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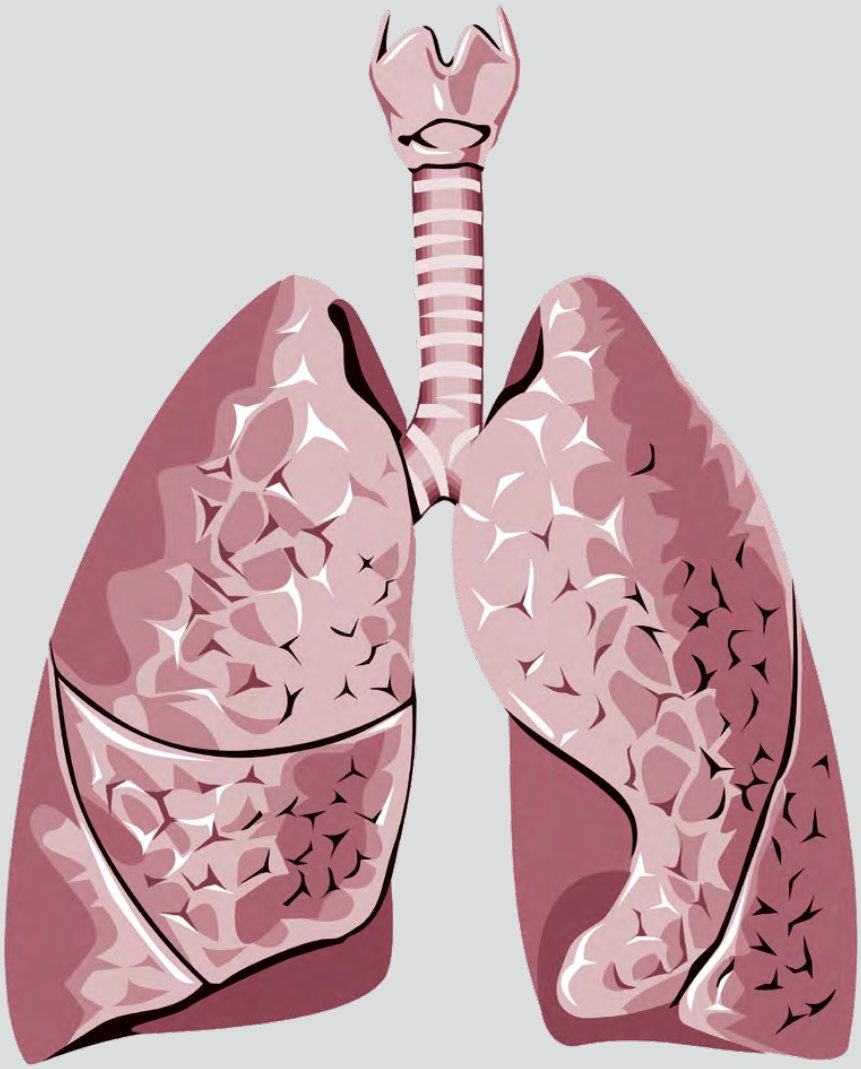

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# Recommendations for Use of Respiratory Syncytial Virus Vaccines in Older Adults: A Clinical Practice Recommendation

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**Background:** Respiratory syncytial virus (RSV) affects individuals of all ages, particularly adults. Prevention and management of RSV infections have therefore become critical. This narrative review provides evidence-based recommendations for RSV vaccination in adults, with a focus on Taiwan's epidemiological characteristics.

**Methods:** The PubMed, Embase, and the Cochrane Library databases were searched for studies, clinical trials, and guidelines on RSV infection and vaccination in adults that were published before February 2025. Selected articles were critically appraised, and data were synthesized to generate recommendations. Nine experts in pulmonology, respiratory infectious diseases, and thoracic oncology—representing the Taiwan Society of Pulmonary and Critical Care Medicine—reviewed the evidence, participated in structured discussions, and reached a consensus through iterative feedback.

**Results:** On the basis of epidemiological data, clinical trials, and global guidelines, tailored vaccination strategies were proposed for older adults and at-risk populations. Taiwan has no fixed RSV infection season; thus, RSV vaccination may be administered year-round. Coadministration with RSV and influenza vaccination between August and October is recommended for individuals seeking protection during the influenza season. Vaccination is recommended for adults aged ≥75 years and those aged 60-74 years with risk factors, particularly chronic pulmonary diseases (chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, bronchiectasis, and lung cancer). It may also be considered for adults aged 60-74 years with other risk factors. For adults aged 50-59 years with risk factors, RSV

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vaccine indications have recently been approved and warrant further discussion. For patients with lung cancer, RSV vaccination should be administered ≥2 weeks before each treatment cycle. For patients with acute exacerbations of chronic pulmonary diseases, RSV vaccination should be delayed until corticosteroid dosage is tapered to ≤10 mg of prednisolone/day or equivalent.

**Conclusion:** Our recommendations may guide RSV vaccination in Taiwan to reduce the disease burden in older adults and high-risk groups. ***(Thorac Med 2025; 40: 239-255)***

Key words: respiratory syncytial virus (RSV), vaccination, guidelines, risk factors, older adults

## Introduction

Respiratory syncytial virus (RSV), a common respiratory pathogen with a higher transmission rate than influenza virus, poses a considerable public health challenge [2-3]. It particularly leads to adverse outcomes in high-risk populations, including infants, adults, older adults, and individuals with chronic diseases or compromised immune systems [2]. According to an IQVIA study, an estimated 13,616 older adults in Taiwan were hospitalized because of RSV infection in 2023, with their average medical cost being US$2,271 per patient [4]. These data highlight the substantial health-care and economic burden that RSV imposes on adults.

Given the substantial impact of RSV on adult health, the World Health Organization has indicated a need for prioritizing the development of RSV vaccines over the past 2 decades [5-6]. In 2023, two RSV vaccine formulations demonstrated efficacy in phase III clinical trials, and they have since been approved for use; each has distinct platform characteristics, including the presence or absence of an adjuvant, and different target populations. Adjuvanted RSVPreF3 (Arexvy, GSK) is a nonlive, recombinant protein subunit vaccine containing the prefusion-stabilized RSV F (pre-F) protein and the AS01E adjuvant system. It has been approved for use in adults aged ≥60 years and those aged 50-59 years with underlying risk factors. RSVPreF (Abrysvo, Pfizer) is also a nonlive, recombinant protein subunit vaccine containing the pre-F protein but without an adjuvant; it is approved for use in adults aged ≥60 years and pregnant individuals at 24-36 weeks of gestation. Both vaccines are administered as a single intramuscular injection.

Considering these developments, establishing practical vaccination strategies informed by the epidemiological landscape of RSV in Taiwan and the world, clinical trial outcomes, real-world data on approved vaccines, and international guidelines is imperative. Such a consensus can provide health-care professionals in Taiwan with recommendations for the use of RSV vaccines to reduce disease burden among adults at high risk of RSV infection.

## Methods

A thorough literature review was conducted using electronic databases, namely, PubMed,

Embase, and the Cochrane Library, covering articles published up to February 2025. Nine experts in pulmonology, respiratory infectious diseases, and thoracic oncology, representing the Taiwan Society of Pulmonary and Critical Care Medicine, reviewed the evidence, participated in structured discussions, and reached a consensus through iterative feedback. The Medical Affairs Department of GSK assisted with the collection of literature and verification of publicly available data on adjuvanted RSVPreF3. All interpretations and conclusions were independently made by the authors.

This narrative review was focused on identifying relevant studies, clinical trials, and guidelines on RSV infection and vaccination in adults. The search strategy included keywords such as "respiratory syncytial virus," "adults," and "vaccine," along with other related terms. Each selected article was critically appraised, and the extracted data were synthesized to formulate evidence-based recommendations.

## Epidemiological Overview and Vaccinated Populations

### *Epidemiological status in Taiwan and other countries*

RSV infection is a prevalent, highly contagious respiratory disease. Various studies have reported that the basic reproduction number (R0) of RSV is approximately 3, which is higher than that of other common respiratory viruses, such as adenovirus (R0 ≈ 2), influenza virus (R0 ≈ 1), rhinovirus, or parainfluenza virus [7]. In Taiwan, a subtropical country, RSV infection cases are reported year-round. This pattern is in contrast to that in temperate countries, where distinct seasonal variations lead to RSV infection epidemics peaking in winter [8-9].

RSV infection was traditionally considered a pediatric disease and has long been underestimated in the adult population. In the United States, RSV infection leads to approximately 58,000 hospitalizations and 100–500 deaths annually among children aged <5 years. However, in adults aged ≥65 years, RSV infection results in approximately 177,000 hospitalizations and 14,000 deaths annually—which are significantly higher numbers than those in pediatric populations. Therefore, the National Foundation of Infectious Diseases (NFID) in the United States has called for increased public awareness of the disease burden imposed by RSV infection across all age groups [10].

The body of relevant epidemiological research data has been growing. A meta-analysis using annual statistical data revealed that the annual prevalence of RSV infection in individuals aged ≥60 years was 4.66%; when based on seasonal data, this prevalence among older adults reached 7.8% [11]. The seasonal incidence rate of RSV infection in adults aged ≥60 years is 16.11 per 1,000 person-years. In individuals with cardiopulmonary diseases, this rate increases to 19.15 per 1,000 person-years. In older adults with immunodeficiency, the seasonal incidence rate of RSV infection is as high as 260.89 per 1,000 person-years [12].

In addition to incidence rates, the severity of RSV-related diseases warrants attention. A prospective study in the United States revealed that in adults aged ≥60 years, the risk of RSV infection was higher than that of influenza or coronavirus disease 2019 (COVID-19), regardless of prior vaccination status. This risk was associated with longer hospital stays, a higher likelihood of shortness of breath, lower blood oxygen levels, and a need for oxygen supplementation (Table 1) [13].

**Table 1.** Comparison of Severity Risks of RSV Infection, COVID-19, and Influenza in Vaccinated and Unvaccinated Individuals [13]

| In-hospital outcomes | Patients with RSV, No. (%) (n = 484) | Patients with COVID-19, No. (%) | | RSV vs. COVID-19 by vaccination status | | | | Patients with influenza, No. (%) | | RSV vs. influenza by vaccination status | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | COVID-19 unvaccinated | | COVID-19 vaccinated | | | | Flu unvaccinated | | Flu vaccinated | |
| | No RSV vaccine | Unvaccinated (n = 1,422) | Vaccinated (n = 5,000) | aOR (95% CI) | *P* value | aOR (95% CI) | *P* value | Unvaccinated (n = 699) | Vaccinated (n = 393) | aOR (95% CI) | *P* value | aOR (95% CI) | *P* value |
| **Oxygen supplementation**[c] | 355 (73.4) | 857 (60.3) | 2,924 (58.5) | 1.82 (1.42–2.32) | <0.001 | 2.16 (1.74–2.68) | <0.001 | 460 (65.8) | 249 (63.4) | 1.27 (0.97–1.68) | 0.09 | 1.86 (1.36–2.55) | <0.001 |
| **Advanced respiratory support**[d] | 146 (30.2) | 332 (23.4) | 888 (17.8) | 1.40 (1.10–1.78) | 0.006 | 2.03 (1.64–2.51) | <0.001 | 157 (22.5) | 57 (14.5) | 1.47 (1.12–1.93) | 0.006 | 2.71 (1.89–3.87) | <0.001 |
| **Acute organ failure**[e] | 152 (31.4) | 359 (25.3) | 1,015 (20.3) | 1.32 (1.05–1.68) | 0.02 | 1.84 (1.49–2.26) | <0.001 | 170 (24.3) | 61 (15.5) | 1.38 (1.05–1.81) | 0.02 | 2.62 (1.85–3.71) | <0.001 |
| **ICU admission** | 120 (24.8) | 326 (22.9) | 847 (16.9) | 1.11 (0.86–1.43) | 0.43 | 1.55 (1.24–1.95) | <0.001 | 152 (21.8) | 42 (10.7) | 1.14 (0.86–1.53) | 0.36 | 2.65 (1.78–3.95) | <0.001 |
| **Hospital-free days, median (IQR)**[f] | 23 (18–25) | 23 (17–25) | 23 (19–25) | 1.18 (0.98–1.42) | 0.08 | 0.85 (0.72–1.00) | 0.05 | 24 (20–26) | 24 (22–26) | 0.79 (0.64–0.97) | 0.03 | 0.53 (0.42–0.68) | <0.001 |
| **IMV or death** | 58 (12.0) | 201 (14.1) | 458 (9.2) | 0.82 (0.59–1.13) | 0.22 | 1.38 (1.02–1.86) | <0.03 | 73 (10.3) | 20 (5.1) | 1.20 (0.82–1.76) | 0.35 | 2.81 (1.62–4.86) | <0.001 |

aOR, adjusted odds ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; RSV, respiratory syncytial virus.

According to data from the US Centers for Disease Control and Prevention (CDC), RSV-related hospitalization rates increase with age, particularly in individuals aged ≥75 years. Moreover, most individuals with high rates of intensive care unit (ICU) admissions, mechanical ventilation, and mortality associated with RSV infection are aged 60–75 years or older [14].

Another meta-analysis revealed that in older adults with RSV infection, 27.44% developed pneumonia, 24.48% required hospitalization, and 5.01% were admitted to the ICU. Among high-risk adults (e.g., those with cardiovascular comorbidities, immunodeficiency, or cognitive impairments or residents in long-term care facilities), RSV infection resulted in hospitalization rates as high as 30%, with nearly 30% of cases requiring ICU admission [12].

The US CDC reported that 94.3% of adults hospitalized because of RSV infection have at least one comorbidity. Of them, two-thirds present with three or more comorbidities. The most common comorbidities include cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and asthma [14]. These data highlight the substantial burden of RSV infection on high-risk populations.

Taiwanese CDC data indicate that RSV infection accounted for 9% of respiratory viral infections in Taiwan in 2023, exceeding the 6% attributable to COVID-19 [15]. A consensus published by Taiwanese infectious disease experts in 2024 indicated that the RSV positivity rate in Taiwan typically ranges from 1.2% to 5.7%, with an in-hospital mortality rate of 20%–50% among RSV-infected adults [16]. This consensus also summarized findings from seven studies focusing on adult RSV infections.

Given current data on RSV mortality rates in Taiwan, further research is required before definitive conclusions can be drawn. Nevertheless, for now, the in-hospital mortality data from the US NFID, which reports an 8% rate, may be considered [10].

Some experts have suggested that in Taiwan, RSV infection occurs year-round, without distinct seasonality; this aligns with the RSV infection control guidelines published by the Taiwan CDC. By contrast, other experts have referenced retrospective studies conducted in Taiwan and argued that a seasonal epidemic trend of RSV infection is present in northern Taiwan, with fall being the most common period for RSV infection [17] (Figure 1).

### *Recommended high-risk groups for RSV vaccination*

Age is a critical factor when eligibility for RSV vaccination is assessed. The US CDC recommends RSV vaccination for adults aged ≥75 years and those aged 60–74 years with chronic diseases or other high-risk conditions. To optimize RSV vaccination strategies, year-round vaccination for high-risk populations must be prioritized because it not only mitigates individual infection risks but also reduces community transmission. This approach is particularly relevant given the potential regional variations in RSV seasonal peaks, driven by climatic differences, between northern and southern Taiwan. Consequently, vaccination schedules should not be confined solely to fall and winter. With this approach, vaccine deployment can be aligned with Taiwan's unique epidemiological patterns, ultimately enhancing the overall benefits of RSV prevention efforts.

Current evidence indicates that patients with COPD and asthma are at a higher risk of adverse outcomes after RSV infection [14].

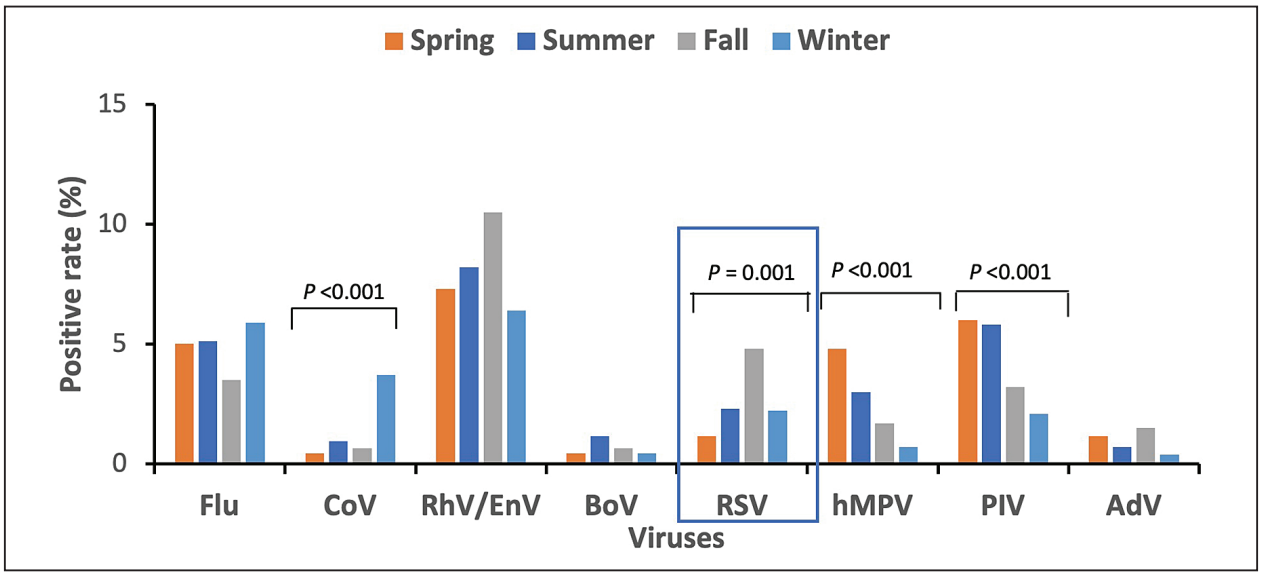


**Fig. 1.** Seasonal Distribution of Positivity Rates for Common Respiratory Viruses.
AdV, adenovirus; BoV, bocavirus; CoV, coronavirus; Flu, influenza; hMPV, human metapneumovirus; PIV, parainfluenza virus; Rhv/Env, rhinovirus/enterovirus; RSV, respiratory syncytial virus.

Consequently, RSV vaccination is strongly recommended for these patient populations. For individuals with interstitial lung diseases, such as idiopathic pulmonary fibrosis and progressive pulmonary fibrosis, no definitive international guidelines regarding RSV vaccination are currently available. Nevertheless, emerging evidence from animal studies indicates that RSV infection may accelerate pulmonary fibrosis development [18]. This is particularly concerning given the extremely high mortality risk associated with acute exacerbations of these chronic pulmonary diseases. Routine RSV testing during acute exacerbation episodes in this population may also enhance diagnostic accuracy.

Data on the risks of severe RSV-related complications in patients with lung cancer remain scarce. However, immunodeficiency is known to increase their risk of severe disease after RSV infection. Therefore, patients with lung cancer should also be prioritized for RSV vaccination.

## Clinical Trials and Real-World Data Regarding RSV Vaccines

Currently, two RSV vaccines have been approved for use in Taiwan: adjuvanted RSVPreF3 OA and RSVPreF; both are indicated for adults aged ≥60 years. Notably, adjuvanted RSVPreF3 OA was approved by the Taiwan Food and Drug Administration in 2025 for an expanded indication to include high-risk adults aged ≥50 years; however, this expanded indication is beyond the scope of this discussion. These two vaccines differ in design: adjuvanted RSVPreF3 OA uses the RSVPreF3 antigen combined with the AS01E adjuvant [19], whereas RSVPreF contains the RSVPreF antigen without an adjuvant [20].

### *Clinical trial results*

The subsequent sections present clinical data regarding each vaccine. Because of differences in study designs and efficacy endpoints,

these data are presented for reference only and should not be compared directly.

### *AReSVi-006 phase III clinical trial [19]*

The AReSVi-006 study was a multinational, multicenter, randomized controlled trial that enrolled 24,966 adults aged ≥60 years. Participants were initially divided into two groups: one group received a placebo, whereas the other received adjuvanted RSVPreF3 OA before the first RSV season. Before the second RSV season, the adjuvanted RSVPreF3 OA group was further subdivided into two groups: one group received an additional dose of adjuvanted RSVPreF3 OA (multidose group), whereas the other received a placebo (single-dose group). With this design, the trial aimed to evaluate the vaccine efficacy (VE) of single-dose and multidose RSV vaccination across two and three consecutive RSV seasons.

The primary endpoint was the VE of adjuvanted RSVPreF3 OA in preventing RSV-associated lower respiratory tract disease (LRTD) during the first RSV season. The secondary endpoints were the protective effects of one or two doses of adjuvanted RSVPreF3 OA against RSV LRTD across two and three RSV seasons.

The results demonstrated that a single adjuvanted RSVPreF3 OA dose provided a VE of 82.6% against RSV LRTD during the first RSV season. Over a median follow-up period of 18 months, spanning two RSV seasons, the VE

**Table 2.** AReSVi-006 Phase 3 Clinical Trial: Vaccine Efficacy of Adjuvanted RSVPreF3 OA in Different Populations (With Season as a Covariate) [22, 23, 24, 25]

| | Vaccine efficacy % (CI) | | |
|---|---|---|---|
| Vaccine efficacy / Study population | Across 1 RSV season (6.7 months) | Across 2 RSV seasons (18 months) | Across 3 RSV seasons (30.6 months) |
| RSV LRTD* | | | |
| All participants | 82.6% (96.95% CI: 57.9, 94.1) | 67.2% (97.5% CI: 48.2, 80.0) | 62.9% (97.5% CI: 46.7,74.8) |
| ≥1 Comorbidity | 94.6% (95% CI: 65.9, 99.9) | 66.7% (95% CI: 41.8, 82.0) | 64.7% (95% CI: 45.1,78.1) |
| ≥1 Cardiopulmonary-related comorbidity | 92.1% (95% CI: 46.7, 99.8) | 73.8% (95% CI: 47.9, 88.2) | 68.1%[a] (95% CI: 45.7, 82.3) |
| Severe RSV LRTD | 94.1% (95% CI: 62.4, 99.9) | 78.8% (95% CI: 52.6, 92.0) | 67.4% (95% CI: 42.4, 82.7) |

*LRTD is defined as the presence of ≥2 lower respiratory tract symptoms or signs persisting for ≥24 hours, including at least 1 lower respiratory tract sign, or as the presence of ≥3 lower respiratory tract symptoms persisting for ≥24 hours. Severe LRTD is defined as LRTD with ≥2 lower respiratory tract symptoms or an episode of LRTD assessed as severe by the investigator (Definition 1). Alternatively, severe LRTD can be defined as LRTD requiring supplemental oxygen, positive-pressure ventilation, or other types of mechanical ventilation (Definition 2). All RSV infection cases were confirmed by RT-PCR; designated comorbidities of interest included COPD, asthma, any chronic respiratory or pulmonary disease, heart failure, type 1 or 2 diabetes, and advanced liver or kidney disease. aUpdated from the original Chinese version.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; OA, older adult; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

was 74.5%. Over a median follow-up period of 30.6 months, covering three RSV seasons, the VE was 62.9% [21].

In patients with at least one comorbidity, single-dose adjuvanted RSVPreF3 OA demonstrated a VE of 94.6%, 66.7%, and 64.7% against RSV LRTD during the first season, across two seasons, and across three seasons, respectively. In patients with cardiopulmonary comorbidities, the VE was 92.1%, 73.8%, and 68.1% against RSV LRTD during the first season, across two seasons, and across three seasons, respectively. Regarding severe RSV LRTD prevention, the VE was 94.1%, 78.8%, and 67.4% during the first season, across two seasons, and across three seasons, respectively (Table 2).

VE did not differ significantly between the single-dose and multidose groups across two RSV seasons. According to these findings, a single dose of adjuvanted RSVPreF3 OA can provide protection lasting at least 2–3 years.

In consideration of the annual variability in RSV seasonal patterns and infection rates, seasonality was included as a covariate in the statistical analysis of the study endpoints. However, because RSV seasons are less defined in Taiwan, data that exclude seasonality as a covariate may be more relevant for local interpretation (Table 3).

