic pain include prolonged immobility, neuromuscular blockade, repeated proneness, and nerve

damage. [25] It has been proposed that patient weakness may contribute to rapid deconditioning and musculoskeletal pain, which are particularly prevalent in critically ill patients in the ICUs. [25] Patients with severe infection were also more likely to develop neurological complications; neurological symptoms were observed in 45.5% of severely ill participants. [27] One meta-analysis of 19 studies (11,324 cases) reported prevalences of post-COVID-19 neurological symptoms of fatigue (37%), brain fog (32%), memory issues (27%), and attention disorders (22%). [28] Severe acute illness was associated with higher frequency of neurological sequelae. [28] The mechanisms underlying the neuropsychiatric sequelae of COVID-19 include direct viral infection, neuroinflammation, neurodegeneration, microvascular thrombosis, and severe systemic inflammation, which are more prominent in critical cases. [2] Mao *et al*. found that severely ill patients had higher D-dimer levels than mildly ill patients, potentially contributing to neurological sequelae. [27] Abdominal pain has been reported to be associated with the severity of COVID-19. [29-30] In a meta-analysis including more than 6000 participants, Mao *et al*. reported that abdominal pain was associated with severe forms of COVID-19, [29] and Zeng *et al*. similarly reported that abdominal pain was associated with an increased risk of severe COVID-19. [30] In that study, only abdominal pain—not diarrhea, vomiting, or nausea—was significantly associated with increased COVID-19 severity, leading the authors to propose that higher gastrointestinal viral load may be required to cause abdominal pain. [30] Accordingly, greater clinical attention to COVID-19 patients who present with abdominal pain is warranted.

Clinical implication

The COVID-19 outbreak has been a major challenge for global health systems, requiring the comprehensive mobilization of health resources. Patients with post-COVID often present with persistent symptoms, sometimes exceeding those during the acute infection. The symptoms of post-COVID are multisystemic, and typically require multidisciplinary management. Healthcare providers should proactively recognize this issue and provide timely, targeted care. Based on the current research, initial COVID-19 symptoms and the severity of illness are factors associated with post-COVID symptoms. We found that initial sore throat and critical cases were associated with a higher risk of post-COVID general symptoms such as fever or general soreness. Initial neuropsychiatric symptoms (fatigue, insomnia, headache, and dizziness), dyspnea, and critical symptoms are associated with a higher risk of post-COVID neuropsychiatric symptoms. Initial chest pain, dyspnea, and insomnia were associated with a higher risk of post-COVID pulmonary symptoms. Initial GI symptoms (diarrhea and abdominal pain) and critical cases were associated with higher post-COVID GI symptoms. An initial skin rash was associated with a higher incidence of post-COVID skin rash. Therefore, a comprehensive assessment of initial symptoms across neuropsychological, pulmonary, cardiac, GI, and dermatological systems, is important. The prioritization of follow-up care should be prioritized for patients with factors associated with a high risk of post-COVID symptoms.

Study limitations

This study had some limitations. First, this was a questionnaire-based study. We could not

provide participants' physical, laboratory, or imaging evaluations. However, based on our study, clinical caregivers should monitor for the initial symptoms associated with a higher risk of post-COVID symptoms and refer these patients for further physical, laboratory, or imaging evaluations. Second, this questionnaire survey was performed a mean of 43.4 ± 30.6 days after infection:186 participants (25.9%) were < 4 weeks after infection, 512 participants (71.4%) were 4–12 weeks after infection, and 19 participants (2.7%) were > 12 weeks post-infection. We conducted an early investigation to identify the post-COVID participants. However, long-term follow-up of post-COVID symptoms at 3 months, 6 months, 1 year, and > 1 year is required. In 2003, 40% of participants had chronic symptoms for 41.3 months after infection. [7]

Conclusion

Although most participants had mild acute disease, a high proportion of survivors reported post-COVID symptoms involving multiple organ systems. Common post-COVID symptoms include fatigue, cough, and cognitive difficulty. Specific initial symptoms were associated with a higher risk of post-COVID symptoms. Critical illness was associated with higher rates of general soreness, difficulty in thinking, and abdominal pain. Therefore, we suggest a comprehensive assessment of initial symptoms across multiple organ systems, including neuropsychological, pulmonary, cardiac, GI, and dermatological systems.

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Late Severe Immune-Mediated Colitis in an Advanced Lung Squamous Cell Carcinoma Patient Treated with Checkpoint Inhibitors

Je-Wei Shen[1], Gee-Chen Chang[1, 2, 3, 4]

Pembrolizumab has significantly improved survival outcomes for patients with metastatic non-small cell lung cancer exhibiting high PD-L1 expression (≥50%). Despite these advantages, immune checkpoint inhibitors (ICIs) are associated with immune-related adverse events, notably immune-mediated colitis, usually within 4–8 weeks of treatment initiation, complicating patient management. We present the case of a 70-year-old advanced lung squamous cell carcinoma patient with late and severe pembrolizumab-induced colitis. The patient had a good response to pembrolizumab only treatment, but after 11 cycles (8 months) of treatment, the patient developed severe colitis, characterized by refractory symptoms including profuse watery and bloody diarrhea. Colonoscopy revealed diffuse mucosal ulceration, erythema, friability, and pseudopolyps, particularly in the sigmoid colon. Biopsies showed mucosal hyperemia, hemorrhage, plasma cell and lymphocyte infiltration. Special stains (periodic-acid Schiff stain, Grocott's methenamine silver stain, acid-fast stain) and cytomegalovirus immunohistochemistry were negative for infectious causes or malignancy. Pembrolizumab was discontinued, and high-dose oral prednisone was initiated, followed by intravenous methylprednisolone. Due to a poor response, vedolizumab was administered 1 week after steroid use, but colitis persisted. Infliximab was started 2 weeks after steroid initiation, leading to gradual symptom improvement. However, infliximab was held after the third cycle due to a severe lung infection. ***(Thorac Med 2026; 41: 178-184)***

Key words: non-small cell lung cancer, immune checkpoint inhibitors, immune-related adverse events, programmed cell death-1, programmed death-ligand 1

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. In recent years, the therapeutic landscape of non-small cell lung cancer (NSCLC) has significantly evolved with the introduction of immune checkpoint inhibitors (ICIs), which have demonstrated improved clinical outcomes, particularly in patients with advanced disease. ICIs have become standard-of-care in various settings, including as first-line monotherapy or in combination with chemotherapy. The advent of ICIs, particularly pembrolizumab, has significantly altered the treatment landscape for metastatic NSCLC, especially in tumors expressing high levels of programmed death-ligand 1 (PD-L1) [2-3]. Pembrolizumab, an anti-PD-1 antibody, has demonstrated superior survival outcomes compared to conventional chemotherapy in pivotal trials, such as KEYNOTE-024 and KEYNOTE-042, establishing it as a standard first-line therapy for patients with high PD-L1 tumor proportion scores (TPS) ≥50% [2-3].

Immunotherapy, unlike conventional cytotoxic chemotherapy, is associated with a unique and potentially wide-ranging spectrum of side effects known as immune-related adverse events (irAEs) [4]. Immune-mediated colitis, characterized by inflammatory injury of the gastrointestinal tract, is becoming increasingly relevant as ICIs are more broadly implemented across diverse oncological settings. Notably, there is a growing body of evidence suggesting that the development of irAEs, including colitis, may correlate with improved clinical outcomes, such as progression-free survival (PFS) and overall survival (OS), potentially serving as surrogate markers for enhanced immune response and treatment efficacy [5]. Nonetheless, severe colitis necessitates vigilant monitoring, prompt diagnosis, and appropriate management, typically involving corticosteroids and biologic therapies such as infliximab or vedolizumab.

In this report, we present a case of pembrolizumab-induced colitis in a patient with metastatic NSCLC, highlighting diagnostic challenges, therapeutic strategies, and clinical implications, and underscoring the necessity of further research into predictive biomarkers, prophylactic interventions, and optimized clinical management to maximize therapeutic benefits while mitigating toxicity.

Case Presentation

A 70-year-old male with a heavy smoking history presented with a 2-month history of progressive dyspnea. Chest imaging revealed a right upper lung mass, and a biopsy of the right supraclavicular lymph node confirmed metastatic squamous cell carcinoma. Staging studies classified the disease as cT3N3M1a (stage IVA, AJCC 8th edition), and PD-L1 immunohistochemistry using the 22C3 pharmDx assay showed a TPS of 80%. No actionable driver mutations were detected on the Oncomine next-generation sequencing panel.

Pembrolizumab (200 mg IV every 3 weeks) was initiated with a partial response, but after 11 cycles, the patient developed profuse watery and bloody diarrhea. Stool analysis revealed abundant pus cells (50–99/HPF) and fecal occult blood positivity. Due to refractory severe colitis, colonoscopy was performed, and revealed diffuse mucosal ulceration, erythema, friability, and pseudopolyps, particularly in the sigmoid colon (Fig. 1). Biopsies showed mucosal hyperemia, hemorrhage, plasma cells and lymphocyte infiltration (Fig. 2, Fig. 3). Special

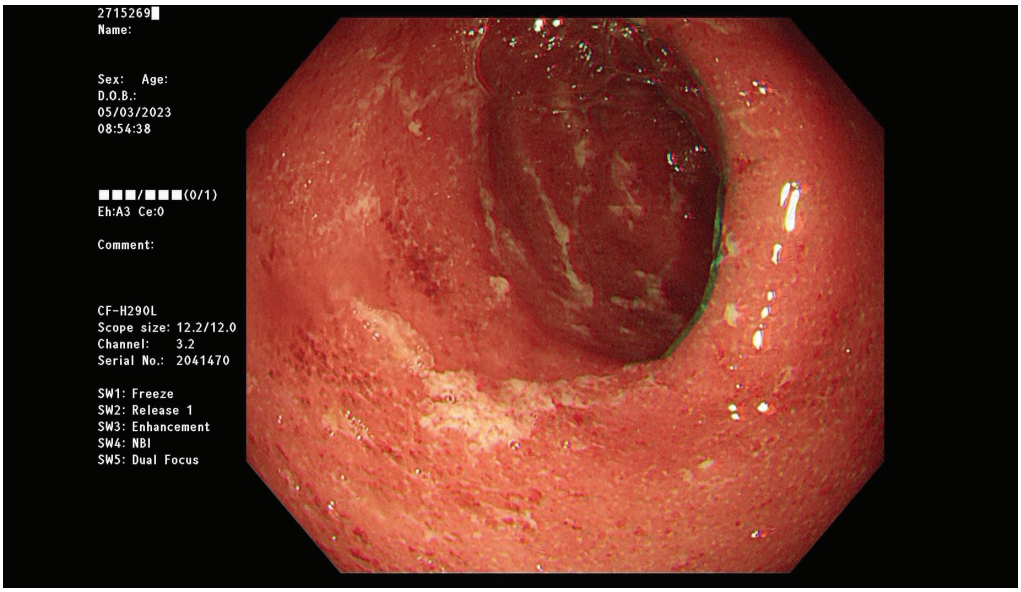


Fig. 1. Colonoscopy revealed multiple mucosal ulceration with extensive friability, erythema, and loss of vascular markings throughout the colon.

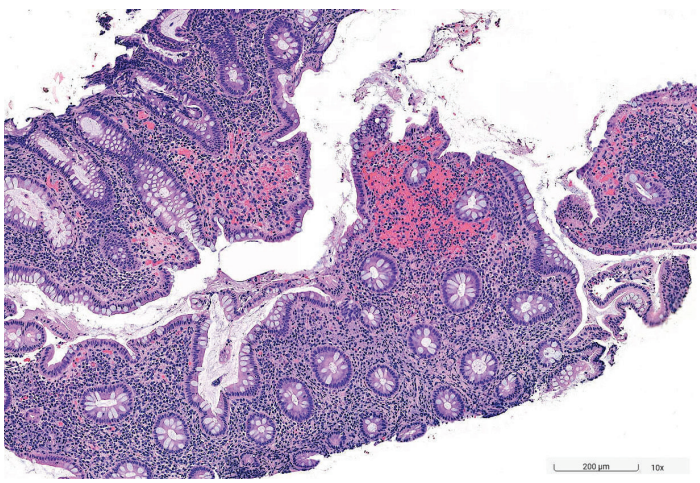


Fig. 2. Pathology showed hemorrhage and abundant lymphoplasma cell infiltration over the colonic mucosa.

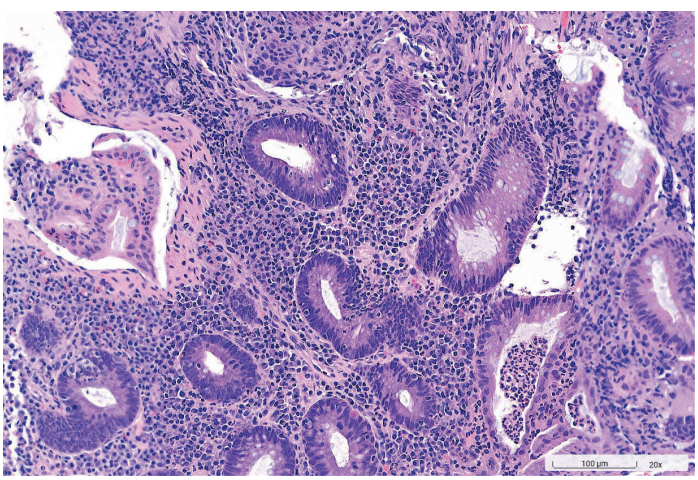


Fig. 3. This section showed crypt abscess, cryptitis and lymphocytic colitis.

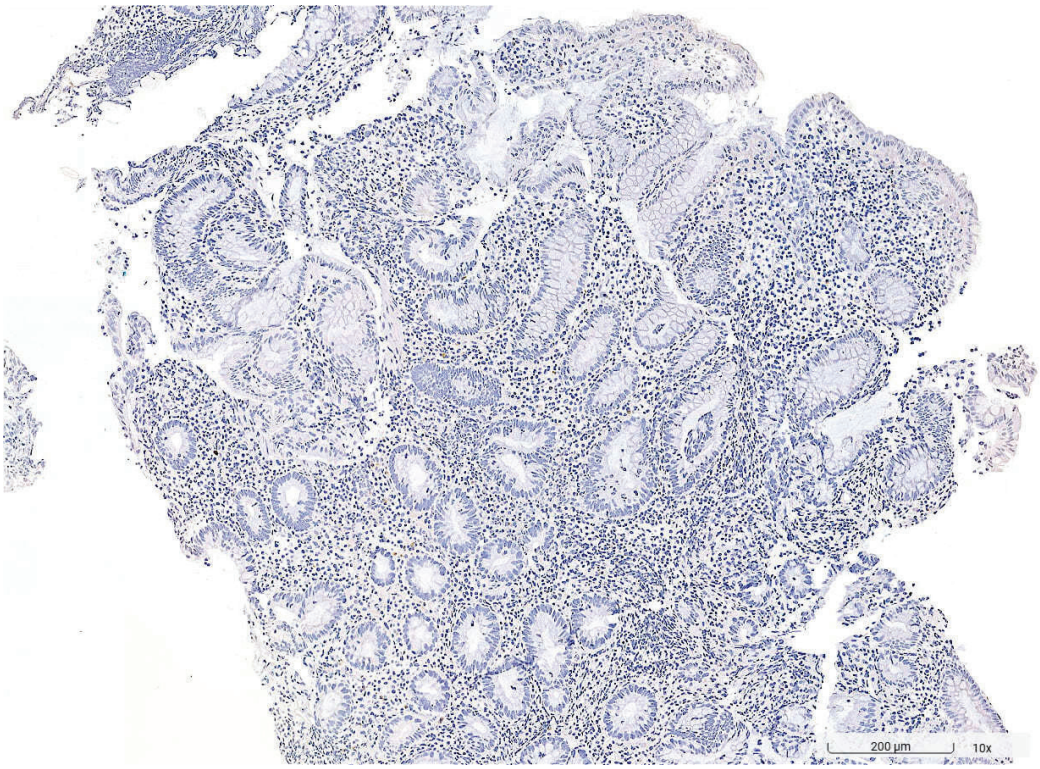


Fig. 4. Immunohistochemical analyses showed negative results for cytomegalovirus infection.

stains (periodic-acid Schiff stain, Grocott's methenamine silver stain, acid-fast stain) and cytomegalovirus immunohistochemistry were negative (Fig. 4) for infectious causes or malignancy.

Pembrolizumab was discontinued, and high-dose oral prednisone (1 mg/kg/day) was initiated, followed by intravenous methylprednisolone. Due to an incomplete response, vedolizumab was administered 1 week after steroid use, but colitis persisted. Infliximab was started 2 weeks after steroid initiation, leading to gradual symptom improvement. However, infliximab was held after the third cycle due to a severe lung infection.

Anti-cancer therapy was held for approximately 7 months. Due to disease progression, multiple systemic therapies were initiated, including platinum-based chemotherapy and later immunotherapy rechallenge with atezolizumab, without recurrence of colitis. Despite treatment adjustments, progressive disease with an enlarging primary tumor and liver metastases developed. Later, the patient died of pneumonia complicated with respiratory failure. The patient's OS was around 30 months.

Discussion

IrAEs are common and potentially serious complications of ICI therapy. Recent studies highlight the importance of early identification and prevention through a combination of clinical risk stratification, cytokine profiling, and real-world data analysis [6-7]. Baseline factors—such as elevated interleukin 6 (IL-6) or

interleukin 17 (IL-17) levels, a high neutrophil-to-lymphocyte ratio (NLR), the presence of autoantibodies (particularly antithyroid antibodies and antinuclear antibody), and certain autoimmune comorbidities—can help predict the risk of developing severe irAEs [6-7]. Early detection strategies include routine symptom checklists, periodic laboratory monitoring (e.g., thyroid function, liver enzymes, glucose), and patient-reported outcome systems [8].

Despite its clinical benefits, pembrolizumab treatment is frequently associated with irAEs, significantly complicating patient management. Our case exemplifies the severe immune-mediated colitis that emerged after 11 pembrolizumab cycles, presenting as profuse bloody diarrhea. The incidence observed in this study aligns with that of prior reports, where immune-mediated colitis has been documented in approximately 2% to 7% of patients, varying by treatment regimen and patient demographics [9].

The immunopathogenesis of ICI-colitis reflects dysregulated intestinal immune homeostasis triggered by checkpoint blockade. Preclinical studies show that anti-cytotoxic T-lymphocyte-associated antigen 4 agents like ipilimumab disrupt gut microbiota and regulatory T cell balance, augmenting T helper 1 cell (Th1) / T helper 17 cell (Th17)-driven inflammation. Similarly, PD-1 blockade facilitates conversion of tissue-resident memory T cells into cytotoxic effectors, promoting mucosal injury via interferon gamma and IL-23–mediated mechanisms [10].

Emerging evidence continues to refine our understanding of the risk factors associated with ICI-colitis. Xu *et al*. [11] conducted a large-scale analysis of 2,103 lung cancer patients and reported an overall incidence of immune-mediated colitis of 3.14%. Their multivariate analysis identified female sex, SCLC, elevated β2-microglobulin, globulin, and lower NLR as independent predictors of increased IMC risk. We observed similar patterns in our clinical cohort. Patients who developed ICI-colitis demonstrated a lower baseline NLR at the time of symptom onset, which rose following immunosuppressive treatment, suggesting a potential correlation between NLR dynamics and colitis activity. This observation supports NLR's utility as a predictive biomarker and potential treatment response indicator, warranting further prospective validation. Other studies have shown that hematologic indices, such as a NLR >2.3 and eosinophilia, may predict a higher risk of irAEs, while a lymphocyte-to-monocyte ratio >1.6 appears to have a protective effect [12]. Liao *et al*. [13] found that early short-course corticosteroids reduced irAEs requiring ICI discontinuation (5.8% vs. 15.7%, p=0.013) without impacting survival. Integrating blood biomarkers with prophylactic corticosteroids may aid early irAE prevention and risk stratification.

ICI-colitis typically presents within 4–8 weeks of treatment initiation, with the majority of patients experiencing grade 1–2 symptoms [14]. However, up to 16.7% of patients progress to grade ≥3 colitis, emphasizing the importance of early recognition and intervention. Our patient developed ICI-colitis much later than typical cases. This is rare, but it was severe, and should remind us to include this in the diagnosis.

Interestingly, patients developing ICI-colitis exhibit significantly improved PFS and OS, suggesting colitis may serve as a surrogate marker for effective immune activation [15]. Our patient initially mirrored this prognostic benefit, maintaining stable disease during active colitis management, despite pembrolizumab

cessation.

Several clinical questions remain unanswered, including whether prophylactic biologic therapy may benefit high-risk populations, such as those with inflammatory bowel disease, and the optimal timing and modality for early diagnosis. As the use of ICIs expands, ICI-colitis will become increasingly prevalent. Advances in immunopathogenesis understanding, refined risk stratification, and evolving treatment algorithms hold promise for improving patient outcomes. Multidisciplinary collaboration and ongoing clinical research will be essential for mitigating ICI-related toxicity while preserving immunotherapy's oncologic benefits.

Conclusion

Patients with high PD-L1-expressing NSCLC typically exhibit better responses to ICI therapy, although this therapeutic benefit is often accompanied by an increased incidence of irAEs. While the development of irAEs, including immune-mediated colitis, can lead to significant end-organ damage and clinical challenges, these events paradoxically correlate with improved prognostic outcomes. Timely recognition and effective management of irAEs are essential to maximize clinical benefits. As demonstrated in our patient, proactive identification and aggressive intervention enabled disease stabilization for approximately 7 months, even though his ICI-colitis developed much later than in typical cases. Thus, clinicians must balance therapeutic efficacy with vigilant monitoring and tailored treatment strategies for irAEs, thereby optimizing patient outcomes through multidisciplinary collaboration and ongoing research into predictive biomarkers and treatment protocols.

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Improvement in Clinical Symptoms and Reduction of IgG4 Levels Following Mepolizumab Therapy in a Patient with Eosinophilic Granulomatosis with Polyangiitis: A Case Report

Mei-Ru Lu[1], Ping-Hung Kuo[1]

Although the exact role of immunoglobulin G4 (IgG4) in eosinophilic granulomatosis with polyangiitis (EGPA) remains unclear, elevated serum IgG4 levels have been frequently observed in previous studies. We reported the case of a 27-year-old man with EGPA presenting with asthma, hypereosinophilia, and elevated IgG4 without positive anti-neutrophil cytoplasmic antibody (ANCA). His condition progressed with pulmonary infiltrates and systemic symptoms, responding initially to corticosteroids. Mepolizumab was introduced as maintenance therapy, resulting in sustained symptom control, tapering of corticosteroids, a significant reduction in the blood eosinophil count and normalization of IgG4 levels. While previous studies have linked IgG4 reduction to EGPA remission, this is, to our knowledge, the first report demonstrating IgG4 improvement following mepolizumab therapy. Further research is needed to clarify the utility of IgG4 as a biomarker in EGPA. ***(Thorac Med 2026; 41: 185-191)***

Key words: eosinophilic granulomatosis with polyangiitis, mepolizumab, IgG4, hypereosinophilia

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare vasculitic disorder characterized by asthma, eosinophilia, and systemic inflammation affecting small- to medium-sized vessels. The disease is considered to be primarily mediated by Th2 cytokines, including interleukin (IL)-4, IL-5, and IL-13. These cytokines promote eosinophil activation and class-switch recombination in B cells, which may lead to the production of immunoglobulin E(IgE) and IgG4 [2]. Elevated serum IgG4 has been observed in a subset of patients with EGPA and appears to correlate with disease activity [1]. However, the significance of IgG4 in EGPA pathogenesis remains controversial. Although mepolizumab, an anti-IL-5 monoclonal antibody, has demon-

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strated efficacy in reducing relapse and steroid dependence in EGPA, its impact on serum IgG4 levels has not been systematically studied. Herein, we present a case of EGPA with markedly elevated IgG4, which responded favorably to mepolizumab therapy with a parallel decline in IgG4 levels, suggesting its potential as a treatment-responsive biomarker.

Case Presentation

A 27-year-old male with a history of allergic rhinitis since childhood presented to our chest clinic in 2022 with a 2-year history of dry cough, nasal congestion, chest tightness, exertional dyspnea, and occasional wheezing, consistent with typical asthma symptoms. He also had a positive family history—his father was diagnosed with asthma. Initial pulmonary function testing revealed preserved spirometry. The ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) was 94.2%. The patient's FEV_1 was 3.40 liters (84.8% of predicted), and his FVC was 3.61 liters (79.5% of predicted). A bronchodilator test showed negative results. Laboratory evaluation showed marked peripheral eosinophilia (up to 3101/μL, 35%) and elevated serum IgE (1,060 IU/mL).

Table 1. Serial changes in Asthma Control Test (ACT), Eosinophil (EOS) Counts and Percentage, IgG4, IgG4/IgG Ratio with Treatments, and Daily Prednisolone (PDN) Dose.

Date	ACT	WBC (k/μL)	Eos (%)	Eos count (/μL)	IgG4 (mg/dL)	IgG4/IgG	PDN daily dose (mg)
2022/08/19	23	8.86	35	3101	608	59.1%	5
2022/09/29	23	5.69	22.8	1297			5
2022/12/02	22	7.46	25.3	1887			5
2023/01/18	21	8.08	22.8	1842			10
2023/03/13	22	8.20	10.7	877			10
2023/04/05	24	6.12	15.5	948			5
2023/05/15	25	7.91	14.0	1107			5
2023/07/12	Flares up with multiple-organ involvement						
	15	14.38	40	5752			
2023/07/25		6.78	20	1356			15
2023/08/15	23	7.07	18.7	1322			15
2023/08/22	Start mepolizumab 300 mg Q4W						
2023/09/13	24	6.41	0.8	51			15
2023/10/11	24	6.28	1.1	69	223	25.3%	2.5
2023/11/14	24	6.23	0.5	31	174		2.5
2024/03/19	24				138	14.5%	2.5
2024/07/05	24	5.80	0.2	12	129		2.5
2025/03/17	24	4.36	0.7	31	120		2.5

Autoimmune screening was negative, including anti-neutrophil cytoplasmic antibody (ANCA) and anti-nuclear antibody (ANA), except for mildly elevated rheumatoid factor (19.72 IU/mL) and significantly elevated serum IgG4 (608 mg/dL). Chest radiography was unremarkable, while chest computed tomography (CT) revealed scattered and ill-defined peribronchial ground-glass opacities and mild bronchial wall thickening in both lungs, suggestive of bronchitis or bronchiolitis. A clinical diagnosis of asthma was made.



Fig. 1. Skin lesions.
*Papulopustules located on his forehead.

The patient was initially treated with inhaled budesonide/formoterol, which led to only partial symptom improvement. Given the marked eosinophilia, FIP1L1::PDGFRα fusion testing was performed and was negative. Bone marrow examination was recommended but declined by the patient. A repeat pulmonary function test 1 month later revealed preserved spirometry but mildly reduced diffusion capacity (DLCOcorr 77.1%). Due to persistent symptoms and biochemical evidence of type 2 inflammation, inhaled therapy was escalated in early 2023 to high-dose inhaled corticosteroid (ICS) with triple therapy. The patient demonstrated a significant improvement in spirometry in March 2023. His FEV_1 increased from 3.40 L in August 2022 to 3.98 L in March 2023, corresponding to a 17.1% (580 mL) increase. However, symptom control remained suboptimal.

In July 2023, the patient presented to the emergency department with an asthma exacerbation following an upper respiratory infection. Systemic features, including generalized faint erythema, digital numbness, and mild arthralgia, were also noted. Chest CT revealed small,



Fig. 2. Chest computed tomography (CT) showed small, randomly distributed patches of ground-glass opacities and mild bronchial wall thickening.

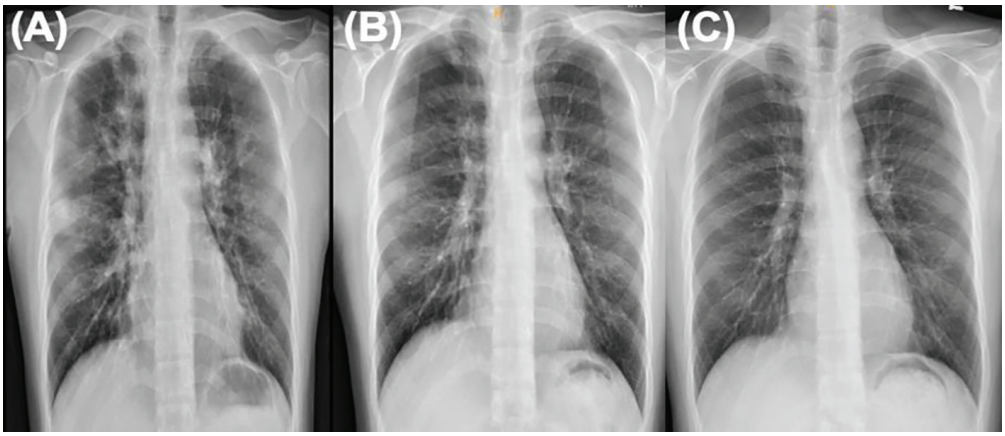


Fig. 3. Serial changes in chest radiography revealed bilateral lung opacities resolved after IV methylprednisolone was started on 2023/07/12. (A: 2023/07/12, before treatment; B: 2023/07/17, after 5-day high dose steroid therapy; C: 2023/07/25, on low dose oral prednisolone).