**Table 3.** AReSVi-006 Phase 3 Clinical Trial: Vaccine Efficacy of Adjuvanted RSVPreF3 OA in Different Populations (Without Season as a Covariate and Considering Taiwan's Indistinct Seasons; Data Adjusted Using "Without Season as a Covariate" as a Covariate Can Be Referenced) [22, 23, 24, 25]

| | Vaccine efficacy % (CI) | | |
|---|---|---|---|
| Vaccine efficacy / Study population | Across 1 RSV season (6.7 months) | Across 2 RSV seasons (18 months) | Across 3 RSV seasons (30.6 months) |
| RSV LRTD* | | | |
| All participants | 82.6% (96.95% CI: 57.9, 94.1) | 74.5% (97.5% CI: 60.0, 84.5) | 69.1% (97.5% CI: 55.8, 78.9) |
| ≥1 Comorbidity | 94.6% (95% CI: 65.9, 99.9) | 74.5% (95% CI: 55.7, 86.1) | 71.1% (95% CI: 55.2, 82.0) |
| ≥1 Cardiopulmonary-related comorbidity | 92.1% (95% CI: 46.7, 99.8) | 80.1% (95% CI: 60.6, 91.0) | 73.9%[a] (95% CI: 55.8, 85.5) |
| Severe RSV LRTD | 94.1% (95% CI: 62.4, 99.9) | 82.7% (95% CI: 61.6, 93.4) | 72.3% (95% CI: 51.3, 85.2) |

*LRTD is defined as the presence of ≥2 lower respiratory tract symptoms or signs persisting for ≥24 hours, including at least 1 lower respiratory tract sign, or as the presence of ≥3 lower respiratory tract symptoms persisting for ≥24 hours. Severe LRTD is defined as LRTD with ≥2 lower respiratory tract symptoms or an episode of LRTD assessed as severe by the investigator (Definition 1). Alternatively, severe LRTD is defined as LRTD requiring supplemental oxygen, positive-pressure ventilation, or other types of mechanical ventilation (Definition 2). All RSV infection cases were confirmed by RT-PCR; the designated comorbidities of interest included COPD, asthma, any chronic respiratory or pulmonary disease, heart failure, type 1 or 2 diabetes, and advanced liver or kidney disease. aUpdated from the original Chinese version.

CI, confidence interval; COPD, chronic obstructive pulmonary disease; LRTD, lower respiratory tract disease; OA, older adult; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

***RENOIR phase 3 clinical trial [20]***

The RENOIR study was a multinational, multicenter, randomized controlled trial enrolling 34,284 individuals aged ≥60 years to evaluate the VE of RSVPreF across two RSV seasons [26-28]. The coprimary endpoints were the VE of RSVPreF against RSV LRTD with two or more symptoms and RSV LRTD with three or more symptoms.

The results demonstrated that during a single RSV season, the VE of RSVPreF against RSV LRTD with two or more symptoms was 64.1%, whereas that against RSV LRTD with three or more symptoms was 88.9%. Across two RSV seasons (16.4 months), the VE for preventing RSV LRTD with two or more symptoms was 55.7%, whereas the VE for preventing RSV LRTD with three or more symptoms was 77.8%.

When the population was limited to patients with one or more comorbidities, the VE of RSVPreF during the first season and across two seasons was respectively 63.6% and 49.3% for preventing RSV LRTD with two or more symptoms and 81.8% and 73.5% for preventing RSV LRTD with three or more symptoms. In individuals with one or more cardiopulmonary comorbidities, the VE during the first season

**Table 4.** RENOIR Phase 3 Clinical Trial: Vaccine Efficacy of RSVPreF in Different Populations (Without Season as a Covariate) [20, 26, 24, 29]

| Vaccine protection / Study population | Across 1 RSV season (7.1 months) | Across 2 RSV seasons (16.4 months) |
|---|---|---|
| RSV LRTD with ≥2 symptoms† | | |
| All participants | 6.1% (95% CI: 35.9, 82.0) | 58.8% (95% CI: 43.0, 70.6) |
| ≥1 Comorbidity | 63.6% (95% CI: 15.2, 86.0) | 49.3 % (95% CI: 23.2, 67.0) |
| ≥1 Cardiopulmonary-related comorbidity | 44.4 % (95% CI: −84.6, 85.4) | 29.0% (95% CI: −26.6, 60.8) |
| RSV LRTD with ≥3 symptoms† | | |
| All participants | 88.9% (95% CI: 53.6, 98.7) | 81.5% (95% CI: 63.3, 91.6) |
| ≥1 Comorbidity | 81.8 % (95% CI: 16.7, 98.0) | 73.5 % (95% CI: 43.6, 88.8) |
| ≥1 Cardiopulmonary-related comorbidity | 66.7 % (95% CI: −86.4, 96.7) | 63.2% (95% CI: 8.5, 86.9) |

†RSV-related acute respiratory illness (ARI) is defined as RSV infection confirmed by RT-PCR within 7 days of ARI symptom onset. ARI symptoms include one or more of the following: sore throat, cough, nasal secretions, nasal congestion, wheezing, sputum production, or shortness of breath. LRTD is defined as the presence of ≥2 or ≥3 of the following signs during an ARI episode: new onset or worsening of cough, wheezing, sputum production, or shortness of breath, and tachypnea (respiratory rate ≥ 25 breaths per minute, or ≥15% increase in respiratory rate from the baseline resting value).

CI, confidence interval; LRTD, low respiratory tract disease; RSV, respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction.

and across two seasons was respectively 44.4% and 29.0% for preventing RSV LRTD with two or more symptoms and 66.7% and 63.2% for preventing RSV LRTD with three or more symptoms (Table 4).

## Real-World Observations and Safety Assessments

### *Real-world effectiveness of RSV vaccines [23]*

RSV vaccines have been available since 2023. According to an observational study conducted by the Virtual SARS-CoV-2, Influenza, and Other Respiratory Viruses Network in collaboration with the US CDC, data from more than 200 emergency departments and hospitals between October 2023 and March 2024 demonstrated that RSV vaccines effectively prevented RSV-associated emergency department visits and hospitalizations.

The results indicated that in individuals aged 60–74 and ≥75 years, the VE of RSV vaccines for preventing RSV-associated emergency department visits and hospitalizations ranged from 75% to 80%. When analyzed by vaccine type, adjuvanted RSVPreF3 OA and RSVPreF demonstrated 77% and 79% VE against RSV-associated emergency department visits in adults aged ≥60 years, respectively. Moreover, adjuvanted RSVPreF3 OA and RSVPreF exhibited a VE of 83% and 73% against RSV-associated hospitalizations in these individuals, respectively.

In a subgroup of ≥60-year-old adults with immunodeficiency, the VE of RSV vaccination for preventing RSV-associated hospitalizations was 73% (Table 5). Notably, no observational study to date has assessed the VE of RSV vaccines for preventing RSV-associated hospitalizations beyond the first RSV season. Although variations are present in the definitions used across different observational studies, the real-world effectiveness of RSV vaccines appears to generally be consistent with the results of the aforementioned clinical trials (Table 6).

### *Safety of RSV vaccines*

The most common adverse event associated with adjuvanted RSVPreF3 OA has been localized pain, occurring in 60.9% of recipients, followed by redness and swelling, occurring in 7.5% of recipients. Frequently reported systemic adverse events include fatigue (33.6%), headache (27.2%), and muscle pain (28.9%). Notably, the occurrence of severe adverse events has not differed significantly between vaccine and placebo groups, and all side effects have generally resolved within 2–3 days [19].

In trials investigating the coadministration of adjuvanted RSVPreF3 OA and the influenza vaccine, the rates of localized pain after individual administration of the influenza vaccine and adjuvanted RSVPreF3 OA have been 20.5% and 39.1%, respectively. After simultaneous administration of these vaccines, these rates have been 28.3% for the influenza vaccine and 47.9% for adjuvanted RSVPreF3 OA. The coadministration of these vaccines did not affect their VE or the occurrence of adverse events [30].

Some clinical trials have reported that the adverse events associated with adjuvanted RSVPreF3 OA are comparable to those associated with the influenza vaccine, without significant differences among recipients. In studies evaluating coadministration of adjuvanted RSVPreF3 OA with the influenza vaccine, the rates of injection site pain after individual administration of the influenza vaccine and adjuvanted RSVPreF3 OA have been 7.6% and 11.5%,

**Table 5.** US CDC VISION Network Real-World Observational Study on RSV Vaccine Efficacy [18]

| **Immunocompetent adults aged ≥60 years** | Total | RSV-Positive, N (row %) | Median interval since last dose, days | Vaccine effectiveness*, % (95% CI) |
|---|---|---|---|---|
| RSV-associated ED visits ≥60 years | | | | |
| Unvaccinated (Ref) | 33,491 | 2,645 (8) | NA | |
| Adjuvanted RSVPreF3 OA | 2,522 | 47 (2) | 67 (40–99) | 77 (70–83) |
| RSVPreF | 506 | 9 (2) | 71 (40–108) | 79 (59–89) |
| RSV-associated hospitalization ≥ 60 years | | | | |
| Unvaccinated (Ref) | 25,816 | 1,567 (6) | NA | |
| Adjuvanted RSVPreF3 OA | 1,812 | 21 (1) | 73 (43–105) | 83 (73–89) |
| RSVPreF | 642 | 13 (2) | 81 (48–116) | 73 (52–85) |
| immunodeficiency + adults aged ≥60 years | | | | |
| RSV-associated hospitalization ≥ 60 years | | | | |
| Unvaccinated (Ref) | 7,615 | 314 (4) | NA | |
| Vaccinated* | 820 | 10 (1) | 72 (43–108) | 73 (48–85) |

*Analysis by brand is unavailable.

+Defined based on the presence of ICD-10 code corresponding to hematologic malignancy, solid malignancy, transplant, rheumatologic or inflammatory disorders, HIV, or other intrinsic immune condition or immunodeficiency in discharge diagnoses.

**Table 6.** RSV Vaccine Efficacy or Effectiveness in Clinical Trials and Real-World Studies [18]

| Outcome/Analysis | **GSK trial** (≥2 or 3 symptoms LRTD, primary endpoint) | **Pfizer trial** (≥2 symptoms LRTD, coprimary endpoint) | **Pfizer trial** (≥3 symptoms LRTD, coprimary endpoint) |
|---|---|---|---|
| Symptomatic RSV LRTD | 83% (58–94) | 67% (29–86) | 86% (32–99) |

| Outcome/ Analysis | **IVY Network**, ≥60 yrs | **VISION**, ≥60 yrs, immunocompetent | **VHA**, ≥60 yrs | **Medicare** ESRD, otherwise immunocompetent, ≥65 yrs | **VISION**, immunocompromised | **Medicare** ESRD, additional immunocompromise, ≥65 yrs |
|---|---|---|---|---|---|---|
| RSV-associated hospitalization | 75% (50–87) | 80% (71–85) | 82% (69–89) | 72% (41–87) | 73% (48–85) | 83% (45–95) |

CI, confidence interval; ESRD, end-stage renal disease; IVY, Influenza and Other Viruses in the Acutely Ill; LRTD, low respiratory tract disease; RSV, respiratory syncytial virus; VHA, Veterans Health Administration; yrs, years.

respectively. After simultaneous administration of these vaccines, the injection site pain rate has been 10.1% for both vaccines. The coadministration of these vaccines did not affect their VE or the occurrence of adverse events [28].

The most common adverse event associated with RSVPreF has been injection site pain, reported in 11% of recipients, followed by redness and swelling, occurring in 3% of recipients. Frequently observed systemic adverse events have included fatigue (16%) and headache (13%). In general, these systemic side effects are similar to those of other vaccines and typically resolve within 2–4 days [20].

Since their introduction to the US market in 2023, no significant safety concerns have been associated with adjuvanted RSVPreF3 OA and RSVPreF use [31].

## International Guidelines and Society Recommendations

Currently, two types of RSV vaccines are available for use in Taiwan. The Taiwan CDC advise individuals requiring vaccination to visit a health-care facility. After evaluation by a physician, one dose of an RSV vaccine may be administered to adults aged ≥75 years, those aged 60–74 years with a high risk of RSV infection (e.g., individuals with chronic pulmonary disease, cardiovascular disease, chronic liver disease, or kidney disease), and residents of long-term care or other institutional care facilities [32].

International health authorities and professional societies are continuing to update their recommendations regarding RSV vaccine use.

### *General recommendations on RSV vaccination use from the Advisory Committee on Immunization Practices and in other countries*

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends that individuals aged ≥75 years and those aged 50-74 years with chronic diseases or a high risk of severe RSV infection receive a single dose of the RSV vaccine [33]. Given the seasonality of respiratory infections in the United States, the ACIP recommends administering an RSV vaccine in late summer to early fall. The vaccine may also be coadministered with other common vaccines, including seasonal influenza, COVID-19, pneumococcal, pertussis, and herpes zoster vaccines. Table 7 summarizes the current RSV vaccination recommendations from the Taiwan and US CDC.

The German National Vaccination Committee (Sächsische Impfkommission, SIKO) has also outlined RSV vaccination for specific high-risk conditions; it recommends vaccination between September and early October, with the possibility of coadministration with a seasonal influenza vaccine [34].

The provincial government of Ontario, Canada, has introduced a publicly funded RSV vaccination program for the broader older adult population since 2023. It provides free RSV vaccination to all residents aged ≥60 years in long-term care facilities.

Several professional medical societies, including the American Academy of Family Physicians, German Respiratory Society, and Japanese Respiratory Society, have published guidelines on adult pneumonia that recommend RSV vaccination for the general population aged ≥60 years [35-38].

### *RSV vaccine recommendations for special populations*

For individuals with underlying medical

**Table 7.** Overview of Current RSV Vaccination Recommendations from Taiwan and US CDC [32] [39]

| Aspect | Taiwan CDC | U.S. CDC |
|---|---|---|
| Eligible age/ target group | One dose after physician evaluation:<br>① Adults ≥75 years;<br>② Adults 60–74 years at high risk of severe RSV disease<br>③ Pregnant women at 28–36 weeks to protect newborns | One dose recommended for:<br>① All adults ≥75 years;<br>② Adults aged 50–74 years at high risk of severe RSV disease |
| Defined risk factors | - Chronic pulmonary disease<br>- Cardiovascular disease<br>- Chronic liver disease<br>- Chronic kidney disease<br>- Residents of long-term care or other institutions | - Chronic lung diseases †<br>- Chronic cardiovascular diseases*<br>- Chronic kidney disease ‡<br>- Chronic liver disease ¶<br>- Diabetes with complications§<br>- Neurologic or neuromuscular conditions affecting airway clearance‖<br>- Hematologic disorders #<br>- Severe obesity **<br>- Immunocompromised state ††<br>- Residents of nursing homes<br>- Other health-care provider-determined high-risk conditions ‡‡ |
| Timing/Seasonality | No fixed epidemic season in Taiwan | Year-round immunization is recommended. Epidemic season is usually from late summer to early fall. |

*Chronic cardiovascular disease (e.g., heart failure, coronary artery disease, or congenital heart disease; excludes isolated hypertension)

†Chronic lung or respiratory disease (e.g., COPD, emphysema, asthma, interstitial lung disease, or cystic fibrosis)

‡Chronic kidney disease (e.g., end-stage renal disease or dependence on hemodialysis or other renal replacement therapy)

§Diabetes mellitus (complicated by chronic kidney disease, neuropathy, retinopathy, or other end-organ damage or requiring treatment with insulin or SGLT2 inhibitors)

‖Neurologic or neuromuscular conditions (causing impaired airway clearance or respiratory muscle weakness; e.g., poststroke dysphagia, amyotrophic lateral sclerosis, muscular dystrophy; excluding history of stroke without airway impairment)

¶Chronic liver disease (e.g., cirrhosis)

#Chronic hematologic disorders (e.g., sickle cell disease and thalassemia)

**Severe obesity (body mass index ≥ 40 kg/m2)

††Moderate or severe immune compromise (e.g., due to solid organ or hematopoietic stem cell transplant, hematologic malignancy, solid tumors, or immunosuppressive therapy)

‡‡Other health-care provider-determined conditions (e.g., frailty, undiagnosed chronic illness suspected, or living in remote or rural areas where access to advanced care for severe RSV may be challenging)

conditions, multiple international guidelines recommend RSV vaccination for high-risk groups. In particular, the Global Initiative for Chronic Obstructive Lung Disease, Global Initiative for Asthma, American Society of Clinical Oncology, and American Diabetes Association recommend that individuals aged ≥60 years with comorbidities, such as COPD, asthma, cancer, and diabetes, receive RSV vaccination [34-35, 40-41].

The German Respiratory Society and German Society for Hematology and Medical

Oncology have recommended RSV vaccination for individuals aged ≥18 years with immunodeficiency and at high risk. The German Respiratory Society also recommends RSV vaccination for adults with severe pulmonary or cardiovascular diseases and substantial immune system impairment. The German Society for Hematology and Medical Oncology specifically indicates RSV vaccination for patients receiving steroid therapy, immunosuppressive treatments, or organ transplantation, as well as those with hematologic malignancies or congenital immunodeficiency disorders [36, 42].

These recommendations reflect the growing recognition of RSV infection as a serious risk for individuals with chronic illnesses and immunodeficiency, emphasizing the importance of vaccination in preventing severe RSV-related complications.

## Discussion and Recommendations from the Taiwan Society of Pulmonary and Critical Care Medicine

At present, two RSV vaccines are available in Taiwan. Clinical trials have demonstrated effective protection in different high-risk populations. Moreover, real-world data indicate that the vaccines confer nearly 70% protection against RSV in individuals with immunodeficiency throughout a full RSV season. Clinical data and real-world evidence indicate that both vaccines are safe.

RSV vaccination in Taiwan need not be restricted to fall and winter. Because of climatic differences between northern and southern Taiwan, the peak period of RSV transmission may vary annually. Furthermore, Taiwan CDC data indicate that RSV infection cases are diagnosed throughout the year [9, 15]. Therefore, year-round RSV vaccination of high-risk individuals is highly recommended. Nevertheless, experts encourage RSV vaccination before the influenza season, allowing for simultaneous administration of RSV and influenza vaccines to provide relatively broad protection against respiratory infections.

The recommended target populations for RSV vaccination in Taiwan include adults aged ≥60 years with high-risk conditions; these conditions include COPD, asthma, interstitial lung disease, bronchiectasis, lung cancer, and other chronic pulmonary diseases. RSV vaccination is recommended for all adults aged ≥75 years, including those without specific risk factors.

In patients with acute exacerbations of COPD, an RSV vaccine should be administered only after their steroid dosage is tapered to ≤10 mg of prednisolone/day or equivalent. Patients with lung cancer should receive RSV vaccination at least 2 weeks or 1 month before each cancer treatment cycle. Additionally, in individuals with immunodeficiency and those receiving organ transplantation, post-RSV vaccination antibody levels should be closely monitored to ensure optimal immune response.

Considering the cost-effectiveness of adjuvanted RSVPreF3 OA in the United States and Japan and the current lack of public funding for RSV vaccines in Taiwan, individuals aged ≥60 years with comorbidities represent a key group for which RSV vaccine access and funding should be prioritized.

## Conclusion and Recommendations

***Seasonal epidemic considerations***

- Taiwan does not have a fixed RSV epidemic season; therefore, vaccination can be administered year-round.

- For individuals who wish to protect themselves against multiple respiratory infections during the influenza season, coadministration of RSV and influenza vaccines is recommended from late summer to early fall (August–October).

***Recommendations by age group***

- Individuals aged ≥75 years: Vaccination is recommended for the general population in this age group.
- Individuals aged 60–74 years with pulmonary risk factors: RSV vaccination is recommended. Pulmonary risk factors include
  - COPD,
  - Asthma,
  - Idiopathic pulmonary fibrosis,
  - Progressive pulmonary fibrosis,
  - Bronchiectasis,
  - Lung cancer, and
  - Other chronic pulmonary diseases.
- Individuals aged 60–74 years with other relevant risk factors: RSV vaccination can be considered.
- Individuals aged 50–59 years with risk factors: RSV vaccine indication has recently been approved; further discussion is upcoming.

***Clinical practice considerations***

- Patients with lung cancer: RSV vaccination should be administered as soon as possible after lung cancer diagnosis and administered at least 2 weeks before the cancer therapy.
- Patients with acute exacerbations of chronic respiratory diseases:RSV vaccination should be delayed until daily corticosteroid dosage is tapered to ≤10 mg of prednislone/day or equivalent.

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# Real-world Efficacy of Dacomitinib in Patients with Previously *EGFR*-TKI-treated Pulmonary Adenocarcinoma

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**Introduction:** Multiple studies have reported that retreatment with erlotinib is an alternative option for patients with *epidermal growth factor receptor* (*EGFR*)-mutant non-small cell lung cancer (NSCLC) who had benefited from previous *EGFR*-tyrosine kinase inhibitor (TKI) therapy and progressed after chemotherapy. Dacomitinib is a second-generation *EGFR*-TKI for the first-line treatment of *EGFR*-mutant advanced NSCLC. However, the efficacy of dacomitinib for previously *EGFR*-TKI-treated pulmonary adenocarcinoma remains unclear in real-world practice.

**Methods:** In this retrospective study, 21 enrolled patients who had progressed on previous *EGFR*-TKI and chemotherapy were treated with dacomitinib 45 mg or 30 mg orally daily until disease progression or intolerability. The progression-free survival (PFS), time-to-treatment failure (TTF), and overall survival (OS) from dacomitinib initiation were analyzed.

**Results:** Among the 21 enrolled patients with advanced pulmonary adenocarcinoma, there were 9 patients with an exon 19 deletion, 11 patients with an L858R mutation, and 1 patient with an exon 18 G719X mutation. Ten patients received dacomitinib 45 mg initially, among whom, 1 patient's dacomitinib was reduced to 30 mg due to adverse events. The other 11 patients received dacomitinib 30 mg without dose reduction. Four partial responses were documented (a 19% objective response rate; 95% confidence interval [CI], 5.4 to 41.9). The duration of response was 4.6 months (95% CI, 0 to 9.9). Of the 4 patients with a partial response, 3 had an original sensitizing *EGFR* L858R mutation and 1 had an exon 19 deletion; 0 of the 7 patients with acquired *EGFR* resistance mutations (T790M) met the response criteria. The median PFS, TTF, and OS were 1.6 months (95% CI, 1.4 to 1.86), 1.87 months (95% CI, 0.9 to 2.8), and 10.2 months (95% CI, 5 to 15.4), respectively. One partial intracranial response (7.1% response rate; 95% CI, 0.2 to 33.9) was recorded among 14 patients with brain metastases. Median PFS, TTF, and OS of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 compared to those with an ECOG PS of 1 were 0.3 vs. 1.87 months (hazard ratio [HR]=5.3, *P*=0.021), 0.3 vs.

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2.5 months (HR=8.5, *P*=0.002), and 0.3 vs. 17.5 months (HR=38.9, *P*=0.001), respectively. Furthermore, patients with an ECOG PS of 2 had a higher risk of death compared to those with an ECOG PS of 1 in multivariable analysis (HR=16.4 [95% CI=1.71-158.13]; *P*=0.015).

**Conclusion:** This study found that dacomitinib in previously *EGFR*-TKI-treated pulmonary adenocarcinoma patients had a modest benefit in real-world practice. Higher risks of disease progression, treatment failure for dacomitinib retreatment, and death were found in patients with a worse PS. ***(Thorac Med 2025; 40: 256-272)***

Key words: Pulmonary adenocarcinoma, epidermal growth factor receptor-tyrosine kinase inhibitor, *EGFR* mutation, dacomitinib, retreatment

## Introduction

The most common targetable drive oncogenes in non-small cell lung cancer (NSCLC) are *epidermal growth factor receptor* (*EGFR*) mutations, being discovered in approximately 10-15% of Caucasian patients [1-2] and in up to about 50% of Asian patients [2-3]. *EGFR*-tyrosine kinase inhibitors (TKIs) for advanced NSCLC harboring *EGFR* mutations have provided an improved survival outcome with first-line treatment. *EGFR*-TKIs consist of 3 generations of TKIs, including the first-generation TKIs, erlotinib and gefitinib; the second-generation TKIs, afatinib and dacomitinib; and the third-generation TKI, osimertinib [4-5].

Acquired resistance to the initial *EGFR*-TKI treatment inevitably occurs regardless of which front-line TKI is used. The subsequent treatment options after disease progression are a major consideration in determining treatment strategy. The most common resistance mechanism to the first and second generations of *EGFR*-TKIs is the exon 20 *EGFR* T790M mutation, which accounts for about 50-60% of cases [6-7]. Osimertinib is the standard of care in previously *EGFR*-TKI-treated NSCLC patients with identification of a T790M mutation. Chemotherapy is the treatment option in *EGFR*-TKI-treated NSCLC patients without identification of a T790M mutation. The other reported strategy is retreatment with *EGFR*-TKI after progression on later-line chemotherapy [8-9].