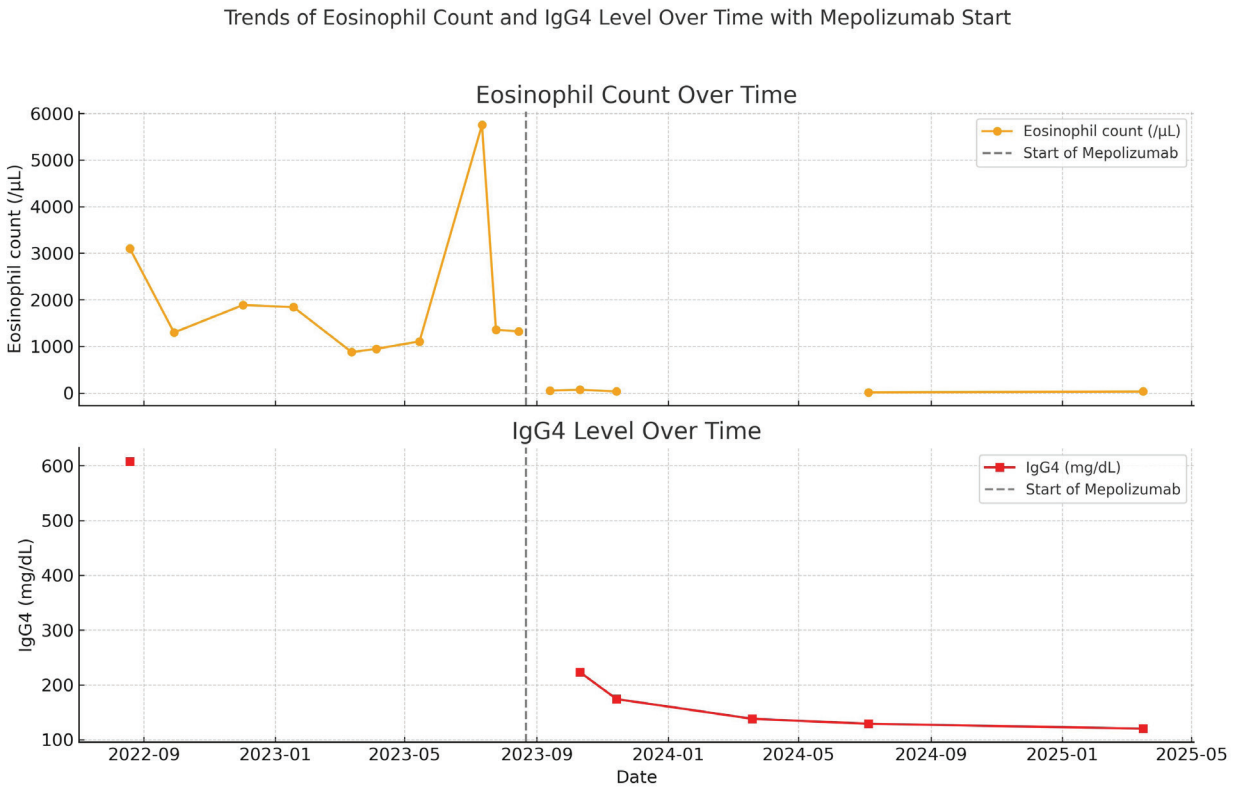


Fig. 4. Trends in eosinophil counts and serum IgG4 levels over time. The dashed line indicates the initiation of mepolizumab therapy (August 22, 2023). Eosinophil counts and IgG4 levels both demonstrated significant decline following treatment initiation.

randomly distributed patches of ground-glass opacities and mild bronchial wall thickening. Intravenous methylprednisolone was administered, resulting in resolution of the rash and symptomatic improvement. Bronchoscopy with transbronchial biopsy revealed benign lung tissue without eosinophilic infiltration or vasculitis, likely due to prior steroid use. Nerve conduction studies confirmed right peroneal nerve entrapment. Based on the combination of asthma, eosinophilia, peripheral neuropathy, transient rash, and radiographic findings, a diagnosis of EGPA was established. Further evaluation showed normal cardiac systolic function and unremarkable urinalysis, indicating no cardiac or renal involvement. Retrospective review of the patient's history revealed chronic gastritis with recurrent left upper quadrant discomfort, requiring endoscopic evaluations in 2008 and 2014. Biopsies from both procedures revealed chronic gastritis with lymphoplasmacytic infiltration.

During follow-up, pulmonary function remained stable with normalized diffusion capacity (DLCOcorr 101%). Mepolizumab (300 mg subcutaneously every 4 weeks) was initiated in August 2023 for long-term disease control and steroid tapering. The patient achieved sustained clinical remission, with stable asthma control (Asthma Control Test, ACT, 23–24), consistent peak expiratory flow (600–690 L/min), and persistent eosinophil suppression (<1%). Notably, serum IgG4 declined from 608 to 120 mg/dL, and IgE levels decreased to 130 IU/mL. Prednisolone was successfully tapered to 5 mg every other day. This case illustrates effective disease control with mepolizumab in EGPA involving the upper airway, gastrointestinal tract, lungs, skin, and peripheral nerves. The clinical and biomarker improvements observed support the potential role of serum IgG4 as a useful marker of treatment response in EGPA.

Discussion

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis characterized by asthma, peripheral eosinophilia, and inflammation of small- to medium-sized vessels. EGPA is widely considered a Th2-mediated disease, with type 2 cytokines—such as interleukin (IL)-4, IL-5, and IL-13—playing central roles in its immunopathogenesis. These cytokines not only promote eosinophil survival and activation but also induce class-switch recombination in B cells, leading to the production of IgG4 [1-2].

Several studies have reported elevated serum IgG4 levels in patients with active EGPA. In a seminal study by Vaglio *et al*. [1], immunoglobulin profiles and tissue immunohistochemistry were assessed in 46 patients with EGPA (formerly Churg–Strauss syndrome), including 24 with active disease. Serum IgG4 levels in active EGPA were significantly higher than those in healthy controls, patients with asthma, and those with granulomatosis with polyangiitis (GPA). Furthermore, IgG4 concentrations positively correlated with both the number of organ manifestations and the Birmingham Vasculitis Activity Score (BVAS), whereas IgE levels showed no such association. Notably, IgG4 levels did not differ significantly between ANCA-positive and ANCA-negative patients. In a subset of 12 patients followed longitudinally, both serum IgG4 levels and the IgG4/IgG ratio significantly decreased during remission, although treatment details were not disclosed. Interestingly, tissue biopsies of the upper airway from the same cohort did not reveal increased

infiltration of IgG4-positive plasma cells, suggesting that serum IgG4 more likely reflects systemic, rather than local, immune dysregulation.

Nevertheless, there are other studies reporting IgG4-positive plasma cells infiltration in EGPA-involved organs [3-4]. A multicenter Japanese study analyzing 22 treatment-naïve patients with newly diagnosed EGPA found increased numbers and proportions of IgG4-positive plasma cells at sites of organ involvement, and yet the pathological significance could not be established [4].

While biologic therapies targeting the IL-5 axis have demonstrated clinical efficacy in treating EGPA, their impact on serum IgG4 levels remains largely unexplored. To date, no study has systematically evaluated the effect of mepolizumab, an anti–IL-5 monoclonal antibody, on IgG4 in EGPA. In contrast, a case report described a patient with corticosteroid-refractory, MPO-ANCA–positive EGPA who achieved complete remission with benralizumab [5]. After 4 weeks of treatment, eosinophils decreased from 1330 to 0/μL, BVAS improved from 16 to 7, and serum IgG4 dropped from 311 to 100 mg/dL. Interestingly, a transient rise in IgG4 between weeks 8 and 32 was associated with increased BVAS despite stable eosinophils, CRP, and MPO-ANCA levels—suggesting that IgG4 may serve as an independent marker of residual disease activity beyond conventional inflammatory parameters.

To date, the pathogenic role of IgG4 in EGPA remains uncertain. However, its dynamic correlation with disease activity and response to IL-5–targeted therapy raises the possibility that serum IgG4 may serve as a surrogate biomarker in a subset of patients with prominent Th2-driven disease. Our case adds to this emerging concept by demonstrating a marked and sustained decline in serum IgG4 following mepolizumab therapy, in parallel with clinical remission and corticosteroid tapering.

In our patient, allergen-specific IgE testing revealed sensitization only to dust mites, with a serum-specific IgE level of 0.91 IU/mL (Class 2), while all other tested inhalant allergens—including pollens, molds, pet dander, and fungal antigens—were within Class 0. These findings suggest limited atopic sensitization. Although dust mite exposure could contribute to baseline Th2 activation, the elevated IgG4 levels in this patient were more likely driven by systemic eosinophilic inflammation rather than persistent allergen exposure. The subsequent decline in both IgE and IgG4 after mepolizumab treatment supports this interpretation.

Nevertheless, our report has limitations. Although the initial IgG4 level (608 mg/dL) was obtained a year before the initiation of mepolizumab, subsequent IgG4 levels were not measured during the interim period of disease progression and systemic corticosteroid treatment. As a result, we were unable to determine whether serum IgG4 demonstrated dynamic fluctuation in response to disease activity prior to the use of biologics. Further studies incorporating longitudinal IgG4 measurements across different phases of EGPA management would help clarify its role as a reliable biomarker of disease activity.

Conclusion

This case report describes the successful clinical and immunological remission of EGPA with mepolizumab, including reduction in serum eosinophils and IgG4 levels. The observed decline in IgG4 paralleled disease control,

despite its previously uncertain role in EGPA. While IgG4 may not be directly pathogenic, its dynamic relationship with disease activity raises the possibility of its use as a surrogate biomarker in Th2-dominant EGPA. Further studies are warranted to validate its reliability for monitoring treatment response and guiding personalized management.

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Hemophagocytic Lymphohistiocytosis Induced by Pembrolizumab in Lung Squamous Cell Carcinoma: Effective Treatment with Tocilizumab

Hua-Tung Fan[1, 2], Chia-Hsin Liu[2]

Background: Haemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening immune-related adverse event (irAE) associated with the use of immune checkpoint inhibitors (ICIs). Non-specific manifestations often mimic infections, leading to delayed diagnosis and treatment.

Case Presentation: A 44-year-old man with advanced squamous cell carcinoma of the right upper lung (cT3N2M1b, stage IV, PD-L1 TPS 55%) received first-line cisplatin, paclitaxel, and pembrolizumab. After the third pembrolizumab cycle, the patient developed HLH, fulfilling the HLH-2004 diagnostic criteria, with fever, cytopenia, splenomegaly, hyperferritinemia, and hypofibrinogenemia. High-dose corticosteroid therapy failed to induce remission; however, tocilizumab led to rapid clinical and laboratory improvements. Chemotherapy was resumed without pembrolizumab, and subsequent surgical resection confirmed a complete pathological response. No lung cancer or HLH recurrence was observed during 3 years of follow-up.

Conclusion: Early recognition of HLH in patients receiving ICIs is critical to prevent life-threatening complications. Tocilizumab may serve as an effective option for steroid-refractory HLH, and durable tumor remission remains achievable despite this severe immune-related event. ***(Thorac Med 2026; 41: 192-199)***

Key words: hemophagocytic lymphohistiocytosis; immune checkpoint inhibitor; pembrolizumab; tocilizumab; immune-related adverse event; lung squamous cell carcinoma

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome characterized by excessive immune activation and a cytokine storm [1]. In recent years, immune checkpoint inhibitors (ICIs) have transformed the therapeutic landscape for various malignancies, including non-small cell lung cancer. However, these

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agents can also cause severe immune-related adverse events (irAEs), among which HLH is increasingly recognized [2-4]. ICI-induced HLH remains challenging to diagnose owing to its non-specific clinical features, such as fever, cytopenia, liver dysfunction, and elevated inflammatory markers, which often mimic infection or disease progression. Prompt recognition and appropriate immunosuppressive therapy are essential for preventing rapid clinical deterioration [3]. Here, we describe a case of pembrolizumab-induced HLH in a patient with advanced lung squamous cell carcinoma and highlight the diagnostic challenges and therapeutic strategies, including the role of interleukin-6 (IL-6) blockade in steroid-refractory cases.

Case Presentation

A 44-year-old man with a history of hyperlipidemia, sigmoid colon polyps, and a 30-pack-a-year smoking history presented with right-sided chest pain radiating to the back for 2 months. Chest computed tomography (CT) revealed a 4.7 cm cavitary mass in the right upper lobe invading the first rib. CT-guided biopsy confirmed poorly differentiated squamous cell carcinoma. Staging studies revealed chest wall invasion, right hilar lymphadenopathy, and bone metastasis to the right 11th rib, consistent with stage IV disease (cT3N2M1b, AJCC 8th edition). Molecular profiling revealed no targetable mutations, and the PD-L1 tumor proportion score was 55%.

The patient received first-line cisplatin, paclitaxel, and pembrolizumab (200 mg every 3 weeks) and developed a high-grade fever (40.1 °C) with chills 10 days after the third cycle. Laboratory tests revealed mild cytopenia (ANC 2.12 × 10^3/μL, hemoglobin 10.5 g/dL, platelets 117 × 10^3/μL) and elevated inflammatory markers (C-reactive protein 8.66 mg/dL, procalcitonin 0.34 ng/mL). Despite the administration of empiric broad-spectrum antimicrobials (meropenem, teicoplanin, and voriconazole), the fever persisted. Bacterial cultures of both blood and sputum yielded negative results. Comprehensive microbiological workup, including atypical pathogens, *Mycobacterium tuberculosis*, and viral infections (influenza A/B, SARS-CoV-2, herpes simplex virus types 1 and 2, Epstein–Barr virus, and cytomegalovirus), as well as a FilmArray Pneumonia Multiplex PCR Panel (adenovirus, coronavirus, human metapneumovirus, parainfluenza virus, RSV, *Bordetella pertussis, Chlamydophila* species, *Mycoplasma* species, human rhinovirus/enterovirus, and influenza A/B) performed on a nasopharyngeal swab, were all negative. Fungal studies for *Cryptococcus, Pneumocystis jirovecii, Aspergillus* species, and other fungal pathogens also revealed no evidence of infection.

The patient developed worsening cytopenia (ANC 0.64 × 10^3/μL, hemoglobin 9.9 g/dL, platelets 63 × 10^3/μL), acute hepatitis (AST 149 U/L, ALT 107 U/L), hyperferritinemia (1,792 μg/L), and hypofibrinogenemia (159 mg/dL) during hospitalization. Abdominal CT revealed splenomegaly with a long axis measuring 12.2 cm and no significant abnormal findings in the liver. These findings fulfilled five of the eight HLH-2004 diagnostic criteria: fever, splenomegaly, bicytopenia, hypofibrinogenemia, and hyperferritinemia. The HScore was 239, corresponding to an estimated 98–99% probability of HLH, supporting the diagnosis of immune checkpoint inhibitor-induced HLH in the appropriate clinical context (Figure 1).

High-dose intravenous dexamethasone (10 mg/m^2/day) was started on day 6 after the

Hemophagocytic lymphohistiocytosis-2004 diagnostic criteria			
The diagnosis HLH requires that either 1 or 2 below are fulfilled:			
(1) A molecular diagnosis consistent with HLH: Pathological mutations of PRF1,UNC13D,STXBP1, RAB27A, STX11, SH2D1A, or XIAP			
OR (2) Diagnostic criteria for HLH fulfilled (5 out of the 8 criteria below):			
(A) Initial diagnostic criteria			
		Normal range	Our patient
Fever	38·5°C or more		**40.1°C**
Splenomegaly	present	absent	**Splenomegaly** (CT imaging)
Cytopenias (affecting at least 2 of 3 cell lineages in the peripheral blood):			
- Hemoglobin	<9 g/dL	13.5 - 18.0 g/dL	
- Platelets	<100,000 /μL	150,000 - 400,000 /μL	**63,000 /μL**
- Neutrophils	<1,000/μL	1,800 - 8140 /μL	**635 /μL**
Hypertriglyceridemia and/or hypofibrinogenemia			
- Fasting triglycerides	≥265 mg/dL	<150 mg/dL	**177 mg/dL**
- Fibrinogen	≤150 mg/dL	2001 - 400 mg/dL	**147.5 mg/dL**
Hemophagocytosis in bone marrow or spleen or lymph nodes or liver			Not measured
(B) New diagnostic criteria			
Low or absent NK-cell activity			Not measured
Ferritin	≥500 μg/L	21.81 ~ 277.66 μg/L	**>20,000 μg/L**
Soluble CD25 (i.e., soluble IL-2 receptor)	≥2400 U/mL		Not measured

Fig. 1-1. HLH-2004 Diagnostic Criteria. Our patient fulfilled the required parameters.

The HScore				
Parameter	No. of points (criteria for scoring)		Our patient	Score
		scoring		
Known underlying immunosuppression	no	0	no	0
	yes	18		
Temperature (°C)	<38.4	0	40.1	49
	38.4–39.4	33		
	>39.4	49		
Organomegaly	0	0	Splenomegaly	23
	hepatomegaly or splenomegaly	23		
	hepatomegaly and splenomegaly	38		
No. of cytopenias	1 lineage	0	2 lineages	24
	2 lineages	24		
	3 lineages	34		
Ferritin (μg/L)	<2,000	0	>20,000	50
	2,000–6,000	35		
	>6,000	50		
Triglyceride (mg/dL)	<133	0	177	44
	133–354	44		
	>354	64		
Fibrinogen (mg/dL)	>250	0	147.5	30
	≤250	30		
Serum glutamic oxaloacetic transaminase (U/L)	<30	0	149	19
	≥30	19		
Hemophagocytosis features on bone marrow aspirate	no	0	Not measured	0
	Yes	35		
Total score				239
Probability of HLH	Optimal Cutoff: 169			98–99%*

Fig. 1-2. The HScore and a Total Score of 239 Points. This corresponded to an estimated 98–99% probability of HLH. The optimal cutoff value for the HScore was 169, with a reported sensitivity of 93% and specificity of 86% [18].
* Fardet *et al*., 2014

onset of spiking fever but failed to control the fever and cytopenia. The patient subsequently received two intravenous doses of tocilizumab (200 mg each) on days 7 and 17, resulting in rapid defervescence and normalization of blood counts, ferritin levels, and liver function (Figure 2). Chemotherapy was resumed without pembrolizumab and was well-tolerated. Post-

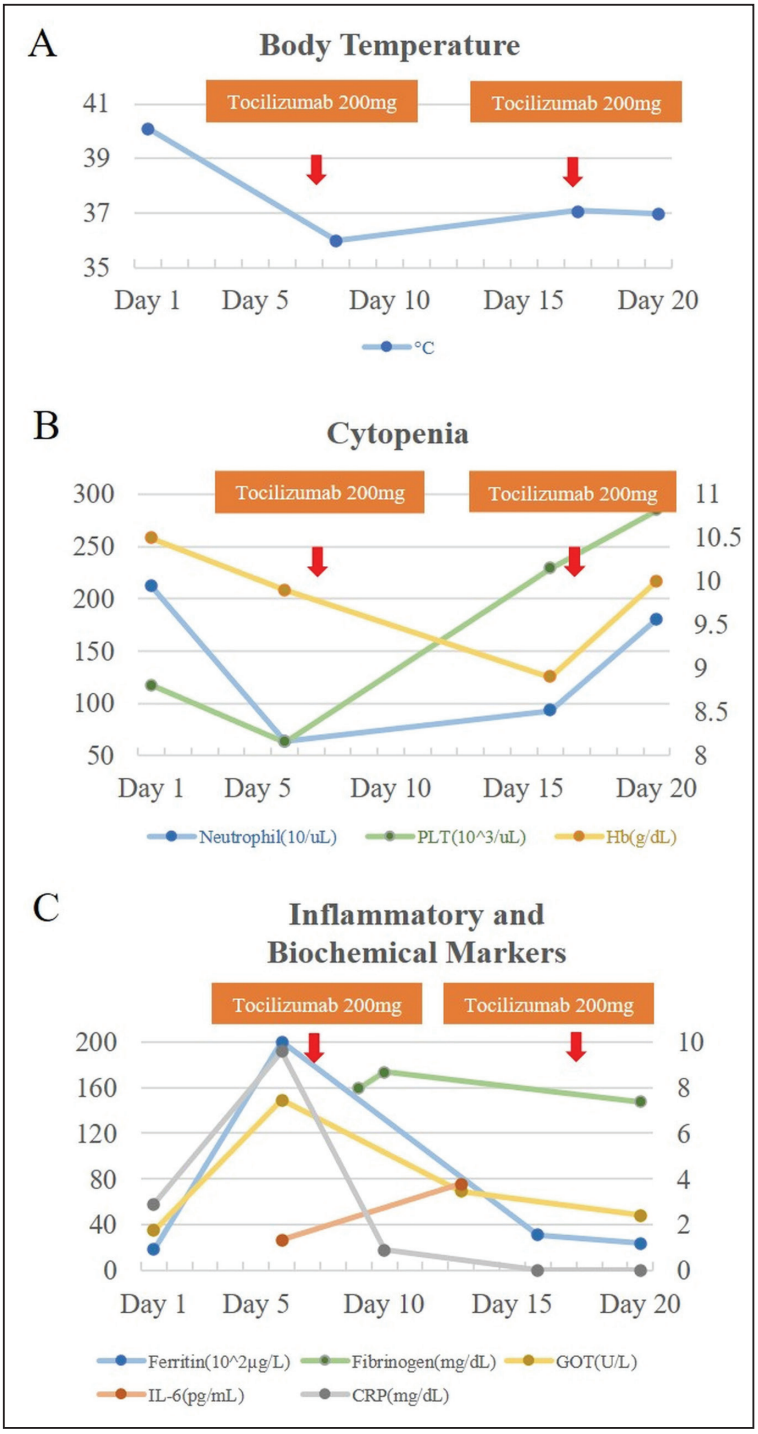


Fig. 2. Clinical Parameters during HLH Management. Day 1: high fever with chills; Day 6: initiation of dexamethasone; Day 7: administration of the first dose of tocilizumab; Day 17: administration of the second dose of tocilizumab . (A) Trends in body temperature over 20 days. Fever persisted after initiation of dexamethasone on day 5 but subsided dramatically following tocilizumab administration. (B) Cytopenias (neutrophil, hemoglobin, platelet) showing improvement after tocilizumab administration. (C) Changes in inflammatory and biochemical markers (ferritin, fibrinogen, GOT, CRP, and IL-6) reflecting treatment response.

treatment PET/CT demonstrated complete metabolic resolution of the lung, hilar, and bone lesions. The patient underwent video-assisted thoracoscopic right upper lobectomy with mediastinal lymph node dissection, which confirmed complete pathologic remission (ypT0N0). The patient remained disease-free without HLH recurrence after 3 years.

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome that results from the uncontrolled activation of cytotoxic T lymphocytes and macrophages, leading to massive cytokine release, tissue injury, and multiorgan failure [1-3]. Secondary HLH in adults is most often triggered by infections, autoimmune disorders, or malignancies; however, drug-induced and immune-related causes are increasingly recognized. Over the past decade, immune checkpoint inhibitors (ICIs) have emerged as additional precipitants, representing rare yet severe immune-related adverse events (irAEs) that can rapidly progress to organ failure if not promptly treated [4-8].

Our patient developed HLH after three cycles of pembrolizumab for metastatic lung squamous cell carcinoma, consistent with the timing and presentation reported in previous pharmacovigilance and case series analyses. The WHO VigiBase study and subsequent literature reviews indicated that HLH most frequently occurs after PD-1 blockade with pembrolizumab or nivolumab, typically emerging within 2–6 weeks after the last dose, and carries a mortality rate exceeding 40% without timely intervention [2, 5-6].

Diagnosing HLH in adults remains challenging because its features, such as persistent fever, cytopenia, hyperferritinemia, and hepatosplenomegaly, often overlap with those of sepsis or tumor progression. The HLH-2004 diagnostic criteria, though originally designed for pediatric use, remain widely adopted in adult practice. Additionally, the HScore provides a validated probability-based tool integrating common laboratory and clinical parameters, although it has not been prospectively or retrospectively validated in ICI-induced HLH [2-3]. In our patient, the presence of fever, splenomegaly, bicytopenia, hypofibrinogenemia, and hyperferritinemia fulfilled five HLH-2004 criteria, and the HScore was 239, corresponding to an estimated 98–99% probability of HLH [18]. Early application of these diagnostic frameworks facilitates rapid recognition and treatment before irreversible organ injury occurs.

At the mechanistic level, ICI-induced HLH represents a state of excessive immune activation, in which PD-1/PD-L1 blockade enhances cytotoxic T-cell function against tumor cells but simultaneously removes critical inhibitory feedback, driving uncontrolled macrophage activation and cytokine storm [1, 4, 9]. Cytokines such as interferon-γ, interleukin (IL)-1, IL-6, and tumor necrosis factor are key mediators of this hyperinflammatory cascade, contributing to fever, cytopenias, and liver dysfunction [1, 10]. This immunopathology mirrors that of other immune-activating therapies, explaining the observed overlap between HLH and cytokine release syndrome (CRS) seen in CAR-T cell and ICI contexts [9-10].

Corticosteroids remain the first-line therapy for both malignancy-associated and immune-mediated HLH, with etoposide traditionally reserved for refractory cases [1-2]. However, concurrent immunosuppression due to che-

motherapy or hepatic dysfunction often limits the use of etoposide. Recent reports, including multiple pembrolizumab- and nivolumab-associated HLH cases, have described successful remission using targeted cytokine inhibition when glucocorticoids alone are insufficient [4, 6-7]. IL-6 blockade with tocilizumab, an established therapy for CRS, has demonstrated rapid defervescence and the reversal of inflammatory markers in several ICI-HLH cases [7, 9-10]. In our patient, HLH was unresponsive to high-dose dexamethasone; however, promptly resolved following two doses of tocilizumab, supporting the therapeutic potential of IL-6 inhibition in steroid-refractory settings.

Although HLH and CRS share overlapping clinical and biochemical features such as fever, cytopenia, hyperferritinemia, and elevated transaminase levels, they are mechanistically distinct yet interconnected syndromes. CRS typically arises within hours to days of T-cell–activating therapy and is characterized by IL-6–driven inflammation. In contrast, HLH involves broader immune dysregulation with impaired cytotoxic lymphocyte control, hypofibrinogenemia, and histiocytic hemophagocytosis [11-12]. In patients treated with ICIs, CRS may precede or evolve into HLH, forming a continuum of hyperinflammatory toxicities. The presence of splenomegaly, hypofibrinogenemia, or hemophagocytosis favors the diagnosis of HLH, whereas pure CRS often lacks these features. Correct distinction is critical, as CRS typically responds to IL-6 blockade alone, while HLH requires broader immunosuppression, including corticosteroids and, sometimes, cytotoxic agents [3, 13].

In line with recent literature, ICI-associated HLH most often follows PD-1 inhibitors such as pembrolizumab and nivolumab, and early detection significantly improves outcomes [7, 8]. Tocilizumab, either alone or in combination with corticosteroids, has emerged as a valuable alternative when etoposide is contraindicated or the risk of infection is high [2, 14]. In our case, IL-6 blockade achieved complete remission, and continued cytotoxic chemotherapy without pembrolizumab led to a pathological complete response and sustained remission for 3 years. This long-term outcome supports prior observations that durable tumor control can still be achieved despite the discontinuation of immunotherapy after severe immune toxicity [2, 4, 15-17].

Conclusion

Pembrolizumab-induced hemophagocytic lymphohistiocytosis should be suspected in patients receiving immune checkpoint inhibitors who develop an unexplained fever, cytopenia, splenomegaly, hyperferritinemia, or hypofibrinogenemia during treatment. Early recognition of this condition is crucial to prevent life-threatening complications. Tocilizumab may represent an effective and well-tolerated therapeutic option for steroid-refractory HLH, particularly when cytotoxic therapy is unsuitable owing to immunocompromise or organ dysfunction. Durable tumor remission can be achieved despite this severe immune-related adverse event, emphasizing that close clinical surveillance and timely intervention are essential to improve survival and achieve favorable long-term outcomes.

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Respiratory Syncytial Virus Vaccination for Adults with Pulmonary Disease: A Clinical Practice Consensus from Taiwanese Pulmonologists

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Background: Respiratory syncytial virus (RSV) causes severe lower respiratory tract disease in adults, disproportionately affecting those with chronic pulmonary disease, lung cancer, or lung transplantation. Three adult RSV vaccines are licensed in Taiwan, but questions specific to thoracic practice remain incompletely addressed.

Methods: In May 2026, the Taiwan Society of Pulmonary and Critical Care Medicine convened 11 specialists, who defined 14 clinical questions. Literature up to September 2026 was reviewed. Recommendations were agreed through structured discussion without formal Delphi or GRADE methodology, and the evidence basis of each is stated.