Dacomitinib, is a second-generation *EGFR*-TKI and an irreversible pan-human epidermal growth factor receptor (HER) family inhibitor for the first-line treatment of patients with advanced NSCLC harboring activating *EGFR* mutations [10]. In a phase III trial, dacomitinib had a superior survival benefit in patients with NSCLC harboring common *EGFR* mutations, compared to first-generation TKIs [11]. A previous case report found that dacomitinib was effective in treating lung adenocarcinoma with the rare *EGFR* L747P mutation and brain metastases after resistance to afatinib, achieving a partial response [12]. Another report describes 2 NSCLC patients who developed *EGFR* L858R/L718Q mutations after becoming resistant to osimertinib. In these cases, dacomitinib was able to overcome this resistance, indicating its potential as a treatment option for NSCLC pa-

tients with *EGFR* L718Q mutations following osimertinib failure [13].

Additionally, a phase I/II trial was conducted to evaluate dacomitinib, both as a monotherapy and in combination with osimertinib, in patients with *EGFR*-mutant lung cancers who experienced disease progression on osimertinib alone, and found an objective response rate (ORR) of 14% [14]. The efficacy of dacomitinib retreatment in previously *EGFR*-TKI-treated pulmonary adenocarcinoma remains unclear in real-world practice, and further research is necessary to evaluate the efficacy of dacomitinib in this context. Therefore, we investigated whether dacomitinib retreatment could provide a survival benefit in *EGFR*-mutant patients after previous TKI treatment.

## Patients and Methods

The medical records of patients with advanced NSCLC who had received *EGFR*-TKIs in Taipei Veterans General Hospital in Taiwan from December 2019 to February 2022 were retrospectively reviewed for eligibility of enrollment. The relevant clinical data, including demographic characteristics, cigarette smoking history, clinical characteristics, *EGFR* mutation status, treatment data, and survival time were collected. Lung cancer stage was evaluated according to the eighth edition of the tumor node metastasis (TNM) staging system for NSCLC [15]. This medical record-based study was approved by the Institutional Review Boards of Taipei Veterans General Hospital (IRB-TPEVGH No.: 2022-08-010BC).

Patients were enrolled in this study if the following inclusion criteria were met: pathologically confirmed stage III (ineligible for surgical resection or local radiotherapy) or stage IV NSCLC with an *EGFR* mutation receiving dacomitinib retreatment due to disease progression from prior treatment. *EGFR* mutations consist of those with exon 18 to exon 21 mutations. Patients underwent *EGFR* mutation testing performed in the standard-of-care evaluation through a polymerase chain reaction (PCR)-based *EGFR* mutation test or next-generation sequencing (NGS) panels [16]. Patients were excluded if they had *EGFR* wild-type NSCLC (*EGFR* mutation testing is not recommended by American Society of Clinical Oncology, College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology [17-18]); have never received *EGFR*-TKIs; or had received first-line dacomitinib. Upon disease progression, an *EGFR* T790M mutation detection assay was performed, based on the judgment of clinical physicians. Prescription of dacomitinib was based on the decision of the clinicians.

The baseline evaluation of lung cancer was performed within 3 weeks prior to dacomitinib treatment. The chest computed tomography scan was performed within 3 weeks before starting treatment, and then, every 3 months thereafter, or when confirmation of treatment response or disease progression was needed. Treatment response assessment was analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) group criteria (version 1.1).

Demographic data and clinical characteristics were analyzed by chi-square test for categorical variables. The primary outcome was to evaluate overall survival (OS), defined as the start date of dacomitinib to death from any reason; those alive or lost to follow-up were defined as censored. The secondary outcome was progression-free survival (PFS) and time-to-

treatment failure (TTF) with dacomitinib. PFS was defined as the time from the start date of dacomitinib to the date of disease progression, as determined by the RECIST criteria, or death from any cause. TTF was defined as the time from the start date of dacomitinib to the date of treatment discontinuation for any cause, such as disease progression, treatment toxicity, or death.

OS, PFS, and TTF were analyzed using the Kaplan-Meier (KM) method and log-rank test. Univariate Cox proportional hazard (Cox) models were used for assessing the association of prognostic factors with survival time. Multivariate Cox models were performed using significant variables ($p<0.10$) in the univariate Cox model, and hazard ratios (HR) with 95% confidence intervals (CI) were calculated [19-20]. All statistical tests were 2-tailed, and *P* levels of <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA).

## Results

A total of 21 patients with stage IVA or IVB *EGFR*-mutant NSCLC were enrolled in this study. Of them, 3 (14%) were men, and 18 (86%) were women. All patients had stage IV pulmonary adenocarcinoma and 14 (67%) had brain metastasis (BM); 21 (100%) patients had an *EGFR* mutation (9 exon 19 deletions, 11 exon 21 L858R point mutations, and 1 exon 18 G719X), and 7 (33%) had a T790M mutation (Table 1). *EGFR*-TKI treatment was administered to 21 (100%) patients, including 6 receiving dacomitinib as 2$^{nd}$-line *EGFR*-TKI treatment, 9 receiving dacomitinib as 3$^{rd}$-line *EGFR*-TKI treatment, and 6 patients receiving dacomitinib as ≥4$^{th}$-line *EGFR*-TKI treatment. Ten patients received dacomitinib 45 mg initially, among whom, 1 patient's dacomitinib was reduced to 30 mg due to adverse events. The other 11 patients received dacomitinib 30 mg without dose reduction during the treatment course. Four partial responses were documented (19% ORR; 95% CI, 5.4 to 41.9). The duration of response (DOR) was 4.6 months (95% CI, 0 to 9.9). The disease control rate (DCR) was 38% (95% CI, 18.1 to 61.6). Three patients with an original sensitizing *EGFR* L858R mutation and 1 patient with an exon 19 deletion had partial responses, whereas 0 of the 7 patients with acquired *EGFR* resistance mutations (T790M) met the response criteria. The intracranial response rate was 7% (95% CI, 0.2 to 33.9).

A 58-year-old female, a never-smoker who was enrolled in this study, was diagnosed with stage IB adenocarcinoma of the lung in the left lower lobe. She underwent a left lower lobe lobectomy, followed by adjuvant chemotherapy with vinorelbine plus carboplatin. Approximately 8 months after the lobectomy, disease recurrence with bilateral lung metastases was detected. *EGFR* mutation testing revealed an exon 19 deletion, and she was treated with gefitinib for approximately 9 months. Her treatments following disease progression included pemetrexed, erlotinib, docetaxel, nivolumab, osimertinib, ifosfamide plus epirubicin, and navelbine plus gemcitabine. Despite these interventions, progressive lung-to-lung metastases (Fig. 1A and 1B) and liver metastases (Fig. 1C and 1D) were observed in the chest CT scan. Dacomitinib at a dose of 30 mg was then administered, and a follow-up chest CT scan after approximately 2 months showed regression in both lung-to-lung metastases (Fig. 1E and 1F) and liver metastases (Fig. 1G and 1H). The pa-

**Table 1.** Previously TKI-treated *EGFR*-mutant NSCLC patients receiving dacomitinib

| | **Total** |
|---|---|
| **Patient no. (%)** | 21 |
| **Gender (%)** | |
| Male | 3 (14%) |
| Female | 18 (86%) |
| **Mean age (range, yr)** | 65 (49-87) |
| **With smoking history** | 1 (5%) |
| **ECOG performance status** | |
| 0 | 0 (0%) |
| 1 | 17 (81%) |
| 2 | 4 (19%) |
| **Lung cancer stage** | |
| IVA | 6 (29%) |
| IVB | 15 (71%) |
| **Histology** | |
| Adenocarcinoma | 21 (100%) |
| **Brain metastasis** | |
| Yes | 14 (67%) |
| No | 7 (33%) |
| **Treatment response** | |
| Partial remission | 4 (19%) |
| Stable disease | 4 (19%) |
| Progressive disease | 13 (62%) |
| ***EGFR* mutation (%)** | |
| With any mutation | 21 (100%) |
| With an exon 19 deletion | 9 (43%) |
| With an L858R point mutation | 11 (52%) |
| With a T790M point mutation | 7 (33%) |
| Wild type | 0 (0%) |
| **Intracranial Treatment response** | |
| Partial remission | 1 (7%) |
| Stable disease | 12 (86%) |
| Progressive disease | 1 (7%) |
| **No. of previous TKIs** | |
| 1 | 6 (29%) |
| 2 | 9 (43%) |
| 3 | 3 (14%) |
| 4 | 2 (10%) |
| 5 | 1 (5%) |
| **Adverse events** | |
| Skin rash (gr. 1-2) | 4 (19%) |
| Diarrhea (3 gr. 1-2; 1 gr. 3) | 4 (19%) |
| Stomatitis (gr. 1-2) | 5 (24%) |
| Paronychia (gr. 1-2) | 2 (10%) |
| **Dose reduction** | |
| 45 mg (n=10)→ 30 mg | 1 (10%) |
| 30 mg (n=11)→ 15 mg | 0 (0%) |

Acronyms: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; Gr., grade; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

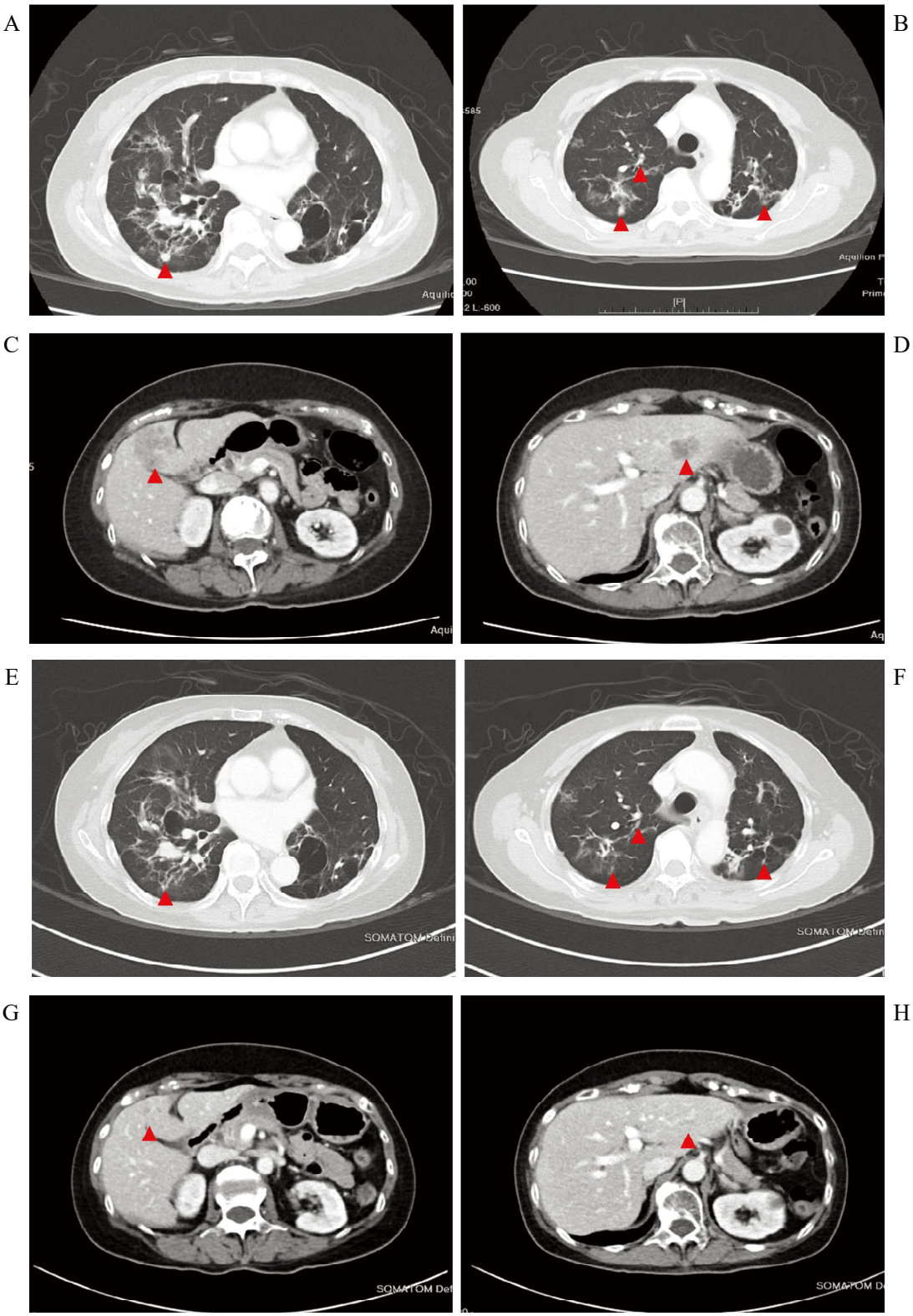


**Fig. 1.** Chest CT scans before and after dacomitinib treatment of a female patient who received multiple treatments, including *EGFR*-TKIs, chemotherapy and immunotherapy.
The chest CT scan before dacomitinib (1A to 1D) revealed multiple lung-to-lung metastases (1A and 1B; red arrowheads indicate lung metastases) and liver metastases (1C and 1D; red arrowheads indicate live metastases). After approximately 2 months of treatment with dacomitinib, the follow-up chest CT scan (1E to 1H) showed regression in lung-to-lung metastases (1E and 1F) and liver metastases (1G and 1H).

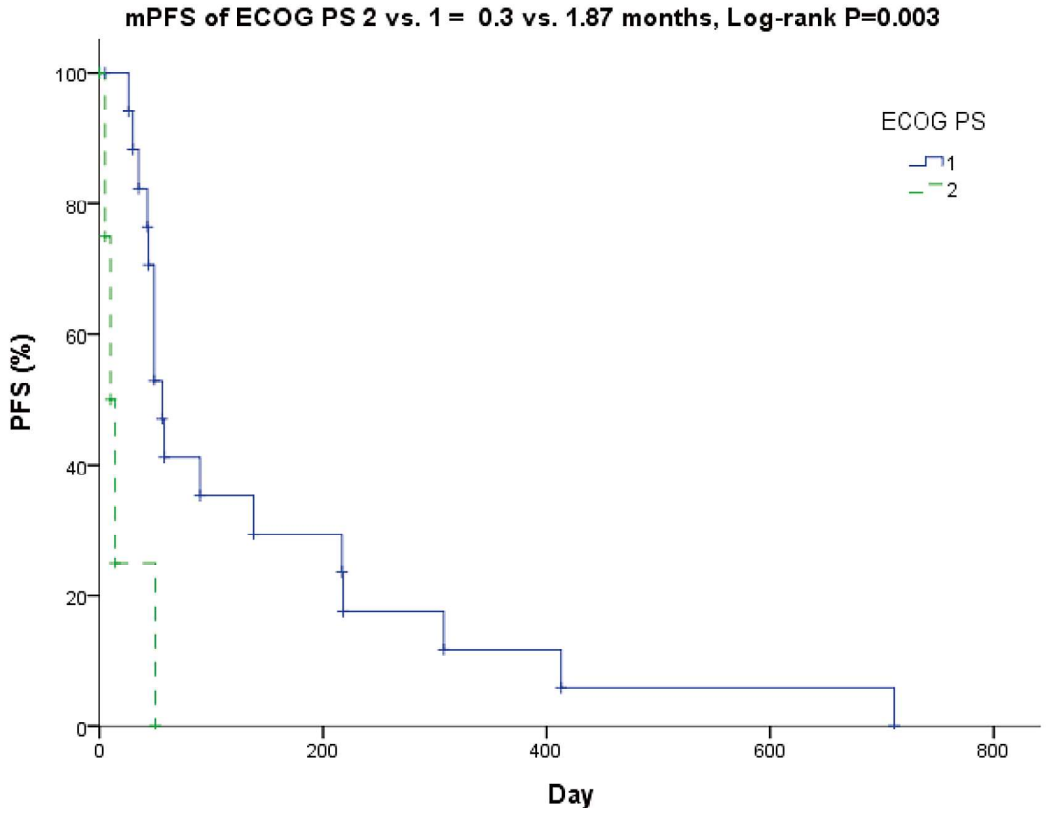


**Fig. 2.** Kaplan–Meier (KM) estimates of progression-free survival (PFS) for patients receiving dacomitinib retreatment (n = 21).
Patients with an ECOG PS of 2 had a PFS that was inferior to that of those with an ECOG PS of 1 (median PFS 0.3 vs. 1.87 months, *P*=0.003).

tient's TTF for dacomitinib was 217 days, demonstrating its efficacy in retreatment.

The most common adverse events (of any grade) in patients given dacomitinib were stomatitis (5 [24%]), skin rash (4 [19%]), and diarrhea (4 [19%]). The grade 3 adverse event was diarrhea (1 [5%] of 21 patients). No grade 4 adverse event was reported. Dose reduction occurred in 1 (5%) of the 21 patients (Table 1).

Significant variables in univariate Cox models of PFS for dacomitinib were analyzed in multivariate Cox models (Table 2), revealing that a higher risk of disease progression with dacomitinib was found in patients with a higher Eastern Cooperative Oncology Group performance status (ECOG PS) (2) (HR=5.25; 95% CI=1.54-17.86; $p$=0.021). The KM estimates of PFS for patients receiving dacomitinib (n=21) indicated that patients with an ECOG PS of 2 had a PFS that was inferior to those with an ECOG PS of 1 (median PFS 0.3 vs. 1.87 months, *P*=0.003, Fig. 2)

Significant variables in univariate Cox models of TTF for dacomitinib were analyzed in multivariate Cox models (Table 3), demonstrating that a higher risk of treatment failure with dacomitinib was also found in patients with a higher ECOG PS (2) (HR=8.52; 95% CI=2.21-32.83; $p$=0.002). The KM estimates of TTF showed that patients with an ECOG PS of 2 remained on dacomitinib for a significantly shorter time than those with an ECOG PS of 1 (median TTF 0.3 vs. 2.5 months, *P*<0.001, Fig. 3).

**Table 2.** Progression-free Survival Based on Clinical Characteristics

| Variable | No. | Median months | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| **Age** | | | | 0.854 | | |
| <70 years | 14 | 1.63 | *Reference* | | | |
| ≥70 years | 7 | 1.67 | 0.92 (0.36-2.31) | | | |
| **Gender** | | | | 0.798 | | |
| Male | 3 | 1.87 | *Reference* | | | |
| female | 18 | 1.63 | 1.18 (0.34-4.07) | | | |
| **Smoking history** | | | | 0.412 | | |
| No | 20 | 1.63 | *Reference* | | | |
| Yes | 1 | 10.26 | 0.43 (0.06-3.29) | | | |
| **ECOG PS** | | | | 0.021 | | 0.021 |
| 1 | 17 | 1.87 | *Reference* | | *Reference* | |
| 2 | 4 | 0.33 | 5.25 (1.54-17.86) | | 5.25 (1.54-17.86) | |
| **Stage** | | | | 0.356 | | |
| IVA | 6 | 1.63 | *Reference* | | | |
| IVB | 15 | 1.63 | 1.60 (0.59-4.32) | | | |
| ***EGFR* mutation** | | | | 0.470 | | |
| Exon 19 deletion | 9 | 1.47 | *Reference* | | | |
| L858R point mutation | 11 | 1.67 | 0.716 (0.29-1.77) | | | |
| **T790M mutation** | | | | 0.817 | | |
| No | 14 | 1.63 | *Reference* | | | |
| Yes | 7 | 1.93 | 0.90 (0.35-2.28) | | | |
| **Previous brain metastasis** | | | | 0.660 | | |
| No | 7 | 1.63 | *Reference* | | | |
| Yes | 14 | 1.63 | 1.24 (0.48-3.22) | | | |
| **Previous EGFR-TKI** | | | | 0.335 | | |
| 1 TKIs | 11 | 1.63 | *Reference* | | | |
| ≥2 TKIs | 10 | 1.63 | 0.64 (0.25-1.60) | | | |
| **Afatinib as 1st-line treatment** | | | | 0.626 | | |
| No | 14 | 1.67 | *Reference* | | | |
| Yes | 7 | 1.17 | 1.28 (0.48-3.40) | | | |
| **Dacomitinib dose** | | | | 0.908 | | |
| Less than 45 mg | 12 | 1.67 | *Reference* | | | |
| 45 mg | 9 | 1.63 | 0.95 (0.38-2.35) | | | |

Acronyms: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; *EGFR: epidermal growth factor receptor*; HR: hazard ratio; No.: number; PS: performance status; TKI: tyrosine kinase inhibitor.

**Table 3.** Time-to-treatment Failure Based on Clinical Characteristics

| Variable | No. | Median months | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| **Age** | | | | 0.9996 | | |
| <70 years | 14 | 1.87 | *Reference* | | | |
| ≥70 years | 7 | 1.83 | 1.00 (0.397-2.53) | | | |
| **Gender** | | | | 0.553 | | |
| Male | 3 | 3.30 | *Reference* | | | |
| female | 18 | 1.67 | 1.46 (0.34-4.07) | | | |
| **Smoking history** | | | | 0.407 | | |
| No | 20 | 1.83 | *Reference* | | | |
| Yes | 1 | 10.27 | 0.42 (0.05-3.25) | | | |
| **ECOG PS** | | | | 0.002 | | 0.002 |
| 1 | 17 | 2.47 | *Reference* | | *Reference* | |
| 2 | 4 | 0.33 | 8.52 (2.21-32.83) | | 8.52 (2.21-32.83) | |
| **Stage** | | | | 0.231 | | |
| IVA | 6 | 3.30 | *Reference* | | | |
| IVB | 15 | 1.83 | 1.83 (0.68-4.93) | | | |
| ***EGFR* mutation** | | | | 0.646 | | |
| Exon 19 deletion | 9 | 1.83 | *Reference* | | | |
| L858R point mutation | 11 | 1.87 | 0.809 (0.33-2.00) | | | |
| **T790M mutation** | | | | 0.980 | | |
| No | 14 | 1.67 | *Reference* | | | |
| Yes | 7 | 2.30 | 0.99 (0.39-2.52) | | | |
| **Previous brain metastasis** | | | | 0.717 | | |
| No | 7 | 1.63 | *Reference* | | | |
| Yes | 14 | 1.87 | 1.19 (0.46-3.12) | | | |
| **Previous EGFR-TKI** | | | | 0.411 | | |
| 1 TKIs | 11 | 1.87 | *Reference* | | | |
| ≥2 TKIs | 10 | 1.67 | 0.68 (0.27-1.71) | | | |
| **Afatinib as 1$^{st}$-line treatment** | | | | 0.521 | | |
| No | 14 | 2.47 | *Reference* | | | |
| Yes | 7 | 1.17 | 1.38 (0.52-3.71) | | | |
| **Dacomitinib dose** | | | | 0.638 | | |
| Less than 45 mg | 12 | 1.67 | *Reference* | | | |
| 45 mg | 9 | 2.30 | 0.81 (0.33-1.99) | | | |

Acronyms: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; *EGFR: epidermal growth factor receptor*; HR: hazard ratio; No.: number; PS: performance status; TKI: tyrosine kinase inhibitor.

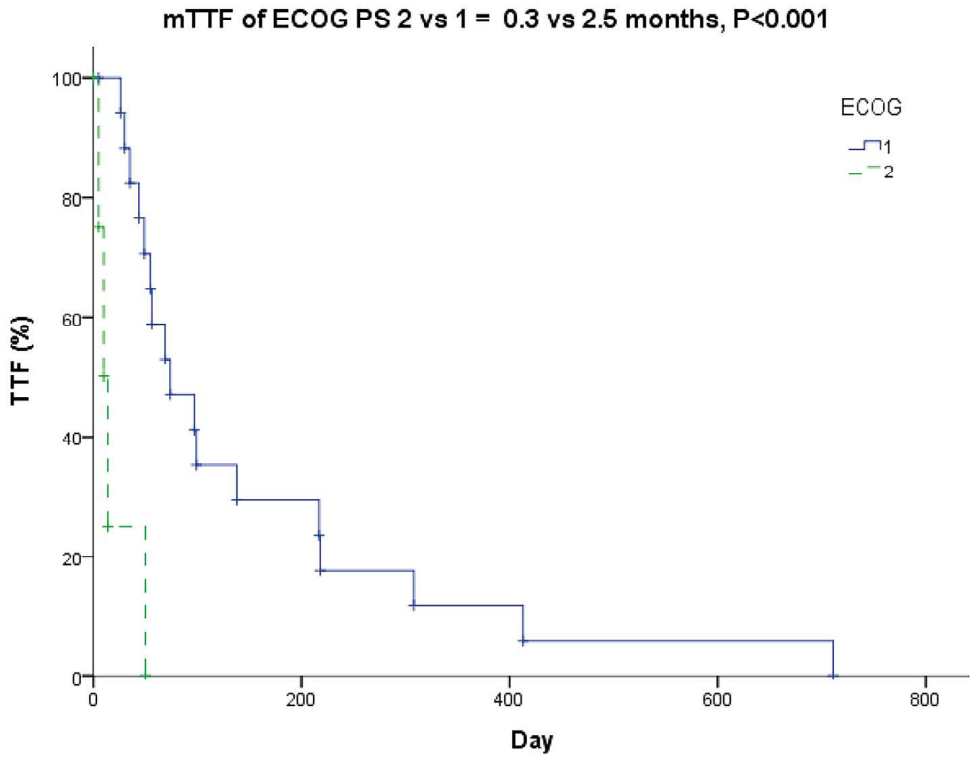


**Fig. 3.** Kaplan–Meier (KM) estimates of time-to-treatment failure (TTF) for patients receiving dacomitinib retreatment (n = 21).
Patients with an ECOG PS of 2 remained on dacomitinib for a significantly shorter time than those with an ECOG PS of 1 (median TTF 0.3 vs. 2.5 months, *P*<0.001).