Results: Severe disease risk should be assessed using age, pulmonary disease severity, comorbidities, frailty, and immune status. Adults aged ≥75 years should receive a single dose; adults aged 50–74 years with these conditions should be routinely evaluated; vaccination may be considered for high-risk adults aged 18–49 years. Vaccination should occur when pulmonary disease is stable, ideally before transplantation or antineoplastic therapy. Because RSV circulates year-round in Taiwan, vaccination need not await a particular season. Current evidence cannot rank the three vaccines by clinical protection; immunogenicity data may inform selection when immune responsiveness is a concern. Coadministration with other

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adult vaccines is acceptable. Pregnant women should receive the approved vaccine at 28–36 weeks of gestation. Eligible immunocompromised adults should be vaccinated within regulatory indications. Evidence is currently insufficient to recommend boosters, and prior RSV infection does not preclude vaccination.

Conclusion: These 14 statements provide pulmonary-specific guidance complementing existing national and international recommendations. ***(Thorac Med 2026; 41: 200-226)***

Key words: Respiratory syncytial virus (RSV), vaccination, pulmonary disease, expert consensus, immunocompromised host

Introduction

The respiratory syncytial virus (RSV) is an enveloped, single-stranded RNA virus of the family *Pneumoviridae* [1]. Early infection is governed largely by two surface glycoproteins: the G protein, which mediates attachment to the respiratory epithelium; and the F protein, which mediates fusion with the host cell membrane [2]. Although RSV was long regarded as a pediatric pathogen, its contribution to serious respiratory illness in adults is now well established. RSV infection can lead to lower respiratory tract disease (LRTD) with symptoms such as cough, dyspnea, and chest pain. In older adults or individuals with specific comorbidities, the infection may progress to severe illness, resulting in hospitalization or even death [3].

Adult RSV infection often leads to worse clinical outcomes than other common respiratory viral infections. Among U.S. adults aged ≥60 years hospitalized with acute respiratory infection, RSV was associated with approximately twice the risk of invasive mechanical ventilation or death compared with influenza, and with roughly 1.5 times the rate of intensive care unit (ICU) admission compared with coronavirus disease 2019 (COVID-19) [4]. According to analyses presented to the U.S. Advisory Committee on Immunization Practices (U.S. ACIP), asthma, chronic obstructive pulmonary disease (COPD) or chronic bronchitis, and immunocompromising conditions were ranked among the top five most common underlying conditions in adults aged 50–59 years hospitalized with RSV; these same conditions were in the top seven among those aged ≥60 years [5]. Therefore, many patients under the care of pulmonologists fall within the population at the highest risk.

Three adult RSV vaccines are currently approved by the Taiwan Food and Drug Administration (TFDA): the AS01E-adjuvanted prefusion F protein vaccine, RSVPreF3 (Arexvy); the non-adjuvanted bivalent prefusion F protein vaccine, RSVpreF (Abrysvo); and the messenger RNA (mRNA) vaccine, mRNA-1345 (mRESVIA) [6–8] (Table 1). Although these three products are now available, current guidance from the Taiwan Centers for Disease Control (Taiwan CDC) and international bodies and earlier recommendations on RSV vaccine use in older adults issued by the Taiwan Society of Pulmonary and Critical Care Medicine [9] address the adult population broadly and do not resolve the questions that arise specifically

Table 1. Adult Respiratory Syncytial Virus Vaccines Licensed by the Taiwan Food and Drug Administration [6–8].

Characteristic	Adjuvanted RSVPreF3	RSVpreF	mRNA-1345
Platform	Recombinant protein subunit	Recombinant protein subunit	mRNA
Antigen	RSVPreF3 (prefusion F)	Bivalent prefusion F (RSV-A and RSV-B)	RSV prefusion F–encoding mRNA
Adjuvant	AS01E	None	None
Route	Single intramuscular dose	Single intramuscular dose	Single intramuscular dose
Licensed population*	Adults aged ≥50 years; adults aged 18–49 years at increased risk of RSV disease	Adults aged ≥60 years; adults aged 18–59 years at increased risk of RSV disease; pregnant women (for passive infant protection)	Adults aged ≥60 years; adults aged 18–59 years at increased risk of RSV disease
Commonly reported adverse reactions†	Injection-site pain (61%), fatigue (34%), myalgia (29%), headache (28%), arthralgia (18%)	Fatigue (23%), headache (20%), injection-site pain (19%), myalgia (16%)	Injection-site pain (55.9%), fatigue (30.8%), headache (26.7%), myalgia (25.6%), arthralgia (21.7%)

*Licensed indications are those in force on September 2, 2026, and are drawn from the Taiwan prescribing information; they should be verified against the current Taiwan Food and Drug Administration prescribing information before use. The Taiwan prescribing information for RSVpreF permits maternal administration between 24 and 36 weeks of gestation. Licensure in other jurisdictions may differ.
†As reported in the respective prescribing information. Reactions were predominantly mild to moderate and of short duration. Frequencies are derived from separate development programs and are not directly comparable.
Abbreviations: mRNA, messenger RNA; RSV, respiratory syncytial virus.

in thoracic practice. Although RSV vaccination for adults with pulmonary disease has been reviewed previously [10], practical questions about eligibility, timing, product selection, and implementation remain incompletely addressed. Therefore, this consensus was developed to complement existing guidance. It incorporates updated clinical evidence and current Taiwanese recommendations and focuses on adults with chronic pulmonary disease, lung cancer, lung transplantation, and immunosuppression associated with the lungs.

Methods

A panel of 11 specialists in pulmonary medicine, respiratory infection, and thoracic oncology was convened by the Taiwan Society of Pulmonary and Critical Care Medicine in May 2026. The panelists were selected for their clinical experience in managing chronic pulmonary disease, lung cancer, or lung transplantation and for previous involvement in adult immunization practice. All 11 panel members are authors of this article. Through preliminary discussion, the panel identified 14 clinical questions judged to be the most frequent and least well resolved in day-to-day thoracic practice.

Articles published up to September 2026 were retrieved through targeted PubMed searches for each clinical question, supplemented by regulatory documents (TFDA product information and U.S. Food and Drug Administration [FDA] communications), material from the

Taiwan CDC and the U.S. Centers for Disease Control and Prevention (U.S. CDC), including ACIP presentations, and guidance from professional societies. As this is a consensus statement based on a narrative review, a pre-specified search strategy was not used; the key search terms for each question are listed in Supplementary Table S1. The panel met once, in May 2026, to define the clinical questions and agree on the draft statements. The evidence summaries were then updated as new data became available, and the draft manuscript was circulated to all panel members and revised iteratively until every panel member indicated agreement with the final wording.

Management suggestions are presented in a question-and-answer format. Each question is followed by the panel's recommendation and its rationale provided as a summary of supporting evidence. A formal Delphi procedure was not used, no anonymous voting was conducted, and no numerical agreement threshold was pre-specified. Where members' comments differed, the wording was revised and recirculated until all members agreed. GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluation) was not employed. Instead, the basis of each recommendation is stated after the recommendation as one or more of the following: direct evidence, from randomized controlled trials or systematic reviews; national or international guidance, where the statement is consistent with current recommendations; indirect evidence, from observational studies, immunogenicity endpoints, or extrapolation from a related population; and expert opinion of the panel. These recommendations reflect the evidence available as of September 2026 and are specific to the Taiwanese context; readers should verify current regulatory and national guidance at the time of use.

An earlier version of this material was prepared in Traditional Chinese as an educational document for healthcare professionals in Taiwan and was not published in a peer-reviewed journal. The present manuscript was independently rewritten, re-verified against the primary literature, and expanded for a wider readership. The Medical Affairs Department of GSK assisted with collecting literature and with verifying publicly available data on the licensed vaccines. GSK had no role in formulating the clinical questions, interpreting the evidence, drafting the statements, and the decision to submit the manuscript. All interpretations and conclusions were made independently by the authors.

Factors Associated with Severe RSV Infection

Immunosenescence and inflammaging

After an RSV infection, innate immunity and adaptive immunity act together to contain and clear the virus. Within adaptive immunity, humoral immunity depends principally on B cell–derived neutralizing antibodies, which limit infection of host cells, whereas cellular immunity is a major determinant of disease severity. After infection with RSV, CD4+ helper T cells differentiate into several subsets, including Th1, Th2, follicular helper T (Tfh), and regulatory T cells. The interferon-γ generated by the Th1-type response assists viral clearance, and Tfh cells provide help to B cells for the generation of neutralizing antibodies. An excessive Th2 response, or an imbalance between Th1 and Th2, is associated with clinical deterioration and progression to severe lower respiratory tract disease. Regulatory T cells restrain excessive inflammation and limit immunopathology, and CD8+ cytotoxic T cells recognize and kill

virus-infected cells [11-12]. In older adults, immunosenescence impairs innate and adaptive immune function, and inflammaging establishes a state of chronic low-grade inflammation, increasing both the susceptibility to infection and the likelihood of a poor outcome [13-14]. In a comparative study of humoral, mucosal, and cellular immunity, adults aged ≥65 years stimulated with the RSV F protein showed significantly fewer interferon-γ-producing T cells and CD8+ T cells compared with adults aged 20–30 years, with a CD4+ T cell response skewed toward Th2 [15]. Consistent with these observations, a prospective study demonstrated that the risk of RSV-associated hospitalization rises with advancing age [16]. A systematic review and meta-analysis of adults aged ≥60 years with RSV infection estimated that 27.4% developed pneumonia, 24.5% were hospitalized, and 5.0% required ICU admission, with a case-fatality rate of 8.2% [17].

Comorbidity

Comorbidity is a major determinant of RSV severity. Among adults aged ≥50 years, the risk of RSV-associated hospitalization among individuals with a single comorbidity was approximately 2.1-fold higher and that of individuals with two or more comorbidities was approximately 7.3-fold higher relative to the risk of those without comorbidities [5]. Chronic pulmonary conditions such as COPD, asthma, pulmonary fibrosis, and lung cancer may also induce or accelerate immunosenescence [18]. RSV in turn is an important driver of deterioration of chronic pulmonary disease, and previous studies have identified it as a leading viral trigger of COPD and asthma exacerbation [19]. Although clinical deterioration after RSV infection has been described for interstitial lung disease and non–cystic fibrosis bronchiectasis, the evidence is limited [20-21].

Immunosuppression

Immunocompromised patients, including lung transplant recipients, patients with solid tumors, and those receiving immunosuppressive therapy, may experience prolonged illness and extended viral shedding. In lung transplant recipients, RSV infection frequently precipitates acute rejection or chronic lung allograft dysfunction accompanied by a decline in lung function [3]. Immunosuppressive agents may further impair T cell function and reduce the capacity to clear RSV, contributing to more severe disease [21].

Efficacy and Safety of the RSV Vaccines Available in Taiwan

Efficacy in pivotal trials

Vaccine efficacy (VE) estimates from pivotal trials are summarized in Table 2. In the AReSVi-006 trial, the efficacy of a single dose of adjuvanted RSVPreF3 (Arexvy) was 82.6% (96.95% confidence interval [CI]: 57.9, 94.1) against RSV-LRTD over the first season [22]; cumulative VE, estimated with season included as a covariate, was 67.2% (97.5% CI: 48.2, 80.0) over two seasons [23] and 62.9% (97.5% CI: 46.7, 74.8) over three seasons at a median follow-up of 30.6 months [24]. In participants with at least one cardiorespiratory condition, VE was 92.1% (95% CI: 46.7, 99.8) in the first season [25], 73.8% (95% CI: 47.9, 88.2) across two seasons [23], and 68.1% (95% CI: 45.7, 82.3) across three seasons [24]. In a post-hoc descriptive analysis over three seasons, VE against RSV-associated complications in patients with COPD and in those with asthma was 74.4% and 60.8%, respectively, and against

Table 2. Adult Respiratory Syncytial Virus Vaccines Licensed by the Taiwan Food and Drug Administration [6–8].

Population and follow-up*	Adjuvanted RSVPreF3 (AReSVi-006)	RSVpreF (RENOIR)	mRNA-1345 (ConquerRSV)
Study endpoint	RSV-LRTD†	RSV-LRTD with ≥2 symptoms/≥3 symptoms‡	RSV-LRTD with ≥2 symptoms/≥3 symptoms§
Primary analysis, all participants	**82.6%** (96.95% CI: 57.9, 94.1); median follow-up, 6.7 months	**66.7%** (96.66% CI: 28.8, 85.8)/**85.7%** (96.66% CI: 32.0, 98.7)	**83.7%** (95.88% CI: 66.0, 92.2)/**82.4%** (96.36% CI: 34.8, 95.3)
Extended follow-up (~18 months), all participants	**67.2%** (97.5% CI: 48.2, 80.0) over two seasons; median follow-up, 17.8 months¶	**58.8%** (95% CI: 43.0, 70.6)/**81.5%** (95% CI: 63.3, 91.6) over two seasons; mean follow-up to end of season 2, 17.6 months	**50.3%** (95% CI: 37.5, 60.7)/**49.9%** (95% CI: 27.8, 65.6) at the 18-month analysis
Extended follow-up, participants with comorbidity‖	≥1 cardiorespiratory condition: **73.8%** (95% CI: 47.9, 88.2) over two seasons; median follow-up, 17.8 months¶	≥1 cardiopulmonary comorbidity: **29.0%** (95% CI: −26.6, 60.8)/**63.2%** (95% CI: 8.5, 86.9) over two seasons	≥1 chronic condition: **63.4%** (95% CI: 45.4, 75.5) against RSV-LRTD with ≥2 symptoms through 24 months
Across three seasons, all participants	**62.9%** (97.5% CI: 46.7, 74.8); median follow-up, 30.6 months¶	Not available	Not available

*Estimates are presented for reference and must not be compared directly. The three pivotal trial programs used different study endpoints, different symptom thresholds, different follow-up durations, and different statistical handling of season, and no head-to-head trial has been conducted. For RSVpreF and mRNA-1345, estimates are shown for RSV-LRTD with ≥2 and ≥3 symptoms, where reported.

†RT-PCR–confirmed RSV with ≥2 lower respiratory symptoms or signs for ≥24 h including ≥1 sign, or ≥3 lower respiratory symptoms for ≥24 h. Symptoms: new or increased sputum, cough, or dyspnea. Signs: new or increased wheezing, crackles/rhonchi, respiratory rate ≥20/min, low or decreased oxygen saturation (<95%, or ≤90% if pre-season baseline <95%), or need for supplemental oxygen.

‡RT-PCR–confirmed RSV with ≥2 or ≥3 signs or symptoms lasting more than one day within seven days of onset. Signs or symptoms include new or increased cough, wheezing, sputum production, shortness of breath, or tachypnea (≥25 breaths/min or ≥15% increase from resting baseline).