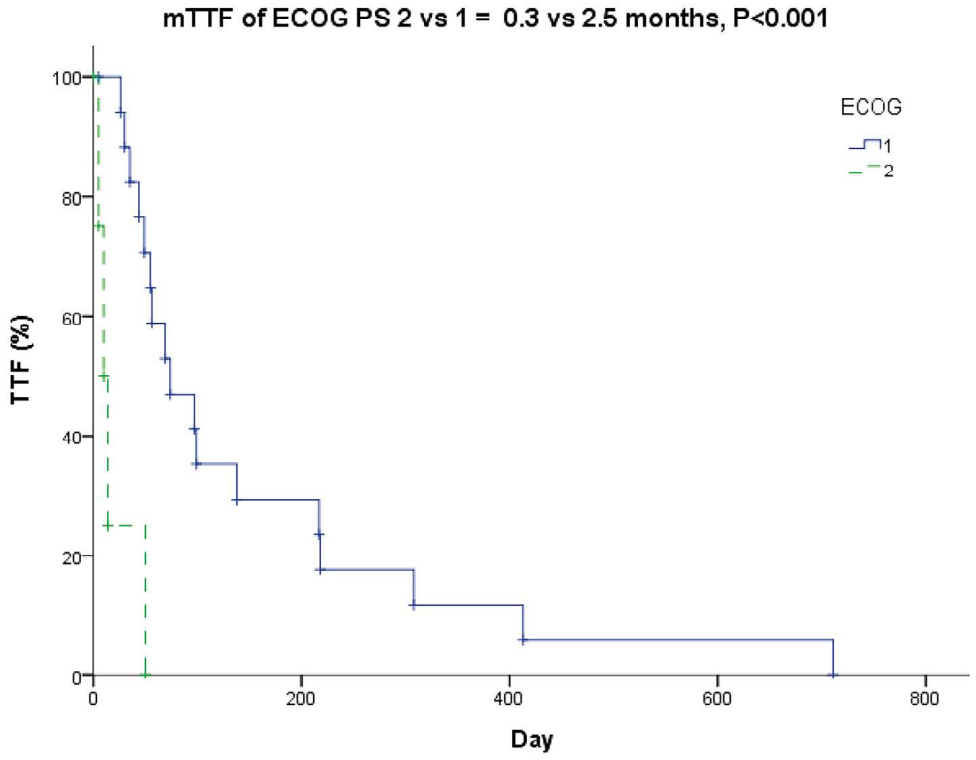


**Fig. 4.** Kaplan–Meier (KM) estimates of overall survival (OS) for patients receiving dacomitinib retreatment (n = 21).
Patients with an ECOG PS of 2 survived for a shorter period than those with an ECOG PS of 1 (median OS 0.3 vs. 17.5 months, *P*<0.001).

**Table 4.** Overall Survival Based on Clinical Characteristics

| Variable | No. | Median months | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|---|---|
| | | | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| **Age** | | | | 0.055 | | 0.053 |
| <70 years | 14 | 17.47 | *Reference* | | *Reference* | |
| ≥70 years | 7 | 3.97 | 2.68 (0.98-7.35) | | 3.97 (0.99-15.97) | |
| **Gender** | | | | 0.240 | | |
| Male | 3 | NR | *Reference* | | | |
| female | 18 | 8.57 | 27.65 (0.11-7024.90) | | | |
| **Smoking history** | | | | 0.383 | | |
| No | 20 | 8.57 | *Reference* | | | |
| Yes | 1 | NR | 0.04 (0.00-55.47) | | | |
| **ECOG PS** | | | | 0.001 | | 0.015 |
| 1 | 17 | 17.47 | *Reference* | | *Reference* | |
| 2 | 4 | 0.33 | 38.93 (4.14-366.08) | | 16.43 (1.71-158.13) | |
| **Stage** | | | | 0.08 | | 0.057 |
| IVA | 6 | 25.63 | *Reference* | | *Reference* | |
| IVB | 15 | 8.40 | 3.17 (0.87-11.54) | | 4.69 (0.95-23.08) | |
| ***EGFR* mutation** | | | | 0.551 | | |
| Exon 19 deletion | 9 | 17.47 | *Reference* | | | |
| L858R point mutation | 11 | 8.57 | 1.38 (0.48-3.91) | | | |
| **T790M mutation** | | | | 0.365 | | |
| No | 14 | 8.57 | *Reference* | | | |
| Yes | 7 | 12.2 | 0.61 (0.21-1.77) | | | |
| **Previous brain metastasis** | | | | 0.426 | | |
| No | 7 | 10.23 | *Reference* | | | |
| Yes | 14 | 8.57 | 1.56 (0.52-4.63) | | | |
| **Previous EGFR-TKI** | | | | 0.479 | | |
| 1 TKIs | 11 | 17.47 | *Reference* | | | |
| ≥2 TKIs | 10 | 8.57 | 1.43 (0.53-3.88) | | | |
| **Afatinib as 1$^{st}$-line treatment** | | | | 0.998 | | |
| No | 14 | 8.57 | *Reference* | | | |
| Yes | 7 | 12.20 | 1.00 (0.36-2.78) | | | |
| **Dacomitinib dose** | | | | 0.397 | | |
| Less than 45 mg | 12 | 8.4 | *Reference* | | | |
| 45 mg | 9 | 22.35 | 0.64 (0.23-1.79) | | | |

Acronyms: CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; *EGFR: epidermal growth factor receptor*; HR: hazard ratio; No.: number; NR, not reached; PS: performance status; TKI: tyrosine kinase inhibitor.

Significant variables in univariate Cox models of OS for all patients were analyzed in multivariate models (Table 4), and revealed that patients with a higher ECOG PS (2) had a higher risk of death (HR=16.43; 95% CI=1.71-158.13; $p$=0.015). Survival analysis showed that patients with an ECOG of 2 survived for a shorter period than those with an ECOG PS of 1 (median OS 0.3 vs. 17.5 months, $P$<0.001, Fig. 4).

## Discussion

This study tested the hypothesis that dacomitinib retreatment could provide a survival benefit in *EGFR*-mutant patients after previous TKI treatment in real-world practice, and our results suggested that dacomitinib retreatment had modest benefit in real-world practice. Moreover, higher risks of disease progression, treatment failure with dacomitinib retreatment, and death were found in patients with a worse PS.

Dacomitinib, a second-generation *EGFR*-TKI, is an oral irreversible pan-ErbB inhibitor that has been approved for 1st-line treatment of advanced *EGFR*-mutant NSCLC patients worldwide [21-23]. A phase III ARCHER 1050 study that compared dacomitinib to gefitinib in treatment-naive patients with *EGFR*-mutant NSCLC found that the PFS benefit was higher in the dacomitinib arm than in the gefitinib arm (14.7 vs. 9.2 months, HR=0.59, 95% CI= 0.47-0.74, $p$<0.0001) [5]. Furthermore, median OS was longer in the dacomitinib arm compared to that in the gefitinib arm (34.1 months vs. 26.8 months, HR 0.76, 95% CI 0.58-0.99, $p$ = 0.0438) [24].

Many patients can now receive other 1st/2nd/3rd-generation TKIs as 1st-line treatment based on guideline recommendations or financial consideration [25-26]. Dacomitinib was not approved for previously TKI-treated NSCLC harboring an *EGFR* mutation. Nevertheless, prior retrospective studies reported that patients with advanced *EGFR*-mutant NSCLC could still be sensitive to *EGFR*-TKI after stopping treatment [27-28]. One retrospective study with a small number of cases reported that patients who were heavily treated and then retreated with erlotinib after a median interval of 9.5 months from the previous *EGFR*-TKI to the subsequent TKI had an ORR of 36% and a DCR of 85.7% [29]. A small series of patients with *EGFR*-mutant NSCLC given *EGFR*-TKI retreatment reported experiencing the beneficial effect of treatment after a TKI-free interval (median time of 11 months). The PFS in heavily-treated patients was 4.4 months [30]. In patients with a sensitizing *EGFR* mutation, continued TKI combined with chemotherapy or retreatment with *EGFR*-TKI after a TKI-free interval could be considered as alternative treatment options [8-9].

A phase I/II trial evaluating dacomitinib, both alone and combined with osimertinib, in *EGFR*-mutant lung cancer patients who progressed on osimertinib reported an ORR of 14% [14]. In addition, a real-world study showed that dacomitinib is both effective and well-tolerated in NSCLC patients with various *EGFR* mutations, including those with BM, in later-line treatment. Patients who responded better to their initial *EGFR*-TKI therapy were more likely to experience benefits from dacomitinib. Consequently, the use of dacomitinib following resistance to first-line TKI therapy could be a viable option [31]. Our findings showed that in pulmonary adenocarcinoma previously treated with *EGFR*-TKIs, dacomitinib achieved an

ORR of 19% and a DCR of 38%, with a DOR of 4.6 months, PFS of 1.6 months, and TTF of 1.87 months, suggesting its efficacy in this context.

In this study, even though there has been a treatment response in patients receiving dacomitinib retreatment, the magnitude of the efficacy is very modest and does not seem to be clinically robust, particularly relative to the side effects and cost of dacomitinib. Comprehensive genetic analysis of post-*EGFR*-TKI lung cancer could provide useful insight into the complex genomic mechanisms of acquired resistance to TKIs after progression of the disease. NGS has been reported to be able to identify resistance mechanisms in *EGFR*-mutant NSCLC with acquired resistance to TKIs, and facilitates the decision for the next line of treatment [32]. Liquid biopsy, which is a minimally invasive alternative to the genetic testing of tumor tissue, has also been used to identify therapeutic resistance in advanced *EGFR*-mutant NSCLC. Nowadays, liquid biopsy has an important role in detecting molecular characteristics at the time of resistance, to help in deciding on further treatment, especially for those patients who are unable to receive tumor biopsy upon progression of the disease [33].

BM is a common occurrence in NSCLC; the incidence of BM has been reported to be about 25% at the initial diagnosis in patients with *EGFR*-mutant NSCLC [34-35]. Dacomitinib was shown to be superior to first-generation *EGFR*-TKIs in the phase III ARCHER 1050 trial [5]. However, the efficacy of dacomitinib in the central nervous system (CNS) remains unclear, as the ARCHER 1050 trial did not enroll patients with baseline BM. One multicentric observational study has shown that the intracranial ORR of dacomitinib was 87.5% and the intracranial disease control rate was 100% among 32 patients with *EGFR*-mutant NSCLC and baseline BM in a real-world setting, suggesting that dacomitinib showed CNS efficacy in treatment-naïve *EGFR*-mutated NSCLC with BM [21]. In our study, the intracranial response rate was 7% in patients with previously *EGFR*-TKI-treated pulmonary adenocarcinoma and BM. Although the intracranial response rate of dacomitinib was worse in TKI-treated pulmonary adenocarcinoma than that in treatment-naïve NSCLC, the efficacy of dacomitinib for BM was still observed in some patients from our study.

The *EGFR* exon 20 T790M mutation is the most common resistance mechanism to first/second-generation *EGFR*-TKIs in about 50-60% of cases [6-7]. Osimertinib could be used in *EGFR*-TKI-treated NSCLC patients with the acquired resistance of the T790M mutation. In our study, 4 partial responses were observed (19% ORR): 3 patients with an *EGFR* L858R mutation and 1 patient with an exon 19 deletion had partial responses, but none of the 7 patients with acquired *EGFR* resistance of the T790M mutation met the response criteria. Dacomitinib, a second-generation irreversible *EGFR*-TKI was developed in part to inhibit the T790M mutation, in addition to the sensitizing *EGFR* mutations [36]. Despite the promising preclinical data and early-phase studies, no obvious efficacy of dacomitinib for NSCLC harboring a T790M mutation was found in the clinical trials and in our study [10].

Previous studies showed that the ECOG PS score was an independent predictor of OS. A good ECOG PS score was associated with better survival in patients with sensitizing *EGFR* mutations who underwent *EGFR*-TKI therapy [37]. A real-world observational cohort study

of first-line first-/second-generation *EGFR*-TKIs in patients with *EGFR* mutation-positive NSCLC showed that an ECOG PS ≥2 was statistically associated with a higher HR of OS [38]. In older patients with *EGFR*-mutant NSCLC receiving TKI treatment, a good PS was associated with a longer PFS and OS [39]. Our findings also showed that patients with an ECOG PS of 2 given dacomitinib retreatment had a higher risk of death compared to those with an ECOG PS of 1 in multivariable analysis (HR=16.4; $p$=0.015), suggesting that patients with relatively good ECOG PS may have a better prognosis.

In our study, the most common adverse events in patients given dacomitinib were stomatitis (24%), skin rash (19%), and diarrhea (19%). No grade 4 adverse event was reported. Dose reduction occurred in 5% of patients. The incidence of adverse events reported in our study is comparable with that reported for other dacomitinib trials, including the ARCHER 1050 study [5, 40-43]. No new safety signals were found in patients with previously *EGFR*-TKI-treated pulmonary adenocarcinoma. The safety profile of dacomitinib retreatment was tolerable and manageable.

The limitations of our study were that the research was conducted in a single tertiary-care referral center and patient numbers were small. The current study was a retrospective real-world study, so selection bias was inevitable, and the efficacy of dacomitinib retreatment in this study might not be completely representative of the general *EGFR*-mutant lung cancer population. Furthermore, first-line dacomitinib treatment in advanced *EGFR*-mutant NSCLC patients without BM is reimbursed by Taiwan's National Health Insurance. As a result, some patients with *EGFR*-mutant NSCLC will undergo first-line dacomitinib treatment and will not have the therapeutic option of dacomitinib retreatment. In addition, the evolving treatment paradigm of NSCLC in recent years might potentially confound the OS analysis of the study population. Further prospective studies may be needed, such as head-to-head clinical trials to find the best strategy for *EGFR*-TKI retreatment.

## Conclusion

To the best of our knowledge, this is the first study to analyze dacomitinib retreatment in patients with previously *EGFR*-TKI-treated pulmonary adenocarcinoma. This study revealed the clinical features and therapeutic efficacy of dacomitinib retreatment in patients with previously TKI-treated pulmonary adenocarcinoma, who often have to undergo chemotherapy treatment. Our finding suggested that dacomitinib use in previously *EGFR*-TKI-treated pulmonary adenocarcinoma had a modest benefit in real-world practice. Additionally, higher risks of disease progression, treatment failure with dacomitinib retreatment, and death were found in patients with a worse PS.

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# Impact of Mechanical Power on 28-Day Mortality in ARDS Patients: A Cohort Study of Diverse Etiologies

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**Introduction:** Recent studies have reported an association between mechanical power (MP) and mortality in patients with acute respiratory distress syndrome (ARDS). The aim of our study was to explore the relationships between various ventilator parameters and patient outcomes in mechanically ventilated ARDS patients across different etiologies.

**Methods:** This single-center retrospective cohort study included adult patients who underwent mechanical ventilation for community-acquired pneumonia-induced ARDS between June 2019 and July 2021. To investigate etiological differences, we also included patients with influenza-related ARDS that developed during the influenza epidemic in 2016. Logistic regression was used to evaluate the association between 28-day mortality and ventilator parameters.

**Results:** The study included 107 patients, categorized into 3 groups: COVID-19-related ARDS (N=33), influenza-related ARDS (N=41), and ARDS of other etiologies (N=33). The overall 28-day mortality rate was 15.9%. The group with ARDS of other etiologies had a higher Charlson Comorbidity Index score. In multivariable logistic regression analysis, MP on the first day was independently associated with 28-day mortality, with an odds ratio of 1.08 (p=0.04); no other factors were associated. Ventilator parameters did not significantly differ between patients with different underlying etiologies.

**Conclusion:** Higher MP was associated with increased 28-day mortality in COVID-19, influenza, and other etiology-related ARDS patients. ***(Thorac Med 2025; 40: 273-283)***

Key words: ARDS, COVID-19, influenza, mechanical power, mortality

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## Introduction

Despite advances in lung-protective ventilation and other therapeutic strategies, mortality rates for patients with acute respiratory distress syndrome (ARDS) remain alarmingly high [1-5]. Previous research has explored the associations between ARDS mortality and various factors, including demographic characteristics, comorbid conditions, and ventilator settings [6-10]. Mechanical power (MP) -- an integrated measure of respiratory rate, airway pressure, and ventilation -- reflects the energy applied to the respiratory system and offers a more comprehensive view than traditional ventilator parameters such as tidal volume, respiratory rate, and driving pressure [6-7, 11-12]. Elevated MP has been associated with increased mortality in adult ARDS patients [13-17].

ARDS can result from diverse etiologies or pathogens, and may present with variable characteristics. While the support strategy for most ARDS cases, including both coronavirus disease 2019 (COVID-19) and non-COVID-19 ARDS, has been similar due to the applicability of lung-protective ventilation across different lung compliances, studies have shown heterogeneous respiratory mechanics between COVID-19 and non-COVID-19 ARDS, even when comparing similar ratios of partial pressure of oxygen in arterial blood (PaO2) to the fraction of inspiratory oxygen concentration (FiO2) [16]. The clinical relevance of these differing respiratory mechanics remains unclear, though some studies have reported that the respiratory mechanics of COVID-19-related ARDS resemble those of other viral causes of ARDS, such as influenza [18-20].

COVID-19 is known for its significant risk of respiratory failure, ARDS, and mortality worldwide, despite treatment [21-23]. Studies have shown that COVID-19 patients requiring higher MP in the early stages of ARDS exhibit increased 28-day mortality [15-16, 24]. Similarly, influenza has been a significant risk factor for ARDS and mortality during past epidemics [25-26]. However, no study to date has specifically examined differences in MP among ARDS patients with COVID-19, influenza, and other etiologies. This study aims to explore the differences in ventilator parameters, especially MP, across these groups, and their association with mortality.

## Material and Methods

### *Study design and population*

This retrospective cohort study was conducted at a 2500-bed medical center in Taipei, Taiwan. The inclusion criteria were adults (aged ≥20 years) with ARDS who initiated mechanical ventilation (MV) for community-acquired pneumonia between June 2019 and July 2021. Exclusion criteria included the use of MV for less than 24 hours and the use of extracorporeal life support. Due to the limited number of influenza-related ARDS cases during the COVID-19 pandemic, we also retrospectively included patients from the 2016 influenza epidemic at our medical center to facilitate comparisons. The primary endpoint was 28-day mortality, measured from the start date of MV for ARDS to the mortality date.

### *ARDS definition*

ARDS and its severity were defined in accordance with the Berlin definition. Criteria include new or worsening respiratory symptoms within 1 week, radiographic evidence of bilateral opacities not fully explained by effusions,

lung collapse or nodules, respiratory failure not fully explained by cardiac failure or fluid overload, and PaO2/FiO2 ≤ 300 mmHg under a positive end-expiratory pressure (PEEP) ≥ 5 cmH2O. ARDS severity was categorized as mild, moderate or severe based on PaO2/FiO2 ratios [27].

***Data collection***

Patient clinical data were retrieved from the hospital's electronic medical records, and included age, sex, body mass index (BMI), comorbidities, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Charlson Comorbidity Index (CCI), arterial blood gas data and ventilator parameters. Ventilator parameters were recorded on the first day after the patient was intubated for MV and every morning thereafter, starting from the second day. Ventilator parameters encompassed tidal volume, respiratory rate, peak inspiratory pressure (PIP), dynamic driving pressure, PEEP and baseline MP on arrival ($MP_{day1}$) and on the second day ($MP_{day2}$). We used dynamic driving pressure, calculated as PIP minus PEEP, instead of driving pressure alone, due to missing data on plateau pressure [14]. MP was calculated with a surrogate equation, as shown below, which has been validated for pressure-targeted MV in previous literature [11, 14-15, 24]. It is important to note that the equation below was based on dynamic MP, excluding PEEP power [28].

MP (J/min) =0.098 × minute ventilation (L/min) × [(PIP+ PEEP)/2]

Additionally, mechanical parameters such as the ratio of $MP_{day2}$ and $MP_{day1}$, calculated as $MP_{day2}/MP_{day1}$, MP difference (MPD), calculated as $MP_{day1}$- $MP_{day2}$, and MP variation rate, calculated as $([MP_{day1} - MP_{day2}]/MP_{day1}) \times 100\%$, were collected to investigate whether the dynamic change in MP-affected mortality.

***Statistical analysis***

Results are presented as means±standard deviations. Categorical variables were compared using Fisher's exact test, and continuous variables were analyzed with the Kruskal-Wallis rank sum test. Binary univariate and multivariable logistic regression analyses were employed to evaluate the independent risk factors for 28-day mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and p values less than 0.05 were considered statistically significant.

In the multivariable logistic regression analysis, respiratory rate, tidal volume, PIP, dynamic driving pressure, and PEEP were not included as covariates, as they are components of MP. The CCI was employed in multivariable logistic regression, instead of individual underlying disease, to avoid redundancy with other covariates. The APACHE II score was excluded from the analysis for the same reason.

The receiver operating characteristic curve (ROC) and the Youden index were employed to determine the optimal cut-off point value for predicting 28-day mortality. Subsequently, Kaplan-Meier survival analysis was performed to compare the survival times of patients with MP at arrival, either below or above this optimal cut-off point. The Log-rank test was applied, with a p value less than 0.05 considered as statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows.

## Results

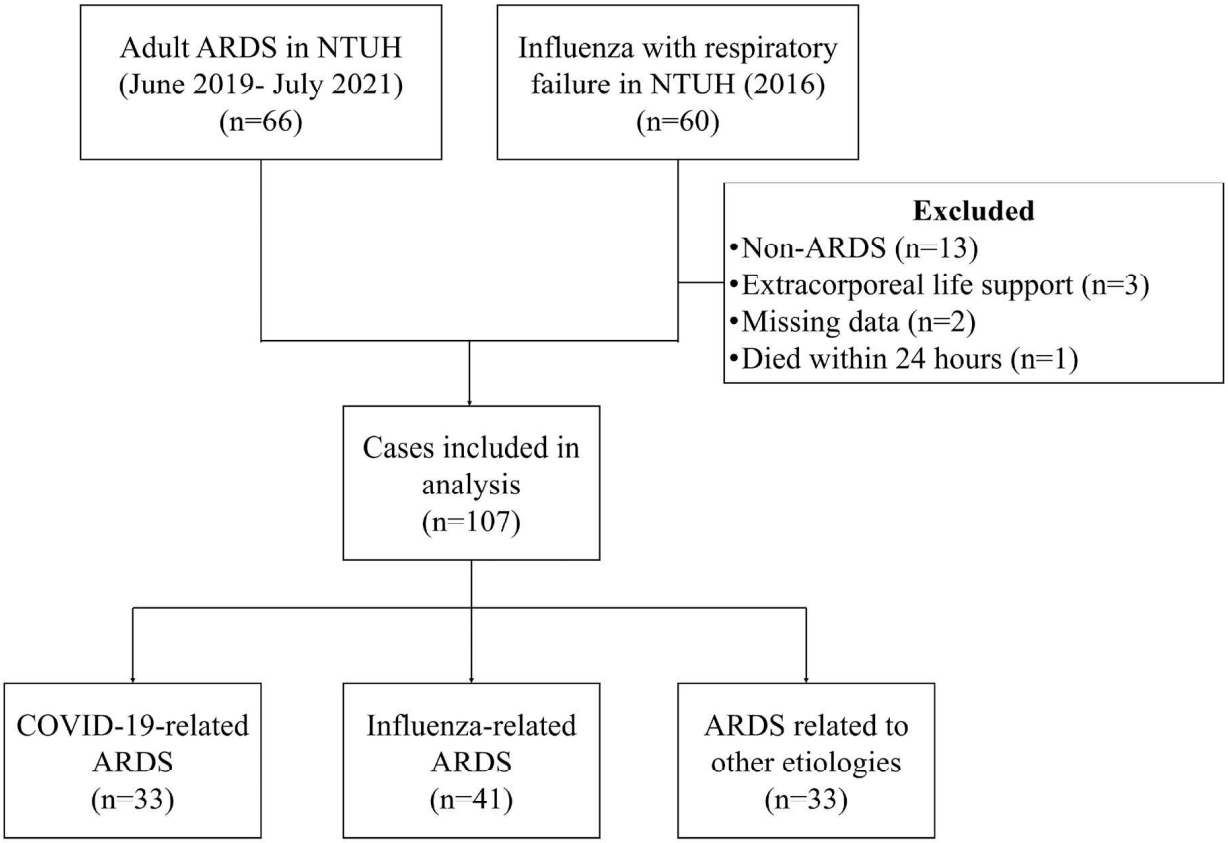


**Fig. 1.** Flowchart of patient selection.
CAP: community-acquired pneumonia; ARDS: acute respiratory distress syndrome; NTUH: National Taiwan University Hospital

The study included a total of 107 adult ARDS patients: 33 (30.8%) with virology-proven COVID-19-related ARDS (C-ARDS), 41 (38.3%) with virology-proven influenza-related ARDS (I-ARDS) and 33 (30.8%) with ARDS of other etiologies (O-ARDS). A flow diagram of the cohort is depicted in Fig. 1. Detailed baseline characteristics are presented in Table 1. The mean age of the patients was 67.2±12.1 years, and the mean scores were as follows: APACHE II, 19.7±7.5; CCI, 4.7±3.0.

Significant differences between the groups were observed in smoking status and CCI, with the O-ARDS group having the highest percentage of smokers (21.2/12.2/51.5% for the C-ARDS/I-ARDS/O-ARDS groups, respectively; p <0.01), and the highest CCI score (3.7 ±2.1/4.3 ±3.0/6.1 ±3.3 for the C-ARDS/I-ARDS/O-ARDS groups, respectively; $p$<0.01). Underlying disease related to cerebrovascular accident ($p$=0.04) or active malignancy ($p$=0.05) also showed a significant difference. The medications used in these groups were also different. Systemic corticosteroid was avoided in the I-ARDS group and caused a significant difference between the groups. There was no significant difference in neuromuscular blocking agents use. Remdesivir was used in 8 (24.2%) of the C-ARDS patients and not used in the other groups. The 28-day mortality and in-hospital mortality rates were 16% and 26%, respectively, with no significant differences observed among the groups.

Ventilator parameter details are provided

**Table 1.** Baseline Characteristics and clinical Outcomes of the Cohort

| Mean | All | COVID-19 | Influenza | Others | *p* Value |
|---|---|---|---|---|---|
| **N (%)** | 107 (100) | 33 (30.8) | 41 (38.3) | 33 (30.8) | |
| **Age, years** | 67.2 ±12.1 | 68.1 ±10.2 | 64.1 ±14.1 | 70.3 ±10.4 | 0.20 |
| **Male (%)** | 67 (62.6) | 21 (63.6) | 21 (51.2) | 25 (75.8) | 0.10 |
| **Body height, cm** | 162.2 ±8.5 | 163.8 ±8.1 | 160.5 ±9.1 | 162.7 ±8.2 | 0.21 |
| **Body weight, kg** | 64.8 ±12.8 | 68.7 ±15.9 | 61.8 ±12.0 | 64.5 ±9.4 | 0.16 |
| **BMI, kg/m$^2$** | 24.5 ±4.3 | 25.5 ±4.9 | 23.8 ±4.2 | 24.4 ±3.6 | 0.33 |
| **BMI ≥27 kg/m$^2$** | 29 (27.6) | 13 (40.6) | 7 (17.5) | 9 (27.3) | 0.09 |
| **Smoker** | 29 (27.1) | 7 (21.2) | 5 (12.2) | 17 (51.5) | <0.01* |
| **Underlying disease** | | | | | |
| Diabetes mellitus | 40 (37.4) | 13 (39.4) | 13 (31.7) | 14 (42.4) | 0.67 |
| Hypertension | 56 (52.3) | 18 (54.5) | 20 (48.8) | 18 (54.5) | 0.86 |
| Coronary artery disease | 16 (15.0) | 2 (6.1) | 9 (22.0) | 5 (15.2) | 0.15 |
| Heart failure | 13 (12.1) | 3 (9.1) | 4 (9.8) | 6 (18.2) | 0.57 |
| COPD/Asthma | 13 (12.1) | 4 (12.1) | 3 (7.3) | 6 (18.2) | 0.35 |
| Cerebrovascular accident | 11 (10.3) | 0 (0.0) | 6 (14.6) | 5 (15.2) | 0.04* |
| Chronic kidney disease | 16 (15.0) | 4 (12.1) | 5 (12.2) | 7 (21.2) | 0.56 |
| End-stage kidney disease | 12 (11.2) | 3 (9.1) | 3 (7.3) | 6 (18.2) | 0.35 |
| Active malignancy | 21 (19.6) | 2 (6.1) | 10 (24.4) | 9 (27.3) | <0.01* |
| Cirrhosis | 7 (6.5) | 2 (6.1) | 2 (4.9) | 3 (9.1) | 0.89 |
| Autoimmune disease | 7 (6.5) | 1 (3.0) | 4 (9.8) | 2 (6.1) | 0.56 |
| **CCI** | 4.7 ±3.0 | 3.7 ±2.1 | 4.3 ±3.0 | 6.1 ±3.3 | <0.01* |
| **APACHE II** | 19.7 ±7.5 | 18.5 ±7.4 | 19.7 ±8.8 | 20.9 ±5.6 | 0.16 |
| **PaO2/FiO2** | 127.7 ±63.9 | 129.7 ±59.5 | 126.9 ±69.9 | 126.7 ±62.4 | 0.81 |
| **ARDS severity** | | | | | 0.34 |
| Mild | 18 (16.8) | 5 (15.2) | 9 (22.0) | 4 (12.1) | |
| Moderate | 42 (39.3) | 15 (45.2) | 11 (26.8) | 16 (48.5) | |
| Severe | 47 (43.9) | 13 (39.4) | 21 (51.2) | 13 (39.4) | |
| **Neuromuscular blocking agent** | 22 (20.6) | 3 (9.1) | 10 (24.4) | 9 (27.3) | 0.136 |
| **Systemic corticosteroids** | 23 (21.5) | 3 (20.0) | 0 (0.0) | 20 (60.6) | <0.01* |
| **MV days** | 19.4 ±23.6 | 17.7 ±15.3 | 22.9 ±31.3 | 16.6 ±19.0 | 0.47 |
| **ICU days** | 21.0 ±17.6 | 21.2 ±12.8 | 21.6 ±20.6 | 20.0 ±18.2 | 0.92 |
| **Hospital days** | 38.5 ±30.0 | 36.2 ±15.9 | 43.1 ±39.5 | 35 ±27.2 | 0.45 |
| **Hospital mortality** | 28 (26.2) | 7 (21.2) | 12 (29.3) | 9 (27.3) | 0.73 |
| **28-day mortality** | 17 (15.9) | 3 (9.1) | 7 (17.1) | 7 (21.2) | 0.39 |

Data are presented as mean ± SD or n (%)

BMI: body mass index; CCI: Charlson Comorbidity Index; APACHE: Acute Physiology and Chronic Health Evaluation; PaO2/FiO2: arterial partial pressure of oxygen/fraction of inspired oxygen ratio; ARDS: acute respiratory distress syndrome; MV: mechanical ventilator

* *p* Value <0.05

in Table 2. No significant differences were observed in $MP_{day1}$ ($p$=0.41), $MP_{day2}$ ($p$=0.05), dynamic driving pressure at arrival ($p$=0.98), dynamic driving pressure on day 2 ($p$=0.16), minute ventilation at arrival ($p$=0.27), and minute ventilation on day 2 ($p$=0.14) across the groups. However, an increase in $MP_{day2}$ was noted in the C-ARDS group with an MPD of -1.0 ±8.4 ($p$= 0.03) and an $MP_{day2}/MP_{day1}$ of 1.17 ±0.5 ($p$=0.02). A post hoc Dunn test indicated significant differences in MPD ($p$=0.02) and $MP_{day2}/MP_{day1}$ ($p$=0.02), specifically between the C-ARDS and the O-ARDS groups (Fig. 2). FiO2 on day 1 was significantly different between the groups, but no differences were seen in PaO2/FiO2.

The optimal cut-off point for $MP_{day1}$ was 15.5 J/min, yielding an area under the ROC curve (AUROC) of 0.614, with a sensitivity of 70.6% and a specificity of 52.2%. The Kaplan-Meier curve suggested a trend towards a higher survival possibility for ARDS patients with $MP_{day1}$ <15.5 J/min compared to those with $MP_{day1}$ ≥15.5 J/min, although this trend did not achieve statistical significance ($p$=0.129) (Fig. 3).

Multivariable logistic regression analysis (Table 3) revealed that $MP_{day1}$ was the only covariate significantly associated with 28-day

**Table 2.** Ventilator Parameters of the Cohort

| | All | COVID-19 | Influenza | Other etiologies | *p* Value |
|---|---|---|---|---|---|
| **N (%)** | 107 (100) | 33 (30.8) | 41 (38.3) | 33 (30.8) | |
| **PIP on day 1, cmH2O** | 25.7 ±3.3 | 26.4 ±2.8 | 25.4 ±3.1 | 25.2 ±3.9 | 0.30 |
| **PEEP on day 1, cmH2O** | 9.1 ±2.9 | 9.8 ±2.8 | 8.8 ±3.3 | 8.7 ±2.4 | 0.22 |
| **FiO2 on day 1, %** | 77.0 ±21.6 | 89.4 ±16.8 | 73.7 ±22.1 | 68.8 ±20.2 | <0.01* |
| **Tidal volume on day 1, ml** | 483.2 ±137.0 | 479.1 ±123.4 | 468.3 ±132.6 | 505.9 ±155.4 | 0.42 |
| **Set RR on day 1, bpm** | 15.5 ±3.7 | 17.5 ±2.7 | 14.0 ±2.9 | 15.2 ±4.5 | <0.01* |
| **Measured RR on day 1, bpm** | 21.2 ±5.9 | 20.2 ±4.2 | 21.0 ±6.4 | 22.6 ±6.5 | 0.41 |
| **VE on day 1, Lpm** | 10.2 ±4.3 | 9.7 ±4.1 | 9.8 ±4.3 | 11.3 ±4.4 | 0.27 |
| **VE on day 2, Lpm** | 9.3 ±3.9 | 10.3 ±3.2 | 8.8 ±3.3 | 9.1 ±5.0 | 0.14 |
| **MP on day 1, J/min** | 17.5 ±8.1 | 17.4 ±9.0 | 16.5 ±7.5 | 18.8 ±8.2 | 0.41 |
| **MP on day 2, J/min** | 16.1 ±7.2 | 18.4 ±6.3 | 15.4 ±6.6 | 14.6 ±8.4 | 0.05 |
| **MP difference, J/min** | 1.4 ±8.4 | -1.0 ±8.4 | 1.2 ±6.0 | 4.2 ±10.3 | 0.03* |
| **MP difference ≥ 0** | 58 (54.2) | 14 (42.4) | 22 (53.7) | 22 (66.7) | 0.15 |
| **MP on day 2/MP on day 1** | 1.00 ±0.47 | 1.17 ±0.50 | 0.98 ±0.36 | 0.87 ±0.52 | 0.02* |
| **MP variation rate, %** | 0.43 ±46.9 | 17.2 ±49.7 | -2.3 ±36.2 | -13.0 ±51.8 | 0.02* |
| **Dynamic DP on day 1, cmH2O** | 16.6 ±3.0 | 16.6 ±2.4 | 16.6 ±3.7 | 16.6 ±2.6 | 0.98 |
| **Dynamic DP on day 2, cmH2O** | 15.2 ±2.8 | 15.8 ±1.9 | 15.2 ±3.3 | 14.6 ±2.8 | 0.16 |

Data are presented as mean ± SD or n (%)

PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; FiO2: fraction of inspired oxygen ratio; RR: respiratory rate; bpm: beats per minute; VE: minute ventilation; Lpm: liters per minute; MP: mechanical power; DP: driving pressure

* $p$ Value <0.05

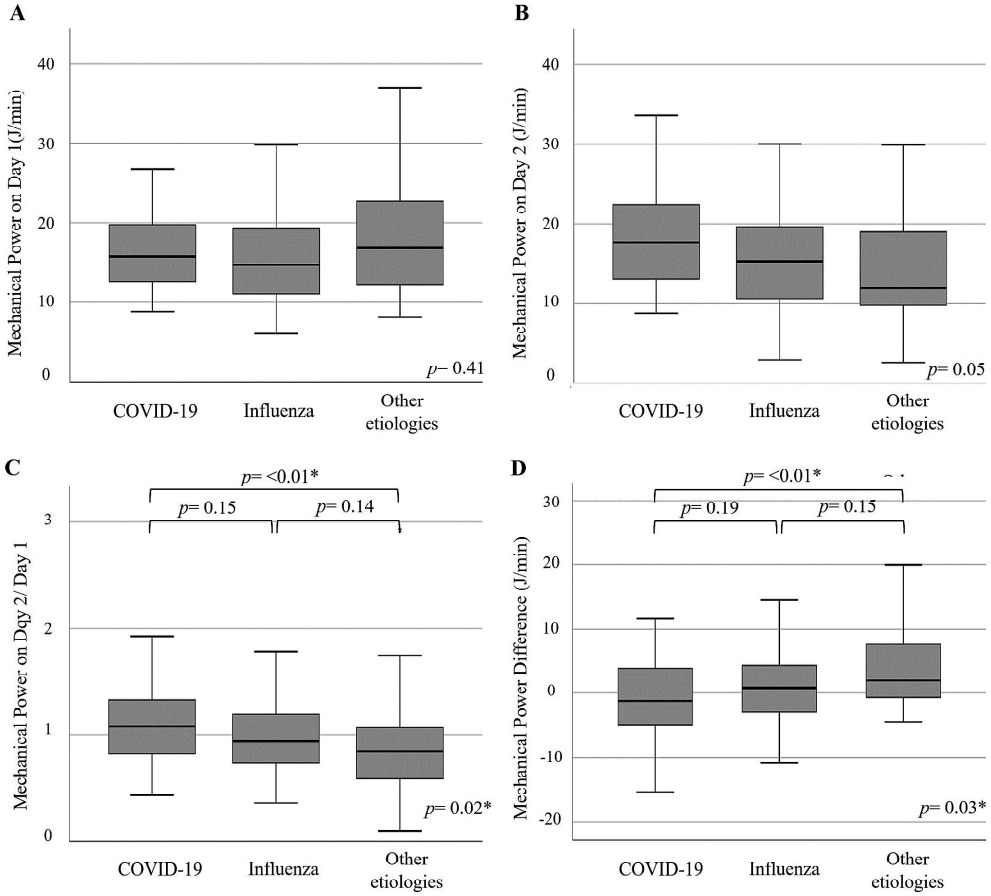


**Fig. 2.** Comparison of mechanical power parameters across COVID-19, influenza, and other etiologies in ARDS patients.
* *p* Value <0.05

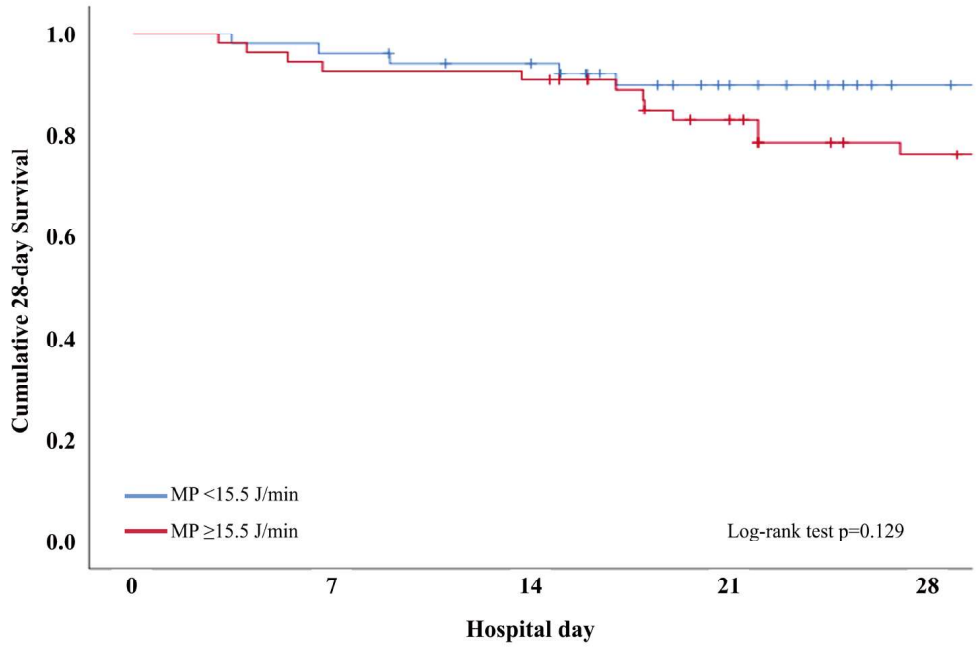


**Fig. 3.** Kaplan-Meier survival analysis comparing 28-day ICU mortality rates between patients with mechanical power less than 15.5 Joules/minute and those with 15.5 Joules/minute or more at arrival.
MP: Mechanical power; J/min: Joules per minute. Above, use "28-day survival" and "Hospital days".

**Table 3.** Binary Univariable/Multivariable Logistic Regression used to Analyze the Independent Factors of 28-day Mortality

| | Univariable OR (95% CI) | *p* Value | Multivariable aOR (95% CI) | *p* Value |
|---|---|---|---|---|
| **Age, year** | 1.03 (0.99-1.08) | 0.19 | 1.02 (0.96- 1.09) | 0.47 |
| **Sex (male)** | 0.83 (0.42-3.48) | 0.73 | 0.56 (0.13- 2.32) | 0.42 |
| **BMI, kg/m$^2$** | 0.96 (0.84-1.10) | 0.54 | 1.00 (0.84- 1.18) | 0.95 |
| **BMI ≥27, kg/m$^2$** | 0.95 (0.28-3.25) | 0.93 | | |
| **Smoker** | 2.16 (0.74-6.36) | 0.16 | | |
| **Underlying disease** | | | | |
| Diabetes mellitus | 0.46 (0.14-1.53) | 0.21 | | |
| Hypertension | 1.37 (0.48-3.90) | 0.56 | | |
| Coronary artery disease | 2.99 (0.88-10.13) | 0.08 | | |
| Heart failure | 2.77 (0.74-10.32) | 0.13 | | |
| COPD/Asthma | 1.71 (0.42-7.02) | 0.45 | | |
| Cerebrovascular accident | 5.83 (1.54-22.10) | <0.01* | | |
| Chronic kidney disease | 0.72 (0.15-3.52) | 0.69 | | |
| End-stage kidney disease | 4.94 (1.35-18.08) | 0.02* | | |
| Active malignancy | 1.93 (0.60-6.24) | 0.27 | | |
| Cirrhosis | 2.27 (0.40-12.78) | 0.35 | | |
| Autoimmune disease | 0.88 (0.10-7.77) | 0.91 | | |
| **CCI** | 1.21 (1.03-1.43) | 0.02* | 1.16 (0.93- 1.44) | 0.20 |
| **APACHE II** | 1.09 (1.02-1.17) | 0.02* | | |
| **COVID-19** | 0.43 (0.11-1.61) | 0.21 | 0.33 (0.05- 2.09) | 0.24 |
| **Influenza** | 1.15 (0.40-3.31) | 0.79 | 0.77 (0.20- 3.02) | 0.71 |
| **PaO2/FiO2** | 0.99 (0.98-1.00) | 0.05 | | |
| **ARDS severity** | 2.27 (0.97-5.31) | 0.06 | 2.08 (0. 79- 5.46) | 0.14 |
| **Neuromuscular blocking agent** | 1.23 (0.36-4.23) | 0.74 | | |
| **Systemic corticosteroids** | 1.67 (0.52-5.34) | 0.39 | | |
| **Set RR, bpm** | 0.95 (0.81-1.12) | 0.55 | | |
| **Measured RR, bpm** | 1.12 (1.03-1.22) | 0.01* | | |
| **MP on day 1, J/min** | 1.05 (0.99-1.12) | 0.07 | 1.08 (1.00- 1.15) | 0.04* |
| **MP on day 2, J/min** | 1.04 (0.97-1.12) | 0.28 | | |
| **MP difference, J/min** | 1.03 (0.97-1.09) | 0.35 | | |
| **MP difference ≥0** | 1.06 (0.38-3.00) | 0.91 | | |
| **MP on day 2/MP on day 1** | 0.88 (0.28-2.76) | 0.83 | | |
| **MP variation rate** | 1.00 (0.99-1.01) | 0.83 | | |
| **Dynamic DP at arrival, cm$H_2O$** | 0.98 (0.82-1.16) | 0.80 | | |
| **Dynamic DP on day 2, cm$H_2O$** | 1.11 (0.92-1.35) | 0.27 | | |

OR: odds ratio; aOR: adjusted odds ratio; BMI: body mass index; CI: confidence interval; APACHE: Acute Physiology and Chronic Health Evaluation; PaO2/FiO2: arterial partial pressure of oxygen/fraction of inspired oxygen ratio; ARDS: acute respiratory distress syndrome; PIP: peak inspiratory pressure; PEEP: positive end-expiratory pressure; RR: respiratory rate; VE: minute ventilation; MP: mechanical power; DP: driving pressure

* *p* Value <0.05

mortality, with an OR of 1.08 (95% CI, 1.00-1.15, $p$=0.04). Age, sex, BMI, CCI, COVID-19, influenza, and ARDS severity were not significantly different in the model.

## Discussion

In this cohort, multivariable logistic regression analysis revealed $MP_{day1}$ as an independent factor associated with 28-day mortality. Patients with a higher $MP_{day1}$ exhibited an increased risk of 28-day mortality in all groups, with an OR of 1.08 (95% CI, 1.00-1.15, $p$=0.04). No other baseline characteristics or ventilator parameters showed a correlation with 28-day mortality in the multivariable analysis. While an $MP_{day1} \geq$ 15.5 J/min was associated with higher mortality compared to those with < 15.5 J/min, this difference did not achieve statistical significance in the Kaplan-Meier survival analysis. Furthermore, a dominance analysis was performed to compare the different components of MP, ranking them based on adjusted R-square values. Among the components of MP, respiratory rate made the most important contribution to both $MP_{day1}$ and 28-day mortality, and this has been less discussed in previous literature [6, 11, 16, 29].

Our findings corroborate previous research indicating that a higher baseline MP is associated with increased 28-day mortality [12-13, 15-17]. This association persists after accounting for COVID-19 and influenza in the regression model. No previous studies have compared the MP differences among COVID-19, influenza and other etiologies related to ARDS. Our study showed a similar respiratory mechanism across different etiologies, which corroborates the concept that a low MP at baseline is associated with a lower 28-day mortality. As an integrative marker, MP at baseline adds more value than the traditional tidal volume, PEEP targets, and even dynamic driving pressure. However, questions persist on whether a high MP is the cause of lung injury and mortality, a presentation of severity, or merely a predictive indicator. There is also no evidence on MP-guided ventilator adjustment in ARDS patients, and our study did not provide new evidence in this regard.

The surrogate MP formula employed in our study proved to be effective in predicting 28-day mortality, similar to previous studies [14-15, 24]. It provided a simpler, more clinically accessible method for evaluating MP compared to Gattinoni's original formula, making it easier to apply across different ventilator models where MP must be calculated manually [11]. The application of surrogate MP holds promise in enhancing our understanding of lung protective strategies and ventilator-induced lung injury, along with new techniques such as electrical impedance tomography [30].