§First episode of RSV-LRTD with ≥2 or ≥3 lower respiratory signs or symptoms from 14 days to 12 months after injection, RT-PCR-confirmed, with new or worsening signs or symptoms for ≥24 h (or radiologic evidence of pneumonia when signs or symptoms could not be captured). Symptoms include shortness of breath, cough and/or fever (≥37.8 °C [100.0 °F]), wheezing and/or rales and/or rhonchi, sputum production, tachypnea (≥20 breaths per minute, or increase of ≥2 breaths per minute from baseline measurement in those who have baseline tachypnea), hypoxemia (new oxygen saturation ≤93% or new or increasing use of supplemental oxygen), pleuritic chest pain.

‖Comorbidity was defined as ≥1 cardiorespiratory condition (any chronic respiratory or pulmonary disease, including COPD and asthma, or chronic heart failure) in AReSVi-006, ≥1 cardiopulmonary comorbidity in RENOIR, and ≥1 chronic condition (COPD, congestive heart failure, asthma, chronic respiratory disease, diabetes, advanced liver disease, or advanced renal disease) in the mRNA-1345 program; these definitions are not equivalent.

¶Prespecified analysis with season included as a covariate. In a post-hoc analysis without season as a covariate, VE in AReSVi-006 was 74.5% (97.5% CI: 60.0, 84.5) over two seasons [23] and 69.1% (97.5% CI: 55.8, 78.9) over three seasons [24] in all participants and 80.1% (95% CI: 60.6, 91.0) over two seasons in participants with ≥1 cardiorespiratory condition [23]. According to the investigators, this post-hoc analysis was driven by the season with the largest person-years of follow-up (season 1); therefore, its estimates tend to be higher than those of the prespecified analysis [23]. Season was not included as a covariate in the efficacy analyses of RENOIR, in which cases were pooled across seasons [29], or of the mRNA-1345 trial [30]; therefore, corresponding estimates with and without a season covariate are not available for RSVpreF or mRNA-1345.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine efficacy.

respiratory disease exacerbation it was 63.9% and 66.3%, respectively; however, the confidence intervals were wide, and three of the four included zero [26].

In the pivotal RENOIR trial, the efficacy of bivalent RSVpreF (Abrysvo) was 66.7% (96.66% CI: 28.8, 85.8) against RSV-LRTD with ≥2 symptoms and 85.7% (96.66% CI: 32.0, 98.7) against RSV-LRTD with ≥3 symptoms during the first RSV season [27]. With extended follow-up, which showed durable efficacy and a consistent safety profile through two seasons [28], efficacy against RSV-LRTD with ≥2 symptoms was 58.8% (95% CI: 43.0, 70.6) cumulatively over two seasons, while efficacy against disease with ≥3 symptoms was 81.5% (95% CI: 63.3, 91.6) [29]. In participants with at least one cardiopulmonary comorbidity, VE was 44.4% (95% CI: −84.6, 85.4) against RSV-LRTD with ≥2 symptoms in the first season and 29.0% (95% CI: −26.6, 60.8) across two seasons, with corresponding estimates of 66.7% (95% CI: −86.4, 96.7) and 63.2% (95% CI: 8.5, 86.9) against disease with ≥3 symptoms [29].

In the pivotal ConquerRSV trial, the efficacy of mRNA-1345 (mRESVIA) was 83.7% (95.88% CI: 66.0, 92.2) against RSV-LRTD with ≥2 symptoms and 82.4% (96.36% CI: 34.8, 95.3) against RSV-LRTD with ≥3 symptoms in the primary analysis [30]. With extended follow-up (manufacturer presentation to ACIP), efficacy against RSV-LRTD with ≥2 symptoms was 62.5% (95% CI: 47.7, 73.1) at a median follow-up of 8.6 months and 50.3% (95% CI: 37.5, 60.7) at the 18-month analysis, while efficacy against RSV-LRTD with ≥3 symptoms was 49.9% (95% CI: 27.8, 65.6); in participants with at least one chronic condition, efficacy through 24 months was 63.4% (95% CI: 45.4, 75.5) [31].

Direct comparisons of results between these three clinical trials are not warranted given their methodological differences, including variations in case definitions, symptom thresholds, follow-up durations, and statistical handling of season, combined with the lack of head-to-head trials.

Pragmatic randomized evidence

The DAN-RSV trial provides pragmatic randomized evidence for preventing RSV-associated hospitalization. Among adults aged ≥60 years, RSVpreF reduced RSV-related respiratory tract disease hospitalization by 83.3% (95% CI: 42.9, 96.9) during the first season. Unlike observational effectiveness studies, DAN-RSV retained randomized treatment allocation while evaluating clinical outcomes in a routine-care setting [32]. In a prespecified subgroup analysis, the effectiveness of RSVpreF was 76.9% (95% CI: 42.9, 95.8) against hospitalization for RSV-related respiratory tract disease of individuals with chronic pulmonary disease (conference abstract) [33].

Real-world effectiveness

Post-licensure observational studies of RSVPreF3 and RSVpreF in the U.S. have reported an effectiveness of approximately 75%–80% against RSV-associated hospitalization and 76%–79% against RSV-associated emergency department or urgent care encounters for adults aged ≥60 years, with lower estimates for immunocompromised adults, particularly hematopoietic stem cell transplant recipients [34–37]. The effectiveness of adjuvanted RSVPreF3 against RSV-LRTD–associated hospitalization was 81.0% (95% CI: 51.7, 92.5) in adults with pre-existing pulmonary disease [38]. U.S. data indicate an effectiveness against severe RSV-associated exacerbation of 74.4% (95% CI:

59.3, 83.9) in COPD patients and of 61.6% (95% CI: 9.1, 83.7) in asthma patients [39]. For a nationwide Danish cohort of adults aged ≥60 years with COPD, adjuvanted RSVPreF3 was highly effective against RSV hospitalization, with an estimated effectiveness of 100% (95% CI: 71.1, 100.0). No RSV hospitalizations occurred among vaccinated individuals during follow-up, although event numbers were limited [40]. Additional real-world evidence comes from a multicenter test-negative case-control study from England involving adults aged 75–79 years. The effectiveness of bivalent RSVpreF was 82.3% (95% CI: 70.6, 90.0) against RSV-associated hospitalization and 88.6% (95% CI: 75.6, 95.6) against hospitalization for lower respiratory tract infection, including pneumonia. Effectiveness was 77.4% (95% CI: 42.4, 92.8) against hospitalization for exacerbation of chronic lung disease and 72.8% (95% CI: 39.5, 89.3) in immunosuppressed patients [41].

Durability of RSVPreF3 or RSVpreF vaccination has been examined in a cohort of U.S. veterans aged ≥60 years. Effectiveness against documented RSV infection declined from 82.5% (95% CI: 77.5, 86.9) in the first month to 59.4% (95% CI: 55.6, 63.5) over 18 months, with corresponding 18-month estimates of 57.3% (95% CI: 47.3, 66.4) against hospitalization and 71.9% (95% CI: 42.8, 90.0) against ICU admission; waning was more pronounced among immunocompromised participants, in whom effectiveness fell from 75.2% (95% CI: 52.5, 89.3) to 39.7% (95% CI: 23.9, 52.7) [42]. The primary analysis pooled both protein-subunit vaccines; product-specific estimates were reported descriptively, without formal comparison between products or randomized product allocation, and therefore cannot be used to compare durability between products. Complementing these longer-term cohort data, the IVY Network evaluated vaccine effectiveness against hospitalization over two consecutive RSV seasons. Overall effectiveness against RSV-associated hospitalization was 58% (95% CI: 45, 68), with estimates of 69% (95% CI: 52, 81) for adults vaccinated during the same season and 48% (95% CI: 27, 63) for those vaccinated in the preceding season; this difference was not statistically significant. Effectiveness was lower in immunocompromised compared with immunocompetent adults, highlighting the continuing uncertainty about the magnitude and durability of protection in immunocompromised populations [43].

Safety and reactogenicity

For all three products, the most frequent adverse reactions are injection-site pain, erythema, and swelling, together with fatigue, headache, myalgia, and arthralgia. Most adverse reactions are mild to moderate and resolve within a short period [6-8].

Post-marketing surveillance has identified a possible small excess risk of Guillain–Barré syndrome (GBS) for older adults after protein subunit RSV vaccination. The U.S. FDA requires GBS warnings in the prescribing information for both protein-subunit vaccines, Arexvy and Abrysvo, on the basis of a Medicare claims analysis of adults aged ≥65 years that estimated approximately 7 and 9 excess GBS cases per million doses, respectively [44]. A separate U.S. electronic health record–based study of adults aged ≥60 years estimated 5.2 (95% CI: −0.9, 9.2) and 18.2 (95% CI: 9.8, 23.3) excess cases per million doses for adjuvanted RSVPreF3 and RSVpreF, respectively [36]. The two products were not formally compared in either analysis, the estimates are not consistent across surveillance systems and analytic methods, and the

Table 3. Summary of the 14 Questions and Recommendations.

No.	Question	Recommendation	Basis*
1	Which factors influence the risk of developing severe disease after RSV infection in adults, and which pulmonary comorbidities should be considered in clinical assessment?	The risk of severe RSV disease should be assessed using age, pulmonary disease severity, systemic comorbidities, frailty, and immune status. Relevant conditions include COPD, asthma, interstitial lung disease, bronchiectasis, lung cancer, and lung transplantation. These factors should inform clinical assessment without being interpreted as a validated numerical risk score.	G, I
2	What is recommended for adults aged ≥75 years?	Adults aged ≥75 years should receive a single dose of an RSV vaccine licensed for this age group. All three vaccines are licensed in Taiwan, and current evidence is insufficient to rank them by clinical protection. Where immune responsiveness in older adults is a particular concern, clinicians may consider immunogenicity data for the adjuvanted vaccine, recognizing that immunogenicity is a surrogate endpoint and that head-to-head comparisons are lacking.	D, G, I, E
3	What is recommended for high-risk adults aged 50–74 years with pulmonary disease?	All adults aged 50–74 years with chronic pulmonary disease, lung cancer, or lung transplantation should be routinely evaluated for vaccination.	D, G, I, E
4	What is recommended for younger adults aged 18–49 years with pulmonary disease?	RSV vaccination may be considered for adults aged 18–49 years at substantial risk of severe RSV disease, including selected patients with severe pulmonary disease or immunocompromise, using a product licensed for the relevant indication. The decision should account for disease severity, treatment-related immunosuppression, and the limited evidence for direct clinical efficacy in this age group.	I, E
5	How should the timing of vaccination be planned for patients with chronic pulmonary disease?	Vaccination is recommended when pulmonary disease is clinically stable. For patients with an acute exacerbation, vaccination should be deferred until symptoms have stabilized. For patients receiving systemic corticosteroids (particularly ≥20 mg/day of prednisone for ≥14 days), vaccination timing should be individualized by the treating physician.	G, I, E
6	How should the timing of vaccination be planned for lung transplant candidates and recipients?	Lung transplant candidates should ideally receive RSV vaccination before transplantation. After transplantation, timing should be individualized according to immunosuppression and clinical recovery. An adjuvanted RSV vaccine may be considered because vaccine responses may be attenuated in this population, although supporting data are limited to small immunogenicity studies and comparative clinical superiority has not been established.	G, I, E
7	How should the timing of vaccination be planned for patients with lung cancer after diagnosis or during antineoplastic therapy?	Vaccination is recommended as soon as possible after diagnosis, preferably completed 2–4 weeks before antineoplastic therapy begins. If this is not feasible, patients receiving chemotherapy may, after physician assessment, be vaccinated approximately 1–2 weeks before the next cycle. For patients receiving targeted therapy, immune checkpoint inhibitors, radiotherapy, or other antineoplastic treatment, no timing restriction is imposed apart from	G, I, E

No.	Question	Recommendation	Basis*
		that for immune-related adverse events; scheduling should be determined by the physician together with the patient through shared decision-making. Vaccination may generally be considered once a grade 1–2 immune-related adverse event has improved, whereas for a grade ≥3 event it should generally be deferred until the event has improved to grade 1 or resolved.	
8	What is recommended for maternal immunization of pregnant women with pulmonary disease to prevent neonatal RSV infection?	Pregnant women should be vaccinated in accordance with prevailing national and international guidance, at 28–36 weeks of gestation, using the non-adjuvanted bivalent RSVpreF vaccine approved for maternal immunization, to provide passive protection during the infant's first six months of life. Current evidence does not indicate that pregnant women with pulmonary disease should be managed differently from pregnant women in general.	D, G
9	Given Taiwan's climate and epidemiology, what seasonal recommendation applies to RSV vaccination?	RSV circulates year-round in Taiwan, with seasonal peaks varying by year and region. Eligible adults may be vaccinated at any appropriate clinical visit without waiting for a fixed season.	I, E
10	How should a vaccine be selected in clinical practice, and how should individual patient characteristics be taken into account?	Vaccine selection should be based on the patient's age, immune status, comorbidities, safety, and practical accessibility. All three vaccines are licensed in Taiwan, and current evidence is insufficient to rank them by clinical protection. Where immune responsiveness in older or immunocompromised patients is a particular concern, clinicians may consider immunogenicity data for the adjuvanted vaccine, recognizing that immunogenicity is a surrogate endpoint and that head-to-head comparisons are lacking.	I, E
11	Can the RSV vaccine be given at the same time as the influenza, COVID-19, pneumococcal, or herpes zoster vaccine?	The RSV vaccine can be coadministered with other adult vaccines during the same clinical visit, using separate injection sites. Scheduling should consider the vaccine combinations studied, potential reactogenicity, the patient's condition, and the feasibility of a return visit.	G, I, E
12	What is recommended for immunosuppressed patients other than lung transplant recipients?	Eligible immunocompromised adults should receive RSV vaccination within applicable regulatory indications. Timing should be individualized according to immunosuppressive treatment and expected immune recovery.	G, E
13	Is a booster or repeat dose of RSV vaccine required?	Evidence is currently insufficient to recommend a booster or revaccination; a single dose is recommended by current U.S. CDC and Taiwan CDC guidance.	G, I, E
14	If a patient has recently had an RSV infection, is vaccination still indicated?	Previous RSV infection does not preclude vaccination. Eligible patients may be vaccinated after recovery from the acute illness. No evidence-based fixed interval after natural infection has been established; timing should reflect clinical recovery and the patient's ongoing risk of exposure and severe disease.	I, E

*Basis of the recommendation. D, direct evidence from randomized controlled trials or systematic reviews; G, consistent with current national or international guidance; I, indirect evidence from observational studies, immunogenicity endpoints, or extrapolation from a related population; E, expert opinion of the panel. GRADE methodology was not employed (see Methods).