This study has several limitations. Primarily, it was a single-center retrospective study, which limits the number of cases and may impact the generalizability of our findings. Additionally, our inability to retrieve further ventilator parameters for analysis constrained our ability to obtain driving pressure and compare the surrogate and original MP formulas effectively. This limitation may compromise the depth of our analysis in evaluating the efficacy and equivalence of the surrogate MP formula in predicting 28-day mortality, compared to the original formula proposed by Gattinoni [11]. Secondly, there was no universal ARDS protocol established in the hospital at the time. Ventilator settings were adjusted based on the expertise of respiratory therapists related to blood gas results, PV loop, ARDSnet settings,

etc. Patients in our cohort were randomly scattered in different ICUs and received treatment by random respiratory therapists and physicians. Despite not having a standard protocol, routine weekly respiratory therapist rounds with experienced physicians minimized the difference between each respiratory therapist.

Another limitation is the non-concurrent cohort design, necessitated by the scarcity of influenza-related ARDS (I-ARDS) cases during the COVID-19 pandemic. This design choice could affect the generalizability of our results. As COVID-19 transitions from a pandemic to a more endemic presence, alongside influenza and other etiologies, ARDS from diverse origins will once again become a routine aspect of clinical practice. Expanding the cohort in future studies could provide a more comprehensive understanding of the differences in MP across various etiologies. Furthermore, the influenza cohort during the pandemic year was predominantly influenza A. In contrast, the COVID-19 pandemic has spanned several years, characterized by continuously evolving variants and treatment strategies. This variability introduces significant heterogeneity into the COVID-19 cohort, further complicating comparisons and analyses.

## Conclusion

A higher baseline MP is associated with increased 28-day mortality in MV patients with ARDS. This association remains, independent of the underlying etiology, including COVID-19, influenza, or other causes. The utilization of surrogate MP has been demonstrated to be both simple and effective in ARDS patients undergoing pressure-targeted MV.

### *Institutional Review Board Statement*

Our study received approval from the Institutional Review Board of National Taiwan University Hospital (202106132RIND). The requirement of written informed consent was waived.

### *Acknowledgments*

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# Comparative Survival Analysis of Using Different Doses of Cisplatin and Carboplatin Doublets as Adjuvant Chemotherapy in Resected Early-Stage Non-Small Cell Lung Cancer: A Single Center Retrospective Cohort Study

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Szu-Chun Yang[1]

**Background:** Adjuvant chemotherapy plays a crucial role in improving outcomes for patients with resected early-stage non-small cell lung cancer (NSCLC). While standard-dose cisplatin is commonly used, the effectiveness and safety of low-dose cisplatin, particularly in Asian populations, remains unclear. This study aimed to compare the clinical efficacy and adverse event profiles of low-dose cisplatin, standard-dose cisplatin, and carboplatin in resected early-stage NSCLC patients.

**Methods:** This single-center retrospective cohort study enrolled 253 early-stage NSCLC patients who received platinum-based adjuvant chemotherapy between April 2011 and March 2023. Patients were categorized into 3 groups based on their chemotherapy regimen: low-dose cisplatin (<75 mg/m²), standard-dose cisplatin (75–100 mg/m²), and carboplatin. Event-free survival (EFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and multivariable Cox proportional hazards regression. Adverse events were assessed using the Common Terminology Criteria for Adverse Events, 5th edition.

**Results:** Kaplan-Meier survival analyses showed no statistically significant differences in EFS among the 3 groups ($P$=0.064). Low-dose cisplatin was not associated with a shorter EFS (HR=1.02, 95% CI=0.71-1.49, $P$=0.904), but was associated with a shorter OS compared to standard-dose cisplatin (HR=2.02, 95% CI=1.04-3.90, $P$=0.037). Patients who received low-dose cisplatin experienced fewer adverse events and had a higher chemotherapy completion rate than those receiving standard-dose cisplatin. Carboplatin was associated with a higher risk of disease recurrence in patients with a BMI <24 and without high-risk recurrence features compared to standard-dose cisplatin.

**Conclusion:** Low-dose cisplatin as adjuvant chemotherapy did not compromise clinical outcomes in resected early-stage NSCLC patients and reduced the incidence of adverse events. A prospective randomized trial is warranted to confirm these findings. ***(Thorac Med 2025; 40: 284-294)***

Key words: Non-small cell lung cancer, adjuvant chemotherapy, platinum doublet chemotherapy, survival

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## Introduction

In the era of low-dose computed tomography (LDCT) screening for lung cancer detection, the distribution of stages at diagnosis is shifting toward earlier stages, contributing to improvements in lung cancer survival [1]. In Taiwan, 53.3% of patients with newly diagnosed non-small cell lung cancer (NSCLC) in 2021 were classified as being in operable stages, such as stage I to stage IIIB [2]. For this group of lung cancer patients, adjuvant treatment is recommended after complete resection to prevent disease recurrence [3]. Currently, several types of adjuvant treatments are available, including traditional chemotherapy, tyrosine kinase inhibitors (TKIs), and immunotherapy, all of which have shown survival benefits for patients who meet the treatment criteria [4-6].

However, not all of these treatments are applicable to every patient with completely resected NSCLC. Adjuvant TKIs are beneficial only for patients with specific genetic mutations, such as EGFR or ALK mutations [5, 7]. Furthermore, although some clinical trials have included patients with sensitizing mutations, there is no conclusive clinical evidence showing that PD-1 or PD-L1 immune checkpoint inhibitors provide survival benefits for patients with post-resection NSCLC harboring sensitizing driver mutations [6-8]. Chemotherapy remains the "1-size-fits-all" treatment for patients with completely resected NSCLC, regardless of PD-L1 expression or the presence of driver mutations.

Over the past decades, the benefits of adjuvant chemotherapy with cisplatin plus vinorelbine have been well established by several randomized controlled clinical trials [4, 9-10]. In addition to these prospective studies, numerous retrospective cohort studies have explored the combination of cisplatin or carboplatin with various chemotherapy regimens, including pemetrexed, docetaxel, paclitaxel, gemcitabine, and etoposide, in patients with resected NSCLC. These studies found no significant differences in survival benefits among the different chemotherapy partners [11-13]. Based on this clinical evidence, the NCCN guidelines recommend using cisplatin at 75-100 mg/m² or carboplatin at 5-6 AUC in combination with other chemotherapy regimens for 4 cycles as adjuvant treatment for resected NSCLC [3].

Despite these guideline recommendations, a significant proportion of patients in real-world practice are unable to tolerate the standard treatment dose and may require dose reduction, or may be unable to complete the full course of chemotherapy due to severe adverse events [14-16]. Moreover, the recommended cisplatin dose is based on studies conducted in Western populations, and it remains unclear whether the same high dose of cisplatin is necessary or appropriate for the Asian population.

Therefore, we conducted a retrospective cohort study by enrolling resected NSCLC patients who received cisplatin- or carboplatin-based adjuvant chemotherapy at our hospital. Based on the hypothesis that low-dose cisplatin does not result in lower survival benefits compared to standard-dose cisplatin, we further stratified patients by cisplatin dose to compare survival outcomes and adverse event rates between those who received different doses of cisplatin or carboplatin.

## Methods

### *Study Design and Patient Enrollment*

This study was approved by the Institutional Review Board of National Cheng Kung University Hospital (NCKUH) prior to commencement (IRB number: B-ER-113-266). We retrospectively enrolled patients with resected early-stage NSCLC who underwent platinum-based adjuvant chemotherapy between April 2011 and March 2023. Patients who had a histology other than NSCLC, or patients who had a rare histology presentation, including carcinoid tumor, lymphoepithelial carcinoma, or SMARCA4-deficient thoracic sarcomatoid tumor, who had received neoadjuvant chemotherapy, and those who had received tyrosine kinase inhibitors (TKIs) or immunotherapy as adjuvant chemotherapy, were not included in the study.

Patient information, including age, sex, Eastern Cooperative Oncology Group performance status (ECOG-PS), renal function, cancer histology, cancer stage, features indicating high recurrence risk, chemotherapy regimen and duration, chemotherapy-related adverse events, disease status, and survival, was collected from the electronic medical records of NCKUH. The definition of features indicating a high risk of recurrence is referenced from the NCCN guidelines, and includes poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status [3]. Event-free survival (EFS) and overall survival (OS) were defined as the time from initiation of adjuvant chemotherapy to disease recurrence and death, respectively. The cutoff date for survival status follow-up was July 31, 2024. The grading of chemotherapy-related adverse events was based on the Common Terminology Criteria for Adverse Events (CTCAE), 5th edition [17]. To investigate the clinical effectiveness of different doses and regimens of platinum-based chemotherapy, we categorized patients into 3 groups: standard-dose cisplatin, defined as cisplatin 75–100 mg/m$^2$; low-dose cisplatin, defined as cisplatin < 75 mg/m$^2$; and carboplatin.

### *Statistical Analysis*

Data were summarized as counts (percentages), means (standard deviations [SD]), or medians (interquartile ranges [IQRs]), depending on their characteristics. Continuous variables were assessed using the ANOVA test or Kruskal-Wallis H test, contingent upon the normality of their distribution. Comparisons of categorical variables were performed using Fisher's exact test. The Kaplan–Meier method was utilized to evaluate differences in EFS and OS. We conducted univariable and multivariable Cox proportional hazards regression analyses to investigate the differences in EFS and OS between different regimens of adjuvant chemotherapy. The analysis was adjusted for various covariates, including age, sex, ECOG-PS, lung cancer stage, cancer histology, high-risk features for recurrence, chemotherapy regimen, number of cycles of adjuvant chemotherapy, and receipt of radiotherapy. To quantify the strength and direction of these associations, we estimated hazard ratios (HRs) along with their 95% confidence intervals (CIs). To investigate the effectiveness of different chemotherapy regimens in patients with specific characteristics, we performed subgroup analyses by stratifying patients based on age, ECOG-PS, cancer histology, number of high-risk recurrence factors, pathological stage, cycles of chemotherapy, and chemotherapy doublet regimens. All statistical tests were 2-sided, with p-values less than 0.05 considered statistically significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### *Patient characteristics*

Between April 2011 and March 2023, a total of 304 early-stage lung cancer patients received platinum-based adjuvant chemotherapy following curative lung cancer surgery. After excluding patients who had received combined TKIs or immunotherapy, neoadjuvant chemotherapy, or who had a histology other than NSCLC, 253 patients were included in the analysis. Among these 253 patients, 69 received low-dose cisplatin, 82 received standard-dose cisplatin, and 102 received carboplatin as part of a chemotherapy doublet. The baseline characteristics of these 3 groups are shown in Table 1. Patients in the carboplatin group were older, and those in the low-dose cisplatin group had a poorer performance status and were less likely to receive vinorelbine as adjuvant chemotherapy. Patients in the

**Table 1.** Baseline Characteristics of all Enrolled Patients

| Characteristics | Low-dose cisplatin (N=65) | Standard-dose cisplatin (N=82) | Carboplatin (N=99) | *P*[a] |
|---|---|---|---|---|
| Age (years), mean (SD) | 59.5 (9.3) | 58.1 (8.2) | 63.4 (8.8) | <0.001 |
| Male, n (%) | 33 (50.8) | 45 (54.9) | 42 (42.4) | 0.232 |
| BMI, mean (SD) | 23.8 (3.6) | 24.5 (3.5) | 24.7 (3.7) | 0.270 |
| ECOG-PS 1, n (%) | 31 (47.7) | 20 (24.4) | 28 (28.3) | 0.007 |
| CKD[b] | 1 (1.5) | 1 (1.2) | 13 (13.1) | <0.001 |
| Histology, n (%) | | | | 0.412 |
| Adenocarcinoma | 52 (80.0) | 66 (80.5) | 84 (84.9) | |
| SqCC | 6 (9.2) | 12 (14.6) | 11 (11.1) | |
| Others | 7 (10.8) | 4 (4.9) | 4 (4.0) | |
| Pathologic stage, n (%) | | | | 0.097 |
| 2 | 22 (33.9) | 42 (51.2) | 46 (46.5) | |
| 3 | 43 (66.2) | 40 (48.8) | 53 (53.5) | |
| With a high-risk recurrence feature[c], n (%) | 50 (76.9) | 59 (72.0) | 62 (62.6) | 0.135 |
| Received adjuvant RT, n (%) | 15 (23.1) | 6 (7.3) | 13 (13.1) | 0.024 |
| Adjuvant chemotherapy cycles, median (IQR) | 4 (1) | 4 (1) | 4 (1) | 0.171 |
| Regimen for chemotherapy doublet, n (%) | | | | <0.001 |
| Vinorelbine | 57 (87.7) | 79 (96.3) | 99 (100) | |
| Other chemotherapy | 8 (12.3) | 3 (3.7) | 0 (0) | |

BMI, body mass index; CKD, chronic kidney disease; ECOG-PS, Eastern Cooperative Oncology Group - performance status; IQR, interquartile range; RT, radiation therapy; SD, standard deviation; SqCC, squamous cell carcinoma.

a:Independent t test, Mann-Whitney U test and Fisher's exact test were used to calculate continuous variables and categorical variables, respectively.

b:Defined as eGFR <60 mL/min/1.73 m2.

c:Including poorly differentiated tumors, vascular invasion, wedge resection, visceral pleural involvement, unknown lymph node status.

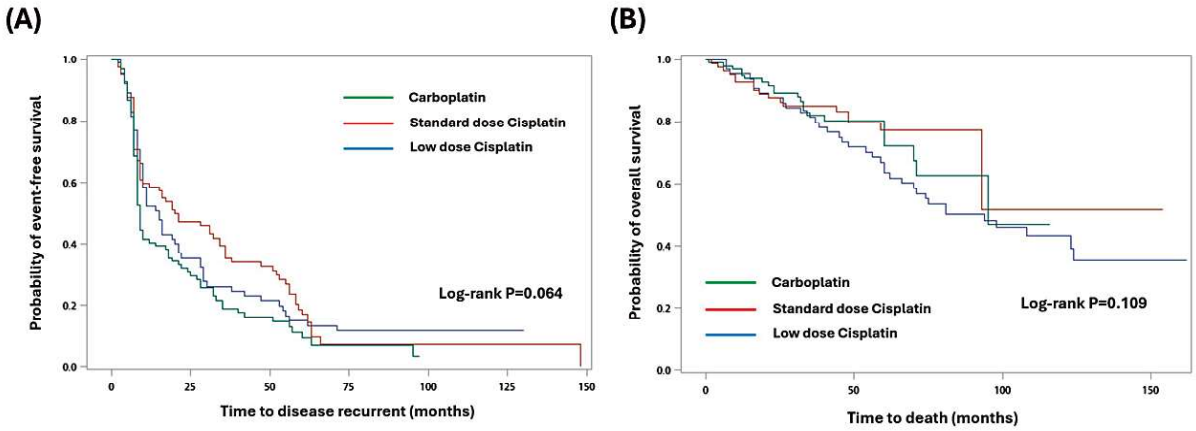


**Fig. 1.** Kaplan–Meier plot and log-rank test for survival across different chemotherapy regimens (A) event-free survival, (B) overall survival.

standard-dose cisplatin group were less likely to receive adjuvant radiation therapy. There were no differences between the 3 groups regarding sex, BMI, cancer histology, pathological stage, high-risk recurrence features, or number of adjuvant chemotherapy cycles.

### *Survival analyses*

When comparing EFS among patients who received low-dose cisplatin, standard-dose cisplatin, and carboplatin, Kaplan–Meier survival analyses showed no statistically significant differences in EFS ($P$=0.064) or OS ($P$=0.109) among the 3 groups (Fig. 1). In the univariable Cox proportional hazards regression analysis, low-dose cisplatin was not associated with a significant difference in EFS (for disease recurrence, HR=1.12, 95% CI=0.80-1.58, $P$=0.515), but it was linked to shorter OS (for death, HR=2.89, 95% CI=1.62-5.16, $P$<0.001). Carboplatin use was associated with shorter EFS (for disease recurrence, HR=1.43, 95% CI=1.06-1.95, $P$=0.021), but no significant difference in OS (for death, HR=1.35, 95% CI=0.71-2.58, $P$=0.358), compared to standard-dose cisplatin. In the multivariable analysis, using carboplatin and low-dose cisplatin was not associated with shorter EFS, but using low-dose cisplatin was associated with shorter OS (for death, HR=2.03, 95% CI=1.04-3.94, $P$=0.037) (Table 2).

Subgroup analyses revealed that, compared to standard-dose cisplatin, patients receiving low-dose cisplatin did not have a higher risk of disease recurrence. However, carboplatin was associated with a higher risk of disease recurrence in patients with a BMI <24 (HR=1.80, 95% CI=1.12-2.89, $P$=0.015), and in those without high-risk recurrence features (HR=1.99, 95% CI=1.14-3.48, $P$=0.016), compared to patients receiving standard-dose cisplatin (Table 3). There was a trend suggesting that chronic kidney disease (CKD) patients treated with low-dose cisplatin or carboplatin had a lower risk of disease recurrence compared to those treated with standard-dose cisplatin (low-dose cisplatin group: HR = 0.03, 95% CI = 0.001–1.19, $P$=0.062; carboplatin group: HR = 0.23, 95% CI = 0.01–5.23, $P$=0.354).

### *Chemotherapy-related adverse events*

Patients who received low-dose cisplatin, standard-dose cisplatin, and carboplatin experienced any-grade adverse events at rates of 51 (62.2%), 46 (70.8%), and 57 (57.6%), respec-

**Table 2.** Multivariable Cox Proportional Hazards Regression Analysis for Survival of the Enrolled Patients

| Characteristics | Disease recurrence | | | Death | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age ≥65 years old | 1.07 | 0.78-1.47 | 0.668 | 1.11 | 0.63-1.95 | 0.724 |
| Male | 0.98 | 0.75-1.28 | 0.882 | 1.11 | 0.68-1.80 | 0.686 |
| BMI <24 | 1.15 | 0.87-1.53 | 0.322 | 0.91 | 0.56-1.48 | 0.699 |
| ECOG-PS ≥1 | 0.88 | 0.66-1.19 | 0.422 | 1.60 | 0.97-2.64 | 0.065 |
| CKD | 0.98 | 0.59-1.62 | 0.928 | 1.14 | 0.49-2.66 | 0.769 |
| Histology | | | | | | |
| Adenocarcinoma | | Reference | | | Reference | |
| Squamous | 0.78 | 0.47-1.26 | 0.312 | 1.99 | 0.96-4.12 | 0.065 |
| Other | 1.13 | 0.58-2.20 | 0.731 | 1.85 | 0.80-4.29 | 0.152 |
| Pathologic stage 3 | 1.22 | 0.93-1.61 | 0.156 | 1.97 | 1.16-3.37 | 0.013 |
| High-risk recurrent feature | 0.93 | 0.69-1.24 | 0.614 | 0.95 | 0.54-1.68 | 0.870 |
| Not combined vinorelbine | 1.25 | 0.57-2.77 | 0.575 | 1.23 | 0.52-2.93 | 0.636 |
| Adjuvant chemotherapy <4 cycles | 2.69 | 1.53-4.74 | <0.001 | 3.50 | 1.75-7.00 | <0.001 |
| Treatment regimen | | | | | | |
| Standard-dose cisplatin | | Reference | | | Reference | |
| Low-dose cisplatin | 1.02 | 0.70-1.49 | 0.908 | 2.03 | 1.04-3.94 | 0.037 |
| Carboplatin | 1.26 | 0.91-1.75 | 0.168 | 1.00 | 0.51-1.97 | 0.999 |
| Received adjuvant RT | 1.15 | 0.76-1.76 | 0.508 | 1.26 | 0.71-2.21 | 0.430 |

a Independent t test, Mann-Whitney U test and Fisher's exact test were used to calculate continuous variables and categorical variables, respectively.

tively. Additionally, grade ≥3 adverse events occurred in 8 (12.3%), 12 (14.6%), and 10 (10.1%) patients, respectively (Table 4). A higher proportion of patients receiving low-dose cisplatin had any-grade or grade ≥3 adverse events compared to those receiving standard-dose cisplatin. In terms of chemotherapy completion, 3 (3.7%) patients on low-dose cisplatin, 4 (6.2%) on standard-dose cisplatin, and 10 (10.1%) on carboplatin received fewer than 4 cycles of adjuvant chemotherapy. Patients receiving standard-dose cisplatin had a lower rate of completing at least 4 cycles of adjuvant chemotherapy compared to those on low-dose cisplatin.

## Discussion

In this single-center retrospective cohort study, we enrolled a total of 253 early-stage NSCLC patients who received platinum-based adjuvant chemotherapy doublets following curative surgery. Based on Kaplan–Meier analysis and multivariable Cox proportional hazards regression analyses, we found that the use of low-dose cisplatin or carboplatin in chemotherapy doublets did not reduce clinical treatment effec-

**Table 3.** Subgroup Analyses of Multivariable Cox Proportional Hazards Regression Analysis of Disease Recurrence in the Enrolled Patients

| Characteristics | Low-dose cisplatin vs standard-dose cisplatin | | | Carboplatin vs standard-dose cisplatin | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age ≥65 years old | 1.02 | 0.52-2.00 | 0.953 | 1.10 | 0.58-2.07 | 0.780 |
| Age <65 years old | 0.97 | 0.61-1.54 | 0.908 | 1.33 | 0.88-2.01 | 0.176 |
| Male | 1.04 | 0.63-1.71 | 0.871 | 1.27 | 0.78-2.08 | 0.332 |
| Female | 1.15 | 0.66-2.00 | 0.621 | 1.38 | 0.84-2.28 | 0.204 |
| BMI ≥24 | 0.92 | 0.57-1.48 | 0.719 | 1.02 | 0.65-1.61 | 0.930 |
| BMI <24 | 1.20 | 0.69-2.10 | 0.520 | 1.80 | 1.12-2.89 | 0.015 |
| ECOG-PS ≥1 | 0.77 | 0.40-1.49 | 0.430 | 1.03 | 0.48-2.25 | 0.932 |
| ECOG-PS <1 | 1.15 | 0.74-1.79 | 0.528 | 1.27 | 0.86-1.86 | 0.232 |
| CKD | 0.03 | 0.001-1.19 | 0.062 | 0.23 | 0.01-5.23 | 0.354 |
| No CKD | 0.99 | 0.68-1.44 | 0.953 | 1.27 | 0.91-1.78 | 0.158 |
| Adenocarcinoma | 1.13 | 0.76-1.67 | 0.541 | 1.28 | 0.89-1.85 | 0.188 |
| Squamous cell carcinoma | 0.98 | 0.05-18.65 | 0.992 | 1.24 | 0.13-11.68 | 0.848 |
| Pathologic stage 3 | 1.28 | 0.73-2.27 | 0.391 | 1.11 | 0.67-1.82 | 0.690 |
| Pathologic stage 2 | 0.92 | 0.56-1.51 | 0.743 | 1.27 | 0.82-1.97 | 0.276 |
| With a high-risk recurrence feature | 0.95 | 0.62-1.45 | 0.799 | 1.18 | 0.76-1.82 | 0.467 |
| Without a high-risk recurrence feature | 1.85 | 0.88-3.89 | 0.105 | 1.99 | 1.14-3.48 | 0.016 |
| Adjuvant chemotherapy ≥4 cycles | 0.02 | 0.001-0.44 | 0.018 | 0.01 | 0.002-3.10 | 0.119 |
| Adjuvant chemotherapy <4 cycles | 1.12 | 0.78-1.63 | 0.537 | 1.32 | 0.95-1.84 | 0.094 |
| Received adjuvant RT | 1.04 | 0.71-1.51 | 0.847 | 1.28 | 0.93-1.78 | 0.135 |
| Did not receive adjuvant RT | 1.05 | 0.71-1.54 | 0.809 | 1.23 | 0.86-1.76 | 0.253 |

BMI, body mass index; CKD, chronic kidney disease; ECOG-PS, Eastern Cooperative Oncology Group - performance status; RT, radiation therapy.