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus; Taiwan CDC, Taiwan Centers for Disease Control; U.S. CDC, U.S. Centers for Disease Control and Prevention.

absolute risk is very low. The U.S. CDC judges the benefits of vaccination to outweigh the potential risk of GBS in adults aged ≥75 years and in adults aged 50–74 years at increased risk of severe RSV disease [45]. Post-licensure GBS surveillance data for the mRNA vaccine are limited [45].

Questions and Recommendations

he 14 questions addressed by the panel are set out below and summarized in Table 3.

Risk assessment

Question 1. Which factors influence the risk of developing severe disease after RSV infection in adults, and which pulmonary comorbidities should be considered in clinical assessment?

Recommendation: The risk of severe RSV disease should be assessed using age, pulmonary disease severity, systemic comorbidities, frailty, and immune status. Relevant conditions include COPD, asthma, interstitial lung disease, bronchiectasis, lung cancer, and lung transplantation. These factors should inform clinical assessment without being interpreted as a validated numerical risk score.

Basis: *national or international guidance and indirect evidence*

Rationale: Advancing age is an established risk factor for severe RSV disease and RSV-associated hospitalization [13-16]. Risk assessment should nevertheless take into account other clinically relevant factors, including comorbidity burden, underlying pulmonary disease, frailty, and immune status [3, 5, 12, 19-21, 46]. The severity and recent course of pulmonary disease may further inform clinical judgment, although no validated RSV-specific risk score incorporating these factors is currently available.

Eligible populations by age and risk

Question 2. What is recommended for adults aged ≥75 years?

Recommendation: Adults aged ≥75 years should receive a single dose of an RSV vaccine licensed for this age group. All three vaccines are licensed in Taiwan, and current evidence is insufficient to rank them by clinical protection. Where immune responsiveness in older adults is a particular concern, clinicians may consider immunogenicity data for the adjuvanted vaccine, recognizing that immunogenicity is a surrogate endpoint and that head-to-head comparisons are lacking.

Basis: *direct evidence and national or international guidance for the age-based recommendation; indirect evidence and expert opinion for vaccine selection*

Rationale: Both U.S. CDC and Taiwan CDC recommend RSV vaccination for all adults aged ≥75 years, irrespective of comorbidity [46,47]. In the GRADE evidence review conducted for the U.S. ACIP, the VE of adjuvanted RSVPreF3 (Arexvy) was 67.7% (95% CI: 26.0, 85.9) and that of RSVpreF (Abrysvo) was 74.8% (95% CI: −18.6, 94.7) against RSV-associated LRTD in adults aged ≥75 years, with a pooled estimate of 69.4% (95% CI: 36.6, 85.3) for the protein-subunit vaccines. The VE of the mRNA vaccine (mRNA-1345; mRESVIA), whose trial was not powered to detect a reduction in this age group, was 44.0% (95% CI: −34.6, 78.2) [48-49]. Real-world data from England further support vaccination for this age group, with bivalent RSVpreF showing 82.3% effectiveness against RSV-associated hospitalization

of adults aged 75–79 years [41].

In older adults, immunosenescence not only increases the risk and severity of infection but may also diminish vaccine responsiveness. The addition of adjuvants is an established strategy to boost vaccine-induced immune responses [50]. RSVPreF3 is formulated with the AS01E adjuvant system, which comprises two core immunostimulants: monophosphoryl lipid A (MPL); and Quillaja saponaria Molina, fraction 21 (QS-21) [6]. MPL activates antigen-presenting cells through the Toll-like receptor 4 (TLR4) pathway, stimulating T-cell and antibody responses, whereas QS-21 promotes the generation of cytotoxic T cells and elicits a Th1-type response. The synergy between MPL and QS-21 strengthens the development of both cellular and humoral immunity [51]. In clinical studies evaluating formulations of the RSVPreF3 antigen with or without adjuvant systems, a higher proportion of older adults who received the adjuvanted RSVPreF3 formulation achieved a ≥10-fold increase in neutralizing titers against contemporary clinical isolates one month after vaccination than those receiving the unadjuvanted RSVPreF3 formulation; this was a descriptive comparison without statistical testing [52]. Furthermore, a phase 1/2 trial demonstrated that the addition of the AS01E adjuvant induced higher CD4+ T-cell responses in older adults than the unadjuvanted RSVPreF3 formulation, restoring responses to levels comparable to those in younger adults aged 18–40 years given the unadjuvanted formulation; neutralizing antibody and IgG titers were not significantly affected by the adjuvant [53-54]. All three vaccines are licensed in Taiwan for this age group. Because immunogenicity is a surrogate endpoint and no head-to-head efficacy trial has been conducted, current evidence is insufficient to rank the licensed vaccines by clinical protection. Where immune responsiveness in older adults is a particular concern, clinicians may consider the immunogenicity data for the adjuvanted formulation described above.

Question 3. What is recommended for high-risk adults aged 50–74 years with pulmonary disease?

Recommendation: All adults aged 50–74 years with chronic pulmonary disease, lung cancer, or lung transplantation should be routinely evaluated for vaccination.

Basis: *direct evidence, national or international guidance, and indirect evidence; expert opinion for adults aged 50–59 years*

Rationale: The association between chronic pulmonary disease and RSV burden is well established. In a prospective study from the U.S., RSV-associated hospitalization rates among adults aged ≥50 years were approximately 2.3–3.6-fold higher for those with asthma and 3.5–13.4-fold higher for those with COPD compared with those without [16]. In an analysis of the 2017–2018 RSV season in the U.S., the RSV-associated hospitalization rate among adults aged ≥50 years was approximately 3.1-fold higher for those with asthma and approximately 4.6-fold higher for those with COPD compared with those without these conditions [55]. Among Canadian patients with COPD hospitalized with RSV, 9% required invasive ventilation, 17.9% required ICU admission, and 30-day mortality was 2.8% [56]. A systematic review reported disease exacerbation rates of up to 64.9% for asthma and up to 83.0% for COPD following RSV infection [19]. Recent

effectiveness data further support vaccination of patients with chronic pulmonary disease. RSVpreF showed 76.9% effectiveness against hospitalization for RSV-related respiratory tract disease (conference abstract) [33]. In a post-hoc descriptive analysis, the VE of adjuvanted RSVPreF3 against RSV-related complications in COPD was 74.4% (95% CI: 11.2, 95.2), whereas the estimate for COPD exacerbations had a wide confidence interval that included zero [26]; in observational studies, adjuvanted RSVPreF3 was also effective against severe RSV-associated exacerbations in COPD and asthma [39] and showed high effectiveness against RSV hospitalization in a nationwide Danish COPD cohort [40].

Patients with malignancies are also vulnerable. A study from Singapore reported that cancer patients with RSV (68.5% aged ≥60 years) faced a 1.9-fold higher risk of severe disease compared with those with influenza, independent of cancer type, together with a 2.4-fold higher risk of ICU or high-dependency admission and all-cause mortality [57]. In lung transplant recipients, RSV infection is associated with a decline in forced expiratory volume in 1 second (FEV_1), with the magnitude of decline correlated significantly with one-year all-cause mortality [58].

The U.S. CDC recommends a single dose for adults aged 50–74 years at increased risk of severe RSV disease, including those with chronic pulmonary disease or immunocompromise [46], whereas the Taiwan CDC currently recommends vaccination for adults aged 60–74 years at high risk of RSV disease, including those with chronic pulmonary, cardiovascular, hepatic, or renal disease and residents of long-term care facilities [47]. Immunogenicity in adults aged 50–59 years has been shown to be comparable to that in adults aged ≥60 years for all three vaccines [59–61]. Therefore, the panel recommends that all adults aged 50–74 years with chronic pulmonary disease, lung cancer, or lung transplantation be routinely evaluated for vaccination. For those aged 60–74 years with chronic pulmonary disease, this is in line with prevailing national recommendations; for those aged 50–59 years, who are not yet included in the Taiwan CDC recommendations, the decision to vaccinate should be based on approved indications and individual risk.

Question 4. What is recommended for younger adults aged 18-49 years with pulmonary disease?

Recommendation: RSV vaccination may be considered for adults aged 18–49 years at substantial risk of severe RSV disease, including selected patients with severe pulmonary disease or immunocompromise, using a product licensed for the relevant indication. The decision should account for disease severity, treatment-related immunosuppression, and the limited evidence for direct clinical efficacy in this age group.

Basis: *indirect evidence and expert opinion*

Rationale: RSV is not a negligible threat for younger adults. In the U.S., after adjustment for underdetection, RSV has been estimated to cause approximately 18,000 hospitalizations annually among adults aged 18–49 years, mostly those with chronic medical conditions such as obesity, diabetes, and chronic cardiopulmonary, kidney, or immunocompromising conditions [62]. Among adults aged 18–49 years with asthma or COPD, the risk of RSV-associated hospitalization was approximately 2.0–5.6 times that of those

without these comorbidities [16]. In a systematic review and meta-analysis of high-risk adults aged ≥18 years, 32.8% were hospitalized and 26.7% were admitted to ICU for RSV infection; among immunocompromised adults, RSV was associated with pneumonia in 35.3%, respiratory failure in 20.6%, and mechanical ventilation in 13.7%, with a case-fatality rate of 9.3% [17].

Immunogenicity in adults aged 18–49 years at increased risk is comparable to that observed in adults aged ≥60 years [60,61,63]. Currently, licensed vaccines are available in Taiwan for high-risk younger adults. Adjuvanted RSVPreF3 is approved for adults aged 18–49 years at increased risk [6], and RSVpreF and mRNA-1345 are approved for adults aged 18–59 years at increased risk, which encompasses this younger age group [7-8]. The panel notes that clinical efficacy data and formal recommendations for this age group are limited, and that current U.S. ACIP guidance does not extend to adults aged 18–49 years. Considering that younger adults with pulmonary conditions face a higher risk of severe illness, hospitalization, and disease exacerbation following RSV infection, vaccination may be considered for this population.

Timing of vaccination in specific clinical situations

Question 5. How should the timing of vaccination be planned for patients with chronic pulmonary disease?

Recommendation: Vaccination is recommended when pulmonary disease is clinically stable. For patients with an acute exacerbation, vaccination should be deferred until symptoms have stabilized. For patients receiving systemic corticosteroids (particularly ≥20 mg/day of prednisone for ≥14 days), vaccination timing should be individualized by the treating physician.

Basis: *national or international guidance for deferral during acute illness; indirect evidence and expert opinion for corticosteroid therapy*

Rationale: Efficacy and effectiveness data for patients with chronic pulmonary disease are summarized above and in Table 2.

The U.S. CDC advises that, as a precaution, vaccination should be deferred during moderate or severe acute illness until the illness has improved, while noting that there is no evidence that acute illness reduces vaccine efficacy or increases vaccine adverse events [64]. The Taiwan CDC similarly recommends postponing RSV vaccination for patients experiencing acute, severe illness with fever or acute infection until their condition stabilizes [47]. Patients with severe asthma and those with asthma or COPD experiencing acute exacerbations frequently require systemic corticosteroid therapy [65-66]. Given that an intact immune system is essential for eliciting effective vaccine protection, systemic corticosteroids may attenuate vaccine responses; for example, dexamethasone premedication was associated with lower immunogenicity of COVID-19 vaccines in patients with solid cancer [67]. Direct data for corticosteroid-treated patients with chronic pulmonary disease are lacking. U.S. CDC guidance regards ≥20 mg/day of prednisone for ≥14 days as a large dose of corticosteroids, although this definition was developed for live vaccines [64]. The panel uses this threshold as a practical marker of high-level immunosuppression, for which timing should be individualized

and agreed with the treating physician; the panel does not consider inhaled corticosteroids or short courses (<14 days) a reason to delay vaccination.

Question 6. How should the timing of vaccination be planned for lung transplant candidates and recipients?

Recommendation: Lung transplant candidates should ideally receive RSV vaccination before transplantation. After transplantation, timing should be individualized according to immunosuppression and clinical recovery. An adjuvanted RSV vaccine may be considered because vaccine responses may be attenuated in this population, although supporting data are limited to small immunogenicity studies and comparative clinical superiority has not been established.

Basis: *national or international guidance and expert opinion for timing; indirect evidence and expert opinion for vaccine selection*

Rationale: The Infectious Diseases Society of America (IDSA) recommends RSV vaccination at least two weeks before solid organ transplantation, or at least six months afterwards, with administration as early as one month after transplantation during periods of RSV circulation [68]. A U.S. real-world analysis of 17,315 solid organ transplant recipients aged ≥60 years who received an RSV vaccine (56.7% receiving adjuvanted protein, 39.2% receiving non-adjuvanted protein, and 0.2% receiving mRNA) reported a 30% reduction in infection risk and a 39% reduction in RSV-associated hospitalization [69]. Immunosuppressive agents may inhibit T and B cell proliferation and activation and may attenuate vaccine efficacy [70].

In a single-arm study of lung transplant recipients vaccinated a median of 18.3 months after transplantation, adjuvanted RSVPreF3 elicited significant increases in neutralizing antibody, anti-RSVPreF IgG, and CD4+ and CD8+ T cell responses [71]. In a small non-randomized study of 38 adults with self-reported immunocompromising conditions, of whom 82% were solid organ transplant recipients, significantly more individuals among the 19 participants who achieved high-titer neutralizing antibodies had received the adjuvanted RSVPreF3 vaccine rather than the non-adjuvanted RSVpreF vaccine (79% vs 21%; $p = .02$); more individuals among the 20 participants with a known vaccine type who achieved a ≥4-fold rise in anti-prefusion F IgG four weeks after vaccination had also received the adjuvanted RSVPreF3 vaccine, but the difference was not statistically significant (70% vs 30%; $p = .19$) [72]. A related report restricted to solid organ transplant recipients showed the same direction of effect (conference abstract) [73]. A U.S. observational study of veterans aged ≥60 years [42] noted that vaccine effectiveness waned more rapidly in immunocompromised individuals.

Based on these results, the panel considers that RSV vaccination should ideally be completed before transplantation in order to achieve optimal protection. Where this is not possible, vaccination after transplantation remains appropriate, with timing individualized according to immune status, postoperative recovery, and overall clinical condition. Because the overall immune response is reduced after lung transplantation and high-titer neutralizing antibody responses were more frequent after the adjuvanted RSVPreF3 vaccine in a small preliminary study of immunocompromised adults, with no significant dif-

ference in IgG responses [72], an adjuvanted vaccine may be considered for lung transplant candidates and recipients. This guidance is based on surrogate immunogenicity data from small studies, and comparative clinical superiority has not been established.

Question 7. How should the timing of vaccination be planned for patients with lung cancer after diagnosis or during antineoplastic therapy?