**Table 4.** Treatment-related adverse events in enrolled patients

| Category | Low-dose cisplatin | | Standard-dose cisplatin | | Carboplatin | |
|---|---|---|---|---|---|---|
| | Adverse events, N (%) | | Adverse events, N (%) | | Adverse events, N (%) | |
| | Any grade | ≥ grade 3 | Any grade | ≥ grade 3 | Any grade | ≥ grade 3 |
| TRAE, n (%) | 51 (62.2) | 8 (12.3) | 46 (70.8) | 12 (14.6) | 57 (57.6) | 10 (10.1) |
| Skin and soft tissue | 11 (13.4) | 0 (0) | 5 (7.7) | 0 (0) | 11 (11.1) | 1 (1.0) |
| GI tract | 30 (36.6) | 3 (3.7) | 28 (43.1) | 4 (6.2) | 34 (34.3) | 1 (1.0) |
| Neurology | 15 (18.3) | 0 (0) | 24 (36.9) | 1 (1.5) | 23 (23.2) | 0 (0) |
| Renal system | 11 (13.4) | 0 (0) | 8 (12.3) | 1 (1.5) | 14 (14.1) | 0 (0) |
| Hematology | 6 (9.2) | 3 (4.6) | 15 (18.3) | 9 (11.0) | 18 (18.2) | 9 (9.1) |
| Chemotherapy <4 cycles, n (%) | 3 (3.7) | | 4 (6.2) | | 10 (10.1) | |

GI: gastrointestinal, TRAE: treatment-related adverse events.

tiveness in terms of EFS, compared to standard-dose cisplatin, though low-dose cisplatin was associated with shorter OS. Subgroup analyses showed no difference in EFS between standard-dose and low-dose cisplatin; however, patients with a BMI <24 or without high-risk recurrence features had a higher risk of disease recurrence when treated with carboplatin. Furthermore, low-dose cisplatin was associated with fewer chemotherapy-related adverse events compared to standard-dose cisplatin. Overall, our study found that patients receiving low-dose cisplatin did not experience lower EFS and had fewer chemotherapy-related adverse events compared to those receiving standard-dose cisplatin.

In our study, we found that using a lower dose of cisplatin as adjuvant chemotherapy did not reduce EFS compared to standard-dose cisplatin. Several studies have shown that reduced-dose chemotherapy does not compromise treatment effectiveness across various cancer types [18-20], suggesting that the 'standard dose' may not be fixed. Moreover, the standard dose of chemotherapy was established based on clinical trials conducted approximately 2 decades ago [4, 9]. Given the advances in surgical techniques, radiation therapy, and general care for lung cancer patients, this raises the question of whether the old standard dose is still necessary. However, many questions remain regarding this issue, including the optimal lower dose, number of cycles, and chemotherapy combinations. Further prospective studies are needed to confirm the efficacy of low-dose cisplatin.

Interestingly, our data showed OS was shorter in patients who received low-dose cisplatin compared to those receiving standard-dose cisplatin. A previous meta-analysis of 2,968 advanced-stage lung cancer patients also found that those receiving cisplatin-based chemotherapy had a higher response rate and a non-statistically significant increase in survival, with a significant survival increase in non-squamous cell carcinoma patients, compared to those receiving carboplatin [21]. However, the use of OS data in interpreting treatment efficacy raises questions, as OS can be affected by subsequent treatments. Many lung cancer treatment regimens do not demonstrate OS benefits but are still considered effective [22-23]. Further studies are warranted to investigate the differences in OS between standard-dose and low-dose cisplatin.

In the subgroup analysis, patients with a BMI <24 or without high-risk recurrence features had a higher risk of disease recurrence when treated with carboplatin, compared to standard-dose cisplatin. Survival studies have shown a paradoxical relationship between higher BMI and lower mortality risk in lung cancer patients [24-25]. Furthermore, since carboplatin dosing is adjusted based on the area under the curve (AUC), which is significantly influenced by body weight, patients with lower BMI values may receive a slightly “under-dosed” carboplatin treatment. This could contribute to the relatively higher risk of recurrence observed in the subgroup analysis.

Consistent with our findings, Kicken *et al.* retrospectively analyzed a cohort of 174 stage IV NSCLC patients who received carboplatin-based chemotherapy and reported that patients with a BMI ≥25 had better OS and PFS compared to those with a BMI <25 [26]. One possible explanation for the observation that patients without high-risk recurrence features had a higher risk of disease recurrence when treated with carboplatin is that carboplatin is generally considered to have slightly lower efficacy than cisplatin in platinum-based regimens, as

suggested by some studies and expert opinions [21, 27]. This difference in efficacy may become more pronounced in patients with lower baseline risk, where the treatment's ability to eliminate residual disease is more critical in preventing recurrence. Furthermore, it is worth considering whether these patients, due to their lower-risk clinical profiles, might have received less aggressive or more conservative treatment. The retrospective nature and subgroup analysis of our study limit our ability to adjust all confounders.

There was also a trend suggesting that CKD patients treated with low-dose cisplatin or carboplatin had a lower risk of disease recurrence in the subgroup analysis. The renal toxicity of cisplatin and its increased adverse effects in patients with renal dysfunction are well established. These toxicities may further reduce the tolerance of patients for completing adjuvant chemotherapy, potentially increasing the risk of disease recurrence. Further investigation through large sample sizes in prospective studies is warranted to better understand and validate this relationship.

We found that patients who received low-dose cisplatin and carboplatin experienced fewer adverse events compared to those receiving standard-dose cisplatin. A previous study also found that carboplatin was associated with lower morbidity and healthcare use compared to cisplatin, without significantly affecting survival in NSCLC patients when compared to standard-dose cisplatin [28]. Adverse events can negatively affect the quality of life for lung cancer patients and reduce treatment adherence [29]. A high rate of adverse events may decrease the likelihood of completing adjuvant treatment or receiving further therapy after disease recurrence, particularly in specific groups such as elderly patients or those with a poor performance status [30]. In our study, a higher proportion of patients receiving low-dose cisplatin completed all 4 cycles of chemotherapy compared to those on the standard dose. Since EFS did not significantly differ between patients receiving standard-dose cisplatin and those receiving low-dose cisplatin, low-dose cisplatin appears to be a reasonable choice for adjuvant chemotherapy in NSCLC patients following surgical tumor resection.

This study has several limitations. First, the choice of chemotherapy regimen was determined by the physician, meaning that confounding by indication cannot be entirely excluded. Specifically, physicians may have selected low-dose cisplatin or carboplatin for patients with a poorer performance status or older age. In such cases, these patients inherently had a worse prognosis, though the direction of bias likely did not affect the overall study outcome. Conversely, physicians may have chosen standard-dose cisplatin for patients with larger tumor burdens or more advanced pathological stages, introducing potential selection bias. Although we adjusted for cancer stage using multivariable analyses, this bias cannot be completely excluded. Second, this was a single-center study conducted in Taiwan with a relatively small sample size, so the results should be generalized with caution. Third, the period for patient enrollment ranged from April 2011 to March 2023, during which lung cancer treatment—including medications, surgery, and general care—underwent significant advances, some of which were revolutionary. While we believe these improvements had only a limited impact on EFS after excluding adjuvant immunotherapy and TKIs, their effect on OS cannot be overlooked.

## Conclusion

In conclusion, the use of low-dose cisplatin as adjuvant chemotherapy in resected early-stage NSCLC patients in Taiwan did not result in a shorter EFS. Furthermore, patients receiving low-dose cisplatin experienced fewer adverse events compared to those receiving standard-dose cisplatin. A large prospective randomized controlled trial is needed to further evaluate the clinical efficacy and safety of low-dose cisplatin in combination chemotherapy as adjuvant treatment for early-stage NSCLC patients.

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# Case Report: Recurrent Spontaneous Pneumothorax in a 35-Year-Old Female with Radiologic and Clinical Features Suggestive of Birt-Hogg-Dubé Syndrome

Cheng-Wei Huang[1], Ching-Hong Tsai[2], Kai-Wei Chang[3]

A 35-year-old female presented with recurrent spontaneous pneumothorax and characteristic radiologic findings suggestive of Birt-Hogg-Dubé Syndrome (BHDS). Computed tomography scans revealed multiple thin-walled pulmonary cysts, predominantly in the basomedial lobes, a hallmark of BHDS. Her father had similar clinical and radiological manifestations, suggesting hereditary components. This case highlights the importance of recognizing BHDS as a differential diagnosis for recurrent pneumothorax and the role of imaging and clinical evaluation in the diagnostic process. ***(Thorac Med 2025; 40: 295-298)***

Key words: multiple cystic lung disease, Birt-Hogg-Dubé syndrome, pneumothorax

## Introduction

Birt-Hogg-Dubé syndrome (BHDS) is a rare autosomal dominant disorder caused by mutations in the FLCN gene. It is characterized by dermatological lesions, renal tumors, and pulmonary cysts, the latter of which predispose patients to recurrent spontaneous pneumothorax. Awareness of BHDS in young patients presenting with recurrent pneumothorax is critical, as timely diagnosis enables appropriate management and surveillance for associated complications, including renal malignancies.

## Case Presentation

A 35-year-old woman presented to our clinic with a history of recurrent episodes of left-sided chest pain and dyspnea during the past 5 years. She reported no significant smoking or pulmonary disease history. Her father had recurrent pneumothorax episodes as well. The chest CT scan of her father had similar multiple lung cysts with basomedial lung distribution. She had her first episode of left pneumothorax 5 years ago and was treated with left chest tube thoracostomy. After discharge, she had regular

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follow-up in the chest surgical outpatient department. Two years later, she presented at the emergency department with left chest pain with dyspnea. The chest computed tomography (CT) scan once again revealed massive left pneumothorax. The surgeon then performed video-assisted thoracic surgery left lower lung wedge resection and pleurodesis.

### *Clinical Findings*

Physical examination was unremarkable apart from reduced breathing sounds and percussion hyperresonance at the affected hemithorax. No folliculoma or skin lesion was detected on inspection. Laboratory investigations were within normal limits, excluding autoimmune disease or infectious disease.

### *Imaging Studies*

A chest CT scan revealed multiple, bilateral, irregular, thin-walled pulmonary cysts predominantly located in the basomedial lung and subpleural regions (Fig. 1). The distribution pattern was of concern for cystic lung disease associated with BHDS. No significant parenchymal scarring or emphysema was observed. The imaging findings were highly suggestive of BHDS. An abdominal echography showed no sign of renal tumor.

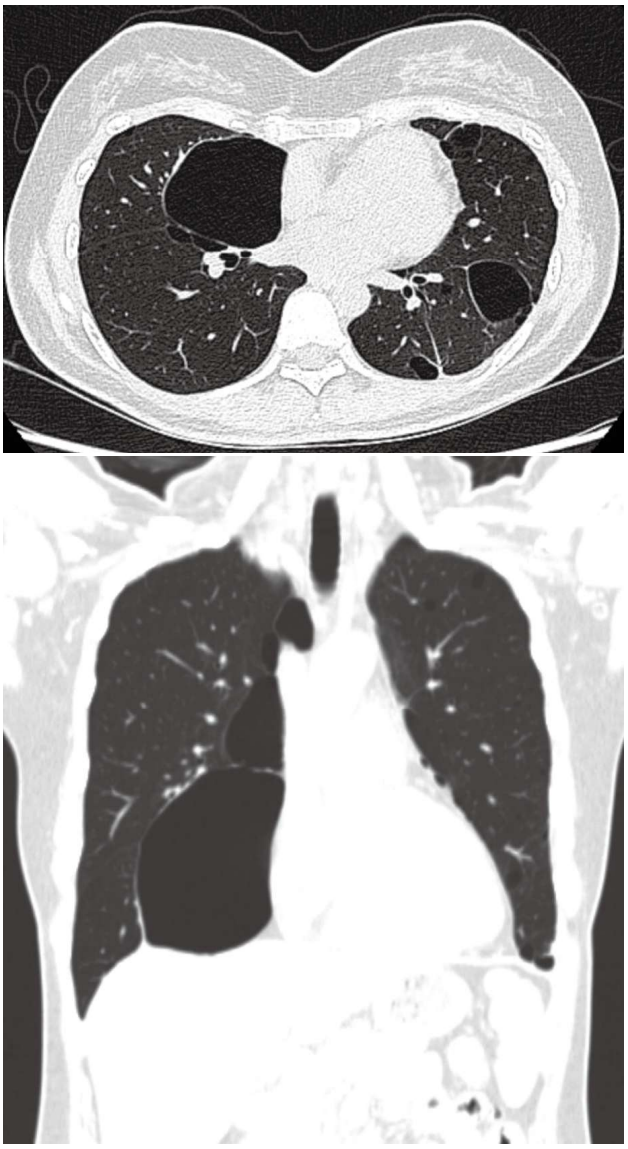

**Fig. 1.** Chest CT showing multiple thin-walled pulmonary cysts predominantly in the basomedial lung. These findings contrast with the typical apical location of air blebs seen in patients with primary spontaneous pneumothorax or pneumothorax secondary to chronic obstructive pulmonary disease.

### *Genetic Analysis*

Given the clinical suspicion of BHDS, genetic testing was proposed to detect a heterozygous pathogenic mutation in the FLCN gene. However, the patient declined because of the time-consuming process and financial burden.

## Discussion

Birt-Hogg-Dubé syndrome (BHDS) is an underrecognized genetic disorder that is often misdiagnosed or diagnosed incidentally through CT screening or pneumothorax workups. Both males and females are equally affected, and a family history of pneumothorax is common [1].

A clinical diagnosis of BHDS can be made, even in the absence of genetic confirmation, if 1 major or 2 minor diagnostic criteria are met.

The major criterion is the presence of more than 5 fibrofolliculomas or trichodiscomas, at least 1 histologically confirmed, all of adult onset. The minor criteria include: first, lung involvement with multiple, bilateral, basally located pulmonary cysts with no other apparent cause; second, kidney involvement with early-onset (<50 years), multifocal, or bilateral renal cancer, or renal cancer with a mixed chromophobe and oncocytic histology; and third, a first-degree relative diagnosed with BHDS [2]. Our patient met 2 minor criteria (lung cysts and family history), making a clinical diagnosis of BHDS reasonable, even though her father was not definitively diagnosed.

Recurrent spontaneous pneumothorax in young adults is uncommon and warrants investigation for underlying causes, including connective tissue diseases and genetic syndromes. BHDS is a rare but important cause of secondary pneumothorax due to its characteristic pulmonary cysts.

Recent studies have shown that up to 84% of patients with BHDS have pulmonary cysts, and approximately 24-38% will develop spontaneous pneumothorax at some point in their lives. The cysts tend to be irregularly shaped and distributed predominantly in the lower lobes, distinguishing them from other cystic lung diseases such as lymphangioleiomyomatosis and pulmonary Langerhans cell histiocytosis [5].

In addition to pulmonary involvement, BHDS is associated with an increased risk of renal neoplasms, primarily chromophobe renal cell carcinoma (RCC) and hybrid oncocytic tumors. Regular surveillance using imaging modalities such as ultrasound or magnetic resonance imaging (MRI) is recommended to detect renal malignancies at an early stage [3]. BHDS patients have a lifelong risk of developing RCC, hence abdominal imaging is recommended at least every 36 months. MRI is preferred over CT because of the high-resolution images obtained without subjecting patients to cumulative radiation exposure. Depending on renal tumor size, some experts suggest surgical resection once a solid renal tumor exceeds a 3-cm diameter threshold [7]. Moreover, BHDS patients may have characteristic skin manifestations, including fibrofolliculomas, which can aid in the clinical diagnosis [6].

The diagnosis of the patient would have been more definitive with the identification of a pathogenic FLCN mutation. The FLCN gene encodes folliculin, a protein involved in cellular growth regulation and metabolism. Nevertheless, a negative FLCN test does not exclude the diagnosis of BHDS [5]. A proportion of patients need alternative diagnostic criteria, as mentioned above. Although the patient had no cutaneous or renal manifestations at diagnosis, periodic screening for renal tumors was recommended due to the increased associated risk.

Management of BHDS focuses on symptomatic treatment of pneumothorax, counseling on lifestyle modifications (e.g., avoiding smoking and high-altitude activities), and long-term surveillance for renal and pulmonary complications. Genetic counseling was also provided for the patient and her family.

## Conclusion

This case underscores the importance of considering BHDS in the differential diagnosis of recurrent spontaneous pneumothorax, particularly in young patients with characteristic radiologic findings. Early recognition and diagnosis through imaging and genetic testing

can guide appropriate management and prevent complications.

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# Significant Resolution of Pulmonary Langerhans cell Histiocytosis after Smoking Cessation

Tzu-Chiang Wu[1], Chen Chang[2], Chung-Ta Lee[2], Tang-Hsiu Huang[1]

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon cystic lung disease predominantly affecting adult smokers, and is characterized histologically by the excessive accumulation of Langerhans-like cells around small airways. Some patients may experience extrapulmonary involvement, but PLCH generally has a better prognosis than its systemic counterpart and may improve or resolve after smoking cessation. This case report described a 62-year-old woman with a 30-pack-year smoking history. Her histology-proven PLCH manifested as a troublesome nonproductive cough and radiographically as multiple nodular and ground-glass opacities mixed with cysts of varying sizes, primarily in the upper and middle lung fields, with no systemic involvement. Following smoking cessation, her cough and radiographic abnormalities significantly resolved. This case report underscores the strong association of PLCH with smoking and highlights the crucial role of smoking cessation in its management. ***(Thorac Med 2025; 40: 299-305)***

Key words: cystic lung disease, histiocytes, Langerin, smoking

## Introduction

Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon cystic lung disease characterized histologically by the excessive accumulation of CD1a+ and CD207 (Langerin)+ Langerhans-like cells around small airways [1-2]. Patients with PLCH may be asymptomatic or present with nonspecific cough and dyspnea, and some may experience non-respiratory symptoms related to extrapulmonary involvement [1-3]. On high-resolution computed tomography (HRCT) images, PLCH typically manifests as scattered nodular and ground-glass opacities interspersed with cavities and irregularly shaped cysts of varying sizes, predominantly involving the upper-to-middle lung zones, while relatively sparing the basal lungs [1]. Cigarette smoking is a crucial risk factor for PLCH, and smoking cessation alone may lead to clinical and radiographic improvements [2]. For patients with progressive disease de-

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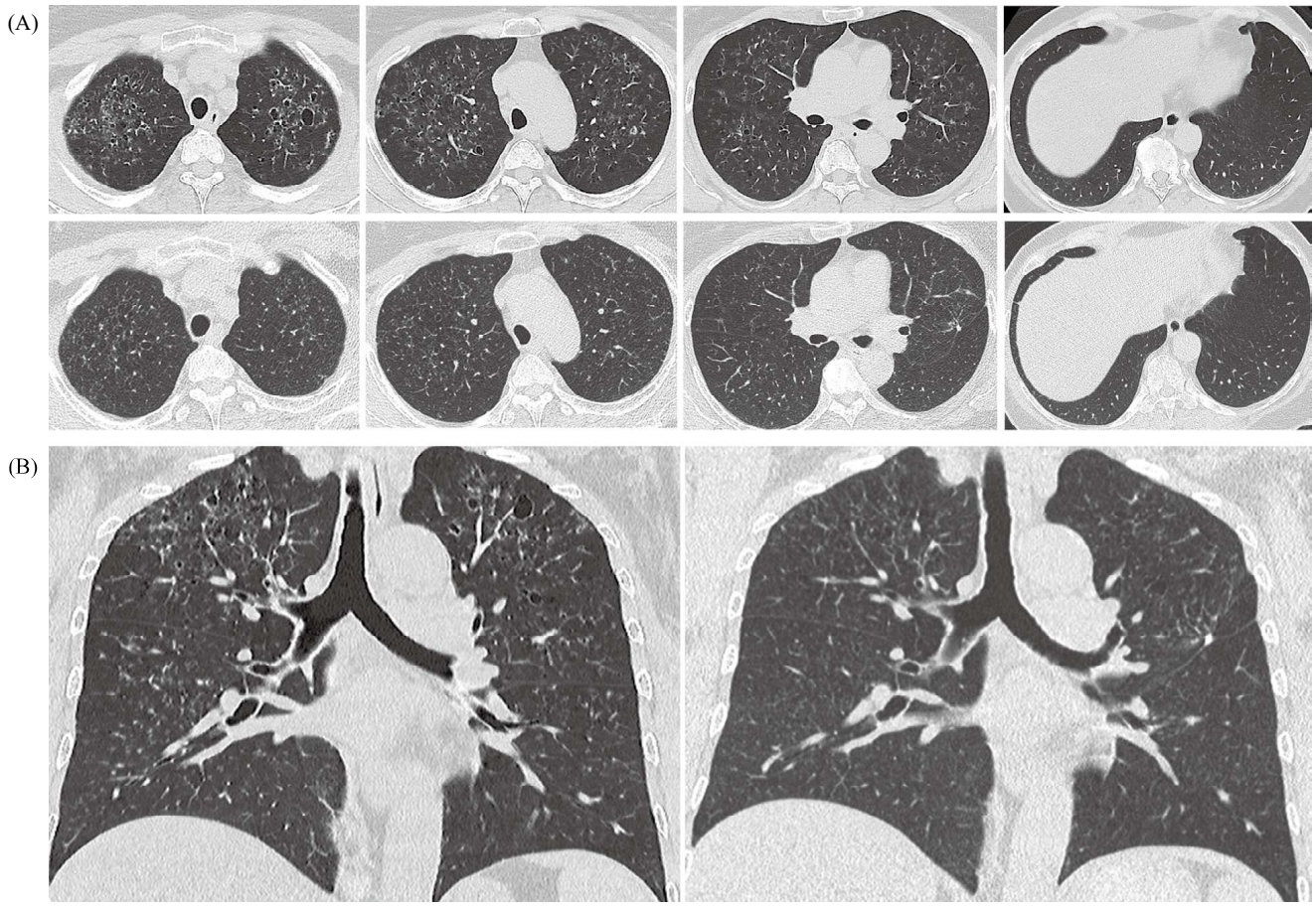


**Fig. 1.** (A) Transverse-view computed tomography (CT) images at initial presentation (upper panels; 2-mm slice) and 12 months later (lower panels; 1-mm slice). The scar from the wedge biopsy is visible in the left lung field. (B) Coronal-reconstruction CT images at initial presentation (left panel; 2-mm slice) and 12 months later (right panel; 1-mm slice).

spite smoking cessation or those with systemic involvement, treatment options may include chemotherapies with certain cytotoxic agents, novel targeted therapies against mutations in the MAPK pathway, and, in advanced cases, lung transplantation [1-3, 11]. Use of inhaled corticosteroids (with or without inhalational bronchodilators) has been described in expert reviews, though the exact dosing and efficacy are still unclear [1-3, 11].

In this case report, we describe the clinical presentation, pulmonary functions, pathology findings, and serial HRCT features of a patient with PLCH who exhibited significant clinical and radiographic improvement within months following smoking cessation and inhalational therapy.

## Case Presentation

A 62-year-old female initially presented to a local hospital with a persistent, nonproductive cough that had lasted several months and was unresponsive to antitussive treatments. A thoracic computed tomography (CT) scan performed at that hospital showed many solid nodules, ill-defined ground-glass opacities, and cysts predominantly in her apical, upper, and middle lung fields (upper panels of Figure 1A and the left panel of Figure 1B). The patient

**Table 1.** Pulmonary Function Tests of the Case Patient at Initial Presentation And 6 Months Later

| Pulmonary function tests | At initial presentation | 6 months later |
|---|---|---|
| **$FVC/FEV_1$, %** | 75 | 72 |
| **FVC, L (% prediction)** | 2.45 (104) | 2.51 (107) |
| **$FEV_1$, L (% prediction)** | 1.84 (101) | 1.81 (100) |
| **TLC, L (% prediction)** | 4.07 (108) | 4.42 (118) |
| **RV/TLC, %** | 37 | 48 |
| **$D_{LCO}$, ml/min/mmHg** | 13.02 | 12.66 |
| **$D_{LCO}$, % prediction** | 71 | 70 |

Abbreviations: DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

was transferred to our medical center for subsequent diagnostic and therapeutic management. Further inquiry into her symptoms revealed that her cough would worsen when talking or after exposure to cold. There was no associated fever, dyspnea, sore throat, hemoptysis, or weight loss. She also denied having headaches, unsteady gait, visual changes, dryness in the eyes and mouth, joint or bone pain, or abnormal skin ulcers or eruptions. Her past medical history included type 2 diabetes mellitus, hypertension, and hyperlipidemia, along with a 30-pack-year history of cigarette smoking. Her family, occupational, and exposure histories were unrevealing.

Physical examination, including auscultation of her breathing sounds, was unremarkable. Her hemogram, blood biochemistry (including levels of sodium, calcium, hepatic transaminases, bilirubin, alkaline phosphatase, C-reactive protein, and alpha-1 antitrypsin), erythrocyte sedimentation rate, rheumatoid factor, thyroid stimulating hormone, and selected serological tests (including antinuclear antibody, anti-Ro, anti-La, and anti-Sm/RNP auto-antibodies) were within normal ranges. Pulmonary function tests reported normal spirometric volumes, but mild impairment in her diffusion capacity for carbon monoxide ($D_{LCO}$; Table 1). X-rays of her skull, ribs, pelvis, and long bones showed no osteolytic lesions.