Recommendation: Vaccination is recommended as soon as possible after diagnosis, preferably completed 2–4 weeks before antineoplastic therapy begins. If this is not feasible, patients receiving chemotherapy may, after physician assessment, be vaccinated approximately 1–2 weeks before the next cycle. For patients receiving targeted therapy, immune checkpoint inhibitors, radiotherapy, or other antineoplastic treatment, no timing restriction is imposed apart from that for immune-related adverse events; scheduling should be determined by the physician together with the patient through shared decision-making. Vaccination may generally be considered once a grade 1–2 immune-related adverse event has improved, whereas for a grade ≥3 event it should generally be deferred until the event has improved to grade 1 or resolved.

Basis: *national or international guidance and indirect evidence; expert opinion for the interval before the next cycle and the irAE thresholds*

Rationale: RSV infection in patients with cancer may cause severe disease [3, 57]. The IDSA recommends RSV vaccination at least two weeks before initiation of chemotherapy for patients with solid tumors, with vaccination during or after treatment being acceptable if vaccination prior to treatment is not feasible [68]. The American Society of Clinical Oncology recommends vaccine administration 2–4 weeks before the start of antineoplastic therapy, where clinical status permits, and notes that nonlive vaccines can be given during or after chemotherapy, immunotherapy, hormonal therapy, radiotherapy, or surgery [74]. Because many patients with lung cancer carry additional risk factors such as a history of smoking and COPD, the panel recommends vaccination as soon as possible after diagnosis. As no absolute recommendation currently exists for the interval relative to a chemotherapy cycle, the schedule should be planned individually. The interval of approximately 1–2 weeks before the next cycle is based on the expert opinion of the panel. Dexamethasone premedication was associated with lower antibody responses to COVID-19 vaccines in patients with solid cancer, particularly when given on the day of vaccination [67]; where feasible, the panel suggests avoiding vaccination on premedication days.

Whether vaccination provokes or aggravates immune-related adverse events (irAEs) in patients receiving immune checkpoint inhibitors (ICIs) is a common clinical concern. A narrative review of 28 studies found no increase in irAE risk after vaccination for ICI-treated patients, with adverse-event severity similar to that of unvaccinated patients; the majority of these data are for influenza and COVID-19 vaccines, and RSV-specific evidence is awaited [75]. No recommendation specific to vaccination during an active irAE currently exists. The panel considers that timing should depend on irAE severity, the organ affected,

reversibility, and whether systemic corticosteroids are in use. irAE severity is graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v6.0 [76]. The panel is of the view that vaccination may generally be considered once a grade 1–2 irAE has improved, without necessarily awaiting complete resolution. For a more severe irAE (grade ≥3), vaccination should generally be deferred until the event has improved to grade 1 or resolved completely.

Maternal immunization

Question 8. What is recommended for maternal immunization of pregnant women with pulmonary disease to prevent neonatal RSV infection?

Recommendation: Pregnant women should be vaccinated in accordance with prevailing national and international guidance at 28–36 weeks of gestation, using the non-adjuvanted bivalent RSVpreF vaccine approved for maternal immunization, to provide passive protection during the infant's first six months of life. Current evidence does not indicate that pregnant women with pulmonary disease should be managed differently from pregnant women in general.

Basis: *direct evidence and national or international guidance*

Rationale: In the MATISSE trial, maternal RSVpreF vaccination reduced medically attended severe RSV lower respiratory tract illness in infants, with an efficacy of 81.8% (99.5% CI: 40.6, 96.3) through 90 days and 69.4% (97.58% CI: 44.3, 84.1) through 180 days after birth. These findings support infant protection through maternal immunization; they do not establish a pulmonary disease–specific benefit for pregnant women or prevention of subsequent childhood asthma [78]. The U.S. CDC recommends a single dose of RSVpreF at 32–36 weeks of gestation and advises against administration beyond 36 weeks, on the grounds that the remaining gestation may be insufficient for adequate maternal antibody generation and transplacental transfer [79]. The Taiwan prescribing information for RSVpreF permits administration between 24 and 36 weeks of gestation [7], while the Taiwan CDC recommends vaccination at 28–36 weeks of gestation to provide passive protection for the infant during the first six months of life [47]. For practice in Taiwan, the panel adopts the Taiwan CDC window of 28–36 weeks. RSVpreF is the only product approved for maternal immunization. Current evidence does not indicate that pregnant women with pulmonary disease should be managed differently from pregnant women in general; therefore, the panel applies the general recommendation to this population.

Seasonality in Taiwan

Question 9. Given Taiwan's climate and epidemiology, what seasonal recommendation applies to RSV vaccination?

Recommendation: RSV circulates year-round in Taiwan, with seasonal peaks varying by year and region. Eligible adults may be vaccinated at any appropriate clinical visit without waiting for a fixed season.

Basis: *indirect evidence and expert opinion*

Rationale: RSV circulates throughout the year in Taiwan [80,81]. A multicenter Taiwanese study predominantly of children found that RSV circulated year-round with a July–September peak before 2020, whereas activity

after 2020 shifted to a sharp September–December epidemic that was more synchronized nationwide [82]. Therefore, vaccination need not be restricted to a fixed calendar season.

Vaccine selection and coadministration

Question 10. How should a vaccine be selected in clinical practice, and how should individual patient characteristics be taken into account?

Recommendation: Vaccine selection should be based on the patient's age, immune status, comorbidities, safety, and practical accessibility. All three vaccines are licensed in Taiwan, and current evidence is insufficient to rank them by clinical protection. Where immune responsiveness in older or immunocompromised patients is a particular concern, clinicians may consider immunogenicity data for the adjuvanted vaccine, recognizing that immunogenicity is a surrogate endpoint and that head-to-head comparisons are lacking.

Basis: *indirect evidence and expert opinion*

Rationale: As the three licensed vaccines vary in characteristics, indicated ages, and target populations [6-8] (Table 1), clinical decisions on vaccine selection should be based on a comprehensive evaluation of each patient's individual status. Available evidence indicates that the addition of the AS01E adjuvant system to the RSVPreF3 antigen induces higher cellular (CD4+ T cell) responses than the unadjuvanted formulation, without a significant effect on neutralizing antibody or IgG titers [53], although a higher proportion of ≥10-fold neutralizing responses with the adjuvanted formulation was described in a descriptive analysis [52]. Furthermore, in a small non-randomized study of adults with self-reported immunocompromising conditions, most of whom were solid organ transplant recipients, those who achieved high-titer neutralizing antibodies had more often received adjuvanted RSVPreF3 than non-adjuvanted RSVpreF (79% vs 21%, $p = .02$), whereas the corresponding difference for a ≥4-fold rise in anti-prefusion F IgG was not significant (70% vs 30%, $p = .19$) [72]. Given that older adults and immunocompromised individuals are both more susceptible to infection and respond less well to vaccination [50, 68], clinicians considering the immune response specifically of these patients may refer to the aforementioned immunogenicity data. However, immunogenicity is a surrogate endpoint and no head-to-head trial has compared clinical protection between products; therefore, the current evidence is insufficient to rank the licensed vaccines by clinical efficacy. Safety considerations, including the small possible excess risk of GBS after protein-subunit vaccination discussed above, should be presented to the patient in a balanced manner [36, 44-45].

Question 11. Can the RSV vaccine be given at the same time as the influenza, COVID-19, pneumococcal, or herpes zoster vaccine?

Recommendation: The RSV vaccine can be coadministered with other adult vaccines during the same clinical visit, using separate injection sites. Scheduling should consider the vaccine combinations studied, potential reactogenicity, the patient's condition, and the feasibility of a return visit.

Basis: *national or international guidance, indirect evidence, and expert opinion*

Rationale: The U.S. CDC states that an RSV vaccine may be coadministered with other

adult vaccines at the same visit [46]. For adjuvanted RSVPreF3, coadministration trials with influenza, COVID-19, pneumococcal, and herpes zoster vaccines met most prespecified immunologic non-inferiority criteria with acceptable safety [82-86]; however, non-inferiority was not met for the influenza A/Darwin (H3N2) strain when coadministered with adjuvanted quadrivalent influenza vaccine [86] and was marginally missed for the SARS-CoV-2 XBB.1.5 response when coadministered with an mRNA COVID-19 vaccine [83]. Coadministration of RSVpreF or mRNA-1345 with influenza and COVID-19 vaccines has likewise been evaluated in clinical trials and in a manufacturer presentation to ACIP [87-90].

The panel notes that coadministration can improve vaccination completion rates and help patients keep to their immunization schedule, avoiding the additional visits or delays that would otherwise leave patients unprotected against respiratory infection, although immunogenicity and reactogenicity data remain limited for some vaccine combinations. Coadministration may increase the frequency of common side effects, and limited data suggest that coadministration with other respiratory virus vaccines may result in lower antibody titers of uncertain clinical significance [46]. Therefore, the decision to coadminister should be evaluated individually, based on the patient's clinical status, characteristics, and tolerance of potential reactogenicity.

Immunosuppression other than lung transplantation

Question 12. What is recommended for immunosuppressed patients other than lung transplant recipients?

Recommendation: Eligible immunocompromised adults should receive RSV vaccination within applicable regulatory indications. Timing should be individualized according to immunosuppressive treatment and expected immune recovery.

Basis: *national or international guidance and expert opinion*

Rationale: The 2025 IDSA guideline makes a strong recommendation for "age-appropriate RSV vaccination in adults and adolescents with compromised immunity", with timing individualized according to treatment cycles, transplant status, and B-cell-depleting therapies [68]. In thoracic practice, this population may include patients with chronic pulmonary disease requiring systemic corticosteroids and patients receiving immunosuppressive therapy. These patients are at high risk of severe disease and death after RSV infection [3,17]. Therefore, the panel regards them as appropriate candidates for vaccination.

Revaccination and vaccination after natural infection

Question 13. Is a booster or repeat dose of RSV vaccine required?

Recommendation: Evidence is currently insufficient to recommend a booster or revaccination; a single dose is recommended by current U.S. CDC and Taiwan CDC guidance.

Basis: *national or international guidance, indirect evidence, and expert opinion*

Rationale: Current Taiwanese and international recommendations specify a single dose, and the need for booster or repeat doses remains under investigation [46-47]. Clinical trial data are available for up to three seasons

after a single dose of adjuvanted RSVPreF3 in patients with cardiorespiratory comorbidity, whereas available follow-up for RSVpreF and mRNA-1345 currently extends to approximately two seasons. However, these data are not directly comparable between products. In the AReSVi-006 trial, the VE of a single dose of adjuvanted RSVPreF3 was 68.1% (95% CI: 45.7, 82.3) against RSV-LRTD in participants with cardiorespiratory conditions across three seasons at a median follow-up of 30.6 months [24]. The cumulative efficacy of RSVpreF against RSV-LRTD with ≥2 symptoms in participants with cardiopulmonary comorbidity was 29.0% (95% CI: −26.6, 60.8) across two seasons [29], and the efficacy of mRNA-1345 in participants with comorbidity was 63.4% through 24 months (manufacturer presentation to ACIP) [31]. Long-term data for all three products continue to accumulate. Observational data also show waning of effectiveness over 18 months, which was more pronounced in immunocompromised adults [42], and lower effectiveness in immunocompromised adults across two seasons [43]; the need for revaccination in these groups therefore remains to be defined. The panel advises clinicians to follow emerging evidence and guidance on booster or repeat dosing, particularly for high-risk groups such as lung transplant recipients and to adjust vaccination strategy accordingly.

Question 14. If a patient has recently had an RSV infection, is vaccination still indicated?
Recommendation: Previous RSV infection does not preclude vaccination. Eligible patients may be vaccinated after recovery from acute illness. No evidence-based fixed interval after natural infection has been established; timing should reflect clinical recovery and the patient's ongoing risk of exposure and severe disease.
Basis: *indirect evidence and expert opinion*
Rationale: An initial RSV infection does not confer lifelong immunity, and reinfection remains possible throughout life. In a study of healthy adults following RSV infection, serum neutralizing antibody and nasal mucosal IgA titers peaked approximately 28 days after infection and subsequently declined, returning to near-baseline concentrations within 6–12 months; RSV-specific antibody-secreting cells peaked around day 10, declined by day 14, and were undetectable by day 28 [93]. This waning underlies the frequency of reinfection in adults. Because RSV circulates in Taiwan throughout the year [81], the risk of reinfection is continuous. The optimal interval after natural infection has not been defined. Vaccination is generally reasonable once the acute illness has resolved, with timing adjusted to the individual patient.

Limitations

Several limitations should be acknowledged. First, this is a consensus statement based on a narrative review rather than a systematic review. In addition, agreement was reached through structured discussion rather than by a formal Delphi procedure, no quantitative agreement threshold was pre-specified, and GRADE methodology was not applied. Therefore, the statements should be read as the collective judgment of the panel rather than as the product of a structured consensus methodology; the basis of each recommendation is stated explicitly for that reason. Second, as the pivotal trials excluded severely immunocompromised patients,

recommendations for lung transplant recipients and other immunosuppressed groups are extrapolated from immunogenicity studies and observational data. Third, no efficacy data specific to interstitial lung disease or bronchiectasis are available. Fourth, comparisons between products are constrained by heterogeneous trial designs and endpoints, and no head-to-head trial has been conducted; in addition, several of the cited studies were sponsored by vaccine manufacturers, and some data were available only as conference abstracts or presentations. Fifth, almost all real-world effectiveness data are from North America and Europe; Taiwan-specific effectiveness and cost-effectiveness data are not yet available. Finally, licensed indications, national recommendations, and safety assessments changed during the preparation of this document and may continue to change; therefore, readers should verify current guidance at the time of use.

Priorities for future research include efficacy and durability data for patients with interstitial lung disease and bronchiectasis, prospective evaluation of vaccination timing relative to systemic corticosteroid therapy and to antineoplastic therapy, definition of the need for and the interval of revaccination for immunocompromised patients, and locally generated effectiveness and economic data to support public funding decisions in Taiwan.

Conclusion

In patients with chronic pulmonary disease, RSV infection is a frequent precipitant of exacerbation, hospitalization, and death rather than being an incidental respiratory illness. The 14 questions addressed here are those that arise most often in thoracic practice, and the recommendations are intended to be acted on in the ordinary outpatient setting, where patients at high risk are identified before they present acutely and both the timing and the choice of vaccine are treated as part of the management plan rather than as an afterthought. Adult RSV vaccines are not currently publicly funded in Taiwan [47], which is likely to limit uptake among exactly those older, comorbid patients who would benefit the most; coverage is more likely to improve if eligible patients are identified systematically within the respiratory clinic itself. The evidence on long-term protection and the need for revaccination continues to accumulate; therefore, these recommendations should be updated regularly.

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Supplementary Material

Supplementary material is available online at https://www.tspccm.org.tw/media/s/CUbFtg

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