Transthoracic echocardiography reported a low probability of pulmonary hypertension. The patient underwent a video-assisted thoracoscopic wedge biopsy of the left upper lobe. Histological examination at low magnification revealed multiple stellate lesions scattered throughout the biopsied alveolar parenchyma and surrounding small bronchioles (Fig. 2A). At higher magnification, these lesions comprised large aggregates of cells exhibiting pale cytoplasm and large nuclei (many of which were reniform), admixed with fibrous extracellular matrix and a lymphoplasmacytic infiltrate (Figs. 2B and 2C). Immunohistochemically, these cells stained positive for CD1a (Fig. 2D) and CD207 (Fig. 2E). There was no microscopic evidence of microbial presence. Tissue cultures for bacteria, mycobacteria, and fungi yielded no growth. A diagnosis of isolated PLCH was established.

The patient gradually ceased smoking

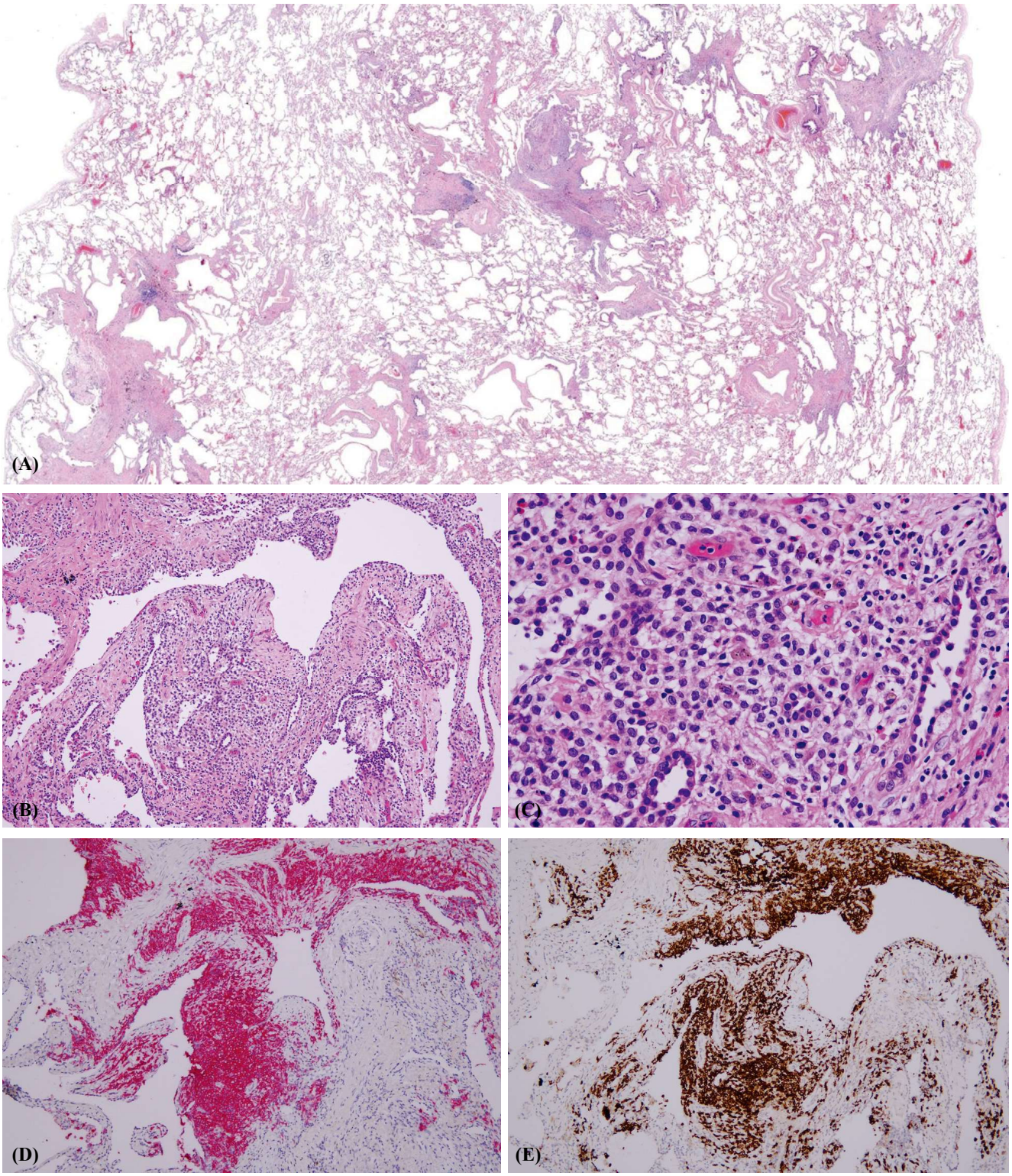


**Fig. 2.** Light microscopic features of the biopsied lung tissue: (A) multiple stellate lesions scattered in the alveolar parenchyma near small bronchioles at low magnification (hematoxylin and eosin, ×6); (B) the stellate lesions consist of aggregates of Langerhans-like cells admixed with fibrous extracellular matrix and a lymphoplasmacytic infiltrate (hematoxylin and eosin, ×100); (C) these Langerhans-like cells exhibit pale cytoplasm and large (and in many cells, reniform) nuclei (hematoxylin and eosin, ×400), and immunohistochemically, they stained strongly positive for (D) CD1a (×100) and (E) CD207 or Langerin (×100).

over the next 4 months. After shared decision making, she also received inhalational therapy with 250 mcg fluticasone propionate plus 25 mcg salmeterol twice daily via a combination metered dose inhaler. Her cough significantly improved following these measures. Her spirometric volumes and $D_{LCO}$ remained stable (Table 1). A follow-up thoracic CT 12 months later showed a significant reduction in nodular and ground-glass opacities, as well as partial shrinkage of the cysts (lower panels of Fig. 1A and the right panel of Fig. 1B).

## Discussion

The pathogenetic hallmark of Langerhans cell histiocytosis (LCH), formerly known as histiocytosis x, is the abnormal recruitment and accumulation of Langerhans-like cells within tissues, accompanied by an inflammatory infiltrate composed of lymphoplasmacytic cells, macrophages, some eosinophils, and rare neutrophils, forming loosely structured, but destructive granulomas [1-2, 4]. LCH is now considered a clonal disorder, with previous studies revealing a high prevalence of MAPK pathway-related mutations in histiocytes isolated from affected organs [5]. Langerhans-like cells resemble dendritic cells in morphology and immunohistochemically stain positive for CD1a and CD207 (Langerin). LCH can present as either a systemic disease involving multiple organ systems or as a localized condition affecting a single organ. Isolated PLCH represents a form of localized LCH. Beyond the lungs, other commonly affected organs include bones, skin, the pituitary gland, liver, spleen, and bone marrow [2, 4, 6-7].

While PLCH in adults has frequently been considered a localized disease, reports over the years have described varying proportions of patients presenting with extrapulmonary involvement [1, 6, 8-9]. Therefore, a critical component of the diagnostic approach for suspected PLCH is the identification or exclusion of extrapulmonary disease [1-3, 10-11]. Based on this rationale, for our patient in this report, we systematically assessed non-respiratory manifestations alongside respiratory presentations and lung-related studies. This involved a comprehensive history-taking that inquired into extrapulmonary symptoms, blood tests for electrolyte and hepatic markers, and skeletal X-rays.

HRCT is a crucial imaging study for the diagnosis of PLCH [3, 11]. In its early stages, PLCH appears on HRCT as bronchiolocentric nodules and ground-glass opacities, predominantly affecting the upper and middle lung zones while sparing the basal costophrenic regions. Over time, cavitation occurs due to the destructive nature of granulomas, transforming nodules and ground-glass opacities into irregular, thin-walled cysts of varying sizes. In advanced disease, PLCH leads to irreversible fibrocystic destruction of the lung parenchyma [1, 6-8, 12-13]. Radiographic differential diagnoses include centrilobular emphysema, sarcoidosis, cystic bronchiectasis, metastatic cavitating cancerous lesions, Birt-Hogg-Dubé syndrome, and, particularly in female patients, lymphangioleiomyomatosis (LAM), as well as lymphocytic interstitial pneumonia (LIP), which may be secondary to connective tissue diseases or, very rarely, idiopathic [12-13].

Tissue sampling for histological analysis remains the diagnostic gold standard. However, for patients unwilling or unsuitable for biopsy, a multi-disciplinary assessment, integrating clinical presentations, a positive history

of cigarette smoking, HRCT imaging features (in particular the morphology and distribution of nodules and cysts), and targeted serological tests for relevant connective tissue diseases, can aid in establishing the correct diagnosis. Based on the characteristic HRCT findings, a history of smoking, and the absence of clinical or serological evidence of connective tissue diseases, PLCH was strongly suspected in our patient, and subsequently confirmed through histological examination.

Unlike systemic LCH, PLCH is strongly associated with smoking. Pulmonary function tests in PLCH patients commonly reveal an obstructive defect. However, restrictive or mixed-pattern abnormalities, as well as normal spirometry results, have also been documented [1, 6, 8, 14-15]. The most frequently reported respiratory physiological abnormality in PLCH is a reduced $D_{LCO}$, which was observed in our patient. Compared to systemic LCH, PLCH generally has a better prognosis. To date there are no well-established guidelines for the treatment of PLCH, and therapeutic strategies must be individualized. In many cases, however, PLCH may improve or resolve spontaneously following smoking cessation alone. The therapeutic efficacy of smoking cessation may be attributed to the chemotactic and anti-apoptotic effects of tobacco smoke, which lead to the excessive recruitment and persistence of pathognomonic Langerhans-like cells [1-2].

For progressive and severe PLCH, potential therapeutic options include systemic treatment with immunosuppressive cladribine, targeted inhibitors of the MAPK pathway, and lung transplantation [1-3, 11]. Therapy combining inhalational corticosteroids and bronchodilators has been discussed in expert reviews, particularly for patients exhibiting obstructive ventilatory defects and wheezing [1-3, 11]. However, this therapeutic option lacks sufficient clinical evidence regarding dosing and efficacy. Additionally, PLCH may be complicated with spontaneous pneumothorax and pulmonary hypertension. Patients with PLCH also exhibit an enhanced risk of developing lung carcinomas as well as Hodgkin and non-Hodgkin lymphoid malignancies.

Our patient underwent treatment with inhalational fluticasone propionate/salmeterol during follow-ups. Nonetheless, smoking cessation likely played the most critical role in the significant symptomatic and radiographic improvements observed in her PLCH. Owing to residual cysts, the mild impairment in her DLCO persisted in follow-up pulmonary function tests, although spirometric volumes remained stable.

In conclusion, we reported a case of PLCH that exhibited substantial clinical and radiographic improvement without the use of cytotoxic or targeted chemotherapy. Our case underscores the strong association of PLCH with cigarette smoking and highlights smoking cessation as the crucial cornerstone in the management of PLCH.

## Acknowledgments

We sincerely thank the patient for granting permission to report her clinical presentation and radiographic imaging data related to her illness.

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# Cryptogenic Organizing Pneumonia Presenting as Progressive Bilateral Pneumonia and Type 1 Respiratory Failure: A Case Report

Shang-Hsun Hsieh[1], Yu-Sheng Chang[2], Chun-Nin Lee[3]

Cryptogenic organizing pneumonia (COP) is a rare lung disease often misdiagnosed as infectious pneumonia due to similar symptoms and imaging findings. It should be considered in patients with pneumonia that do not respond to antibiotics and have negative microbiological test results. Early steroid treatment and multidisciplinary care are essential for better outcomes. Here, we reported a 52-year-old female with progressive bilateral pneumonia and type 1 respiratory failure. Despite treatment with broad-spectrum antibiotics, her condition worsened, and she required mechanical ventilation. After excluding infections and autoimmune causes, COP was suspected. The patient responded well to corticosteroids and later to immunosuppressive therapy, leading to significant clinical improvement. ***(Thorac Med 2025; 40: 306-310)***

Key words: Cryptogenic organizing pneumonia, interstitial lung disease, steroid therapy, immunosuppressant, respiratory failure

## Introduction

Cryptogenic organizing pneumonia (COP), previously referred to as bronchiolitis obliterans organizing pneumonia (BOOP), is an idiopathic interstitial lung disease characterized by intra-alveolar granulation tissue and organizing inflammation. The disease onset is typically in the fifth or sixth decades of life, with males and females affected equally [1]. COP is a rare disease, although its exact incidence and prevalence are unknown. A major teaching hospital in Canada found a cumulative incidence of 6 to 7 cases per 100,000 hospital admissions [2]. Clinically, it may mimic infectious pneumonia but typically fails to respond to antibiotic therapy. Early recognition and corticosteroid administration are key to a favorable prognosis. This report details a case of COP in a 52-year-old female with rapidly progressive bilateral pneumonia leading to respiratory failure, who responded well to steroid and immunosuppres-

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sive treatment.

## Case Report

This 52-year-old previously healthy female presented to the outpatient department with a non-productive cough lasting for 2 months. Initial chest X-ray (Fig. 1a, day 1 of admission) revealed scattered infiltrates in the left upper lobe, right upper lobe, and right lower lobe. The patient was started empirically on intravenous amoxicillin-clavulanate (Curam) for presumed community-acquired pneumonia. However, despite antibiotic therapy, her respiratory symptoms worsened, with increasing dyspnea and oxygen desaturation.

Due to clinical deterioration, antibiotic therapy was escalated to intravenous piperacillin-tazobactam (Tazocin), and levofloxacin (Cravit) was added. A high-resolution computed tomography (HRCT) scan of the chest (Fig. 2a, day 3 of admission) performed on the second day after admission showed patchy lobar and alveolar/airspace consolidation, predominantly involving bilateral upper lobes, the superior segment of the left lower lobe, and bilateral lower lobes.

Despite broad-spectrum antibiotics, her respiratory status continued to decline, and she developed type I respiratory failure on day 6 of admission. Endotracheal intubation was performed, and mechanical ventilation was initiated. She was then transferred to the intensive care unit. Bronchoscopy with bronchoalveolar lavage (BAL) revealed a lymphocyte-predominant cell profile, with no infectious organisms identified. Autoimmune screening by a rheumatologist was unremarkable. COP was suspected.

Pulse steroid therapy with intravenous methylprednisolone 1000 mg per day was initiated on day 8 of admission, leading to clinical

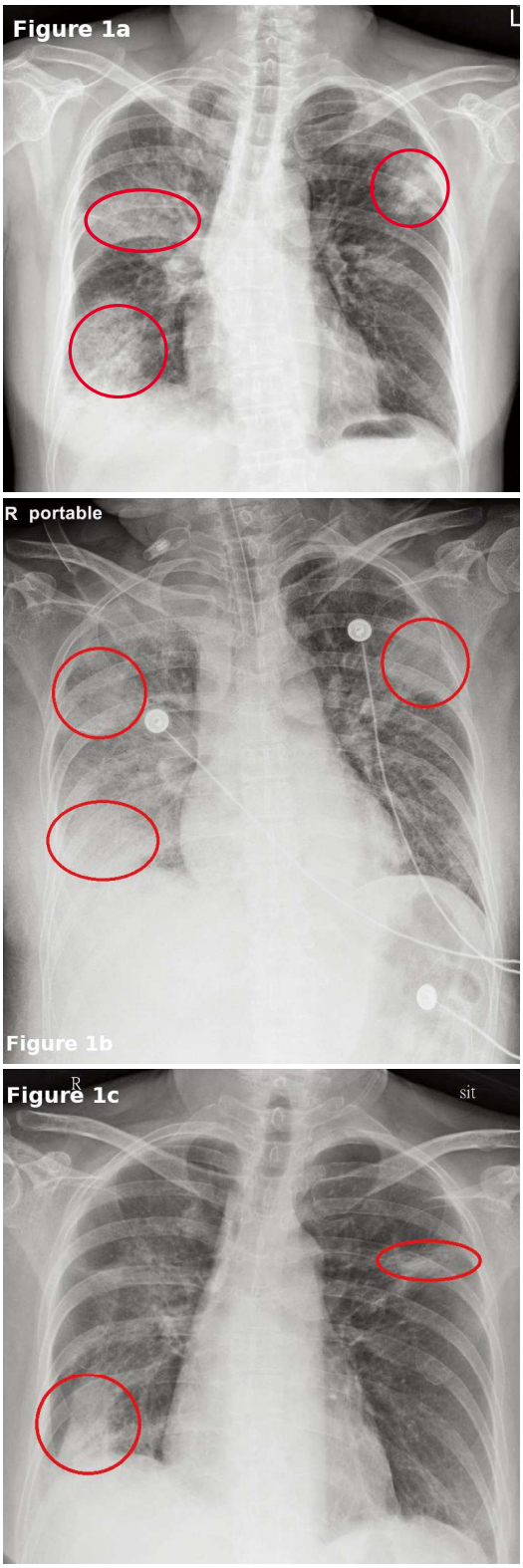


**Fig. 1.** Serial chest X-rays showing disease progression and treatment response. 1a. Chest X-ray on day 1 of admission showing bilateral patchy consolidation. 1b. Chest X-ray on day 6 of admission revealing worsening bilateral infiltration and increased opacities. Endotracheal tube was in place. 1c. Chest X-ray on day 31 of admission showing continued improvement with resolving infiltrates.

improvement. She was subsequently extubated and transferred back to the general ward. Due to persistent oxygen desaturation, a repeat contrast-enhanced CT scan (Fig. 2b, day 19 of admission) was performed and slow improvement was noted. The diagnosis of organizing pneumonia was suspected. Intravenous methylprednisolone (40 mg twice daily) was then resumed. In addition, 1 dose of intravenous cyclophosphamide (Endoxan) and a 5-day course of intravenous immunoglobulin (IVIG) were administered.

Oxygen therapy was successfully tapered off by day 27 of admission. The steroid dosage was gradually reduced, and she was transitioned to oral prednisolone at 20 mg per day. Azathioprine was also initiated for long-term immunosuppression at a dosage of 50 mg taken orally twice a day. Follow-up chest X-rays showed improving infiltrates (Fig. 1c, day 31 of admission). The patient was discharged in a stable condition after a 33-day hospital stay.

At the outpatient follow-up, the patient received a second dose of intravenous cyclophosphamide (Endoxan). Oral steroids were gradually tapered and discontinued within 1 month, and azathioprine was also stopped after 1 month. A chest and heart CT (Fig. 2c) scan performed 1 month after discharge revealed ongoing radiologic improvement with further resolution of the pulmonary infiltrates.

## Discussion

Cryptogenic organizing pneumonia (COP) is a form of idiopathic interstitial pneumonia characterized by the presence of granulation tissue plugs within alveoli, alveolar ducts, and bronchioles, often accompanied by mild interstitial inflammation [3-4]. Clinically, it

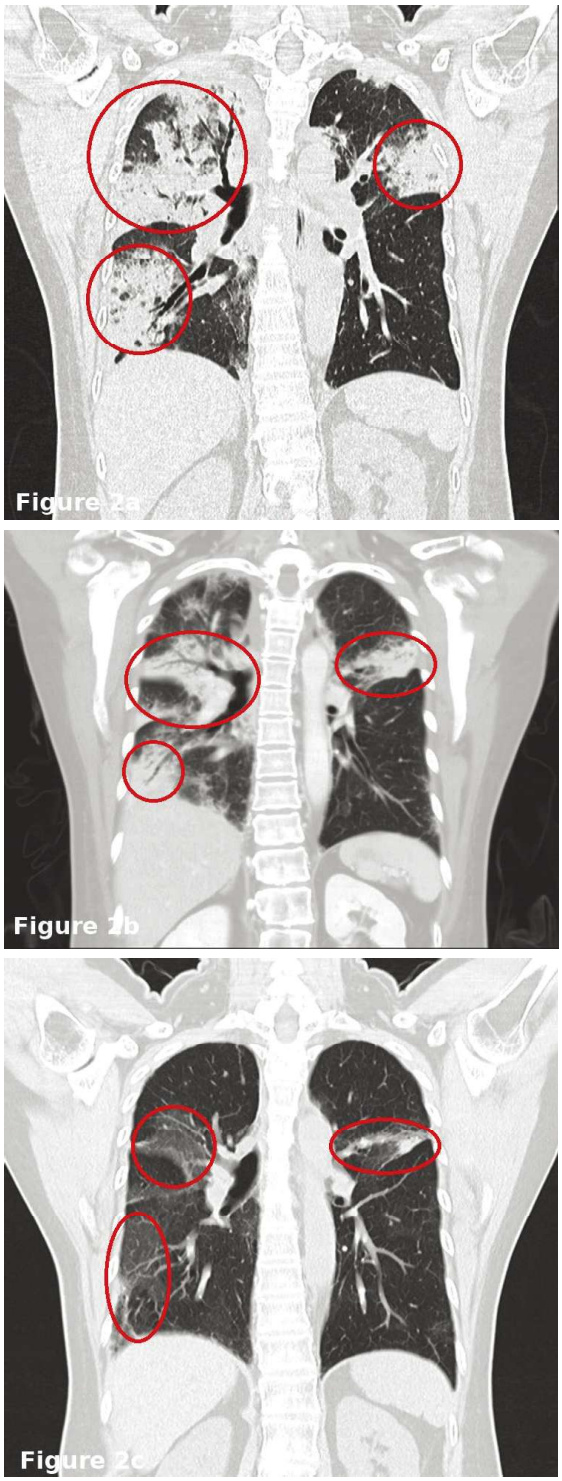


**Fig. 2.** Serial chest CT imaging showing response to immunosuppressive therapy. 2a. HRCT on day 3 of admission showing multifocal patchy consolidation involving bilateral upper lobes, left lower lobe, and bilateral lower lobes. 2b. Chest/heart CT on day 19 of admission revealing persistent consolidation despite antibiotic treatment, raising suspicion of organizing pneumonia. 2c. Chest/heart CT 1 month after discharge showing significant radiologic improvement following steroid and immunosuppressive therapy.

frequently mimics bacterial pneumonia, with symptoms such as cough, dyspnea, fever, and bilateral infiltrates on imaging [1]. The lack of response to antibiotics, lymphocyte-predominant BAL, and typical HRCT findings should raise the suspicion of COP [5-6]. HRCT is crucial for diagnosis, with findings including patchy airspace consolidation and peripheral/subpleural distribution [7]. Corticosteroids are the first-line treatment, with immunosuppressants such as cyclophosphamide and azathioprine reserved for refractory cases [8-9].

In cases where corticosteroids are ineffective or contraindicated, IVIG has been reported as a potential alternative. Several case reports have shown favorable outcomes using IVIG in steroid-refractory COP or in patients with underlying immunoglobulin deficiency. For example, Dimala *et al*. described a 72-year-old male with steroid-induced neurotoxicity who improved significantly after a 5-day course of IVIG combined with mycophenolate mofetil [10]. Another report by Gueta *et al*. presented a patient with selective IgG deficiency and recurrent COP, who achieved sustained remission with monthly IVIG therapy [11]. Although IVIG is not a standard therapy, it may be considered in selected patients when conventional treatment is not feasible.

Lung biopsy is not routinely required in every COP case but should be considered in specific clinical contexts. These include atypical imaging findings, non-diagnostic BAL, failure to respond to corticosteroids, or when alternative diagnoses such as malignancy, vasculitis, or other interstitial lung diseases need to be excluded [4, 12]. In patients being considered for long-term immunosuppressive therapy, histological confirmation via biopsy may also be warranted. The decision to proceed with lung biopsy should ideally follow multidisciplinary discussion and a careful risk-benefit assessment [13-14].

Although histopathologic confirmation via lung biopsy remains the gold standard for diagnosing organizing pneumonia, in our case, the combination of characteristic HRCT findings, lymphocyte-predominant BAL fluid, exclusion of infectious and autoimmune etiologies, and rapid clinical improvement following corticosteroid therapy supported a presumptive diagnosis of COP. Given the patient's significant clinical improvement and the potential risks of an invasive procedure, lung biopsy was deemed unnecessary. Our case highlights the importance of early diagnosis, timely steroid use, and multidisciplinary care in managing severe COP.

## Conclusion

COP should be considered in patients with progressive pneumonia unresponsive to antibiotics and without identifiable pathogens. HRCT and BAL are valuable diagnostic tools. Early steroid therapy can lead to marked improvement, and immunosuppressive therapy may be necessary in persistent or relapsing cases. Multidisciplinary collaboration is essential for optimal management and outcome.

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