นิพนธ์ต้นฉบับ

การศึกษาเปรียบเทียบประสิทธิผลระหว่าง Salmeterol/Fluticasone ชนิด pressurized metered-dose inhaler (pMDI) และ ชนิด dry-powdered inhaler (DPI) ในผู้ป่วยถุงลมโป่งพองในโรงพยาบาลหางดง

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บทคัดย่อ

ความเป็นมา: โรคถุงลมโป่งพองเป็นปัญหาทางสุขภาพที่สำคัญของประเทศไทย การรักษาประกอบด้วยสเตียรอยด์และ long-acting beta-adrenergic agonists (ICS/LABA) หรือ long-acting muscarinic antagonists (LAMA) ชนิดสูดพ่น ด้วยนโยบายหลักประกันสุขภาพถ้วนหน้าระบบสาธารณสุขจึงต้องรับภาระค่ารักษารวมถึงเวชภัณฑ์ ประสิทธิผลและความคุ้มทุนของยาจึงมีความสำคัญ การศึกษานี้มีวัตถุประสงค์เปรียบเทียบประสิทธิผลและค่ารักษาในผู้ป่วยถุงลมโป่งพองที่ได้รับ Salmeterol/Fluticasone ชนิด pMDI และ DPI และเพื่อศึกษาปัจจัยในการเกิดการกำเริบ ผลลัพธ์การรักษา รวมไปถึงค่ารักษาพยาบาล

ระเบียบวิธีวิจัย: การศึกษาย้อนหลังในผู้ป่วยโรคถุงลมโป่งพองที่เข้ารับการรักษาและได้รับยา ICS/LABA อย่างต่อเนื่องที่โรงพยาบาลหางดง ระหว่างเดือนมกราคม ถึง ธันวาคม พ.ศ. 2566 เก็บข้อมูลประชากร การรักษา และผลลัพธ์การรักษา วิเคราะห์ด้วยสถิติเชิงพรรณนาและวิเคราะห์หาด้วย logistic regression และนำปัจจัยที่ค่า $p < 0.1$ เข้าใน multivariable logistic regression นำเสนอค่าด้วย Adjusted odds ratio 95% confidence interval

ผลการศึกษา: ผู้ป่วย 326 ราย เป็น pMDI 215 ราย และ DPI 111 ราย พบว่ากลุ่ม DPI มีอายุน้อยกว่า และมีสัดส่วนของผู้ป่วย GOLD E มากกว่ากลุ่ม pMDI (32.4% vs 18.6%, p-value =0.002) กลุ่ม DPI มีการกำเริบปานกลางมากกว่ากลุ่ม pMDI ซึ่งสัมพันธ์กับความรุนแรงของโรคมากกว่าตัวอุปกรณ์ ส่วนการกำเริบรุนแรงไม่แตกต่างกัน ประวัติการกำเริบรุนแรงอย่างน้อย 1 ครั้ง ในปีก่อนหน้าสัมพันธ์กับการกำเริบรุนแรง (Adj.OR 6.70, 95% CI 1.17-38.32, p-value =0.033) เช่นเดียวกับการใช้ LAMA (Adj.OR 4.71, 95% CI 2.08-10.70, p-value < 0.001) ค่ารักษาผู้ป่วยนอกกลุ่ม DPI สูงกว่า ขณะที่ค่ารักษาผู้ป่วยอาการกำเริบรุนแรงในกลุ่ม pMDI สูงกว่าอย่างมีนัยสำคัญ มีภาวะหายใจล้มเหลวร้อยละ 28.6 (ร้อยละ 14.6 ใน DPI) และอัตราการเสียชีวิตร้อยละ 14.6 (ร้อยละ 0 ใน DPI)

สรุป: อุปกรณ์ทั้งสองชนิดไม่พบความสัมพันธ์กับอาการกำเริบ ประวัติการกำเริบรุนแรงอย่างน้อย 1 ครั้ง ในปีก่อนหน้า และการใช้ LAMA สัมพันธ์กับการเกิดการกำเริบรุนแรง DPI สามารถลดการเกิดภาวะแทรกซ้อนรุนแรงและลดค่ารักษาพยาบาลร้อยละ 13 เมื่อเทียบกับ pMDI

คำสำคัญ: ถุงลมโป่งพอง, อุปกรณ์สูดพ่น, ภาวะถุงลมโป่งพองกำเริบ, ปัจจัยเสี่ยงถุงลมโป่งพองกำเริบ

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Original Article

Comparative effectiveness of pressurized metered-dose inhaler (pMDI) and dry-powdered inhaler (DPI) salmeterol/fluticasone on chronic obstructive pulmonary disease, a single-center study in Hangdong Hospital

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a major public health concern in Thailand. Standard treatment regimens typically include combinations of inhaled corticosteroids with long-acting beta-adrenergic agonists (ICS/LABA) or long-acting muscarinic antagonists (LAMA). Given the financial constraints of the Universal Coverage Program, evaluating both the clinical efficacy and cost-effectiveness of available therapies is essential. This study aimed to compare the effectiveness and cost of Salmeterol/Fluticasone administered via pressurized metered-dose inhaler (pMDI) versus dry powder inhaler (DPI), and to identify risk factors associated with exacerbations and clinical outcomes.

Materials and Methods: This retrospective cohort study included all COPD patients who regularly visited Hangdong Hospital and received ICS/LABA therapy between January and December 2023. Demographic data, treatment details, and clinical outcomes were reviewed and analyzed. Descriptive statistics were applied, and risk factors were identified using logistic regression. Variables with $p < 0.1$ in univariate analysis were included in multivariable models, with results reported as adjusted odds ratios and 95% confidence intervals.

Results: Of the 326 patients included, 215 used pMDIs and 111 used DPIs. The DPI group was significantly younger and had a higher proportion of GOLD stage E patients (34.2% vs. 18.6%). Moderate exacerbations were more frequent in the DPI group, primarily due to greater disease severity, while severe exacerbation rates were similar between groups. The strongest predictors of severe exacerbations were a history of more than one prior exacerbation (Adjusted OR 6.70, 95% CI 1.17–38.32, $p = 0.033$) and LAMA use (Adjusted OR 4.71, 95% CI 2.08–10.70, $p < 0.001$). Outpatient costs were significantly higher for DPI users, whereas inpatient costs were higher for pMDI users, partly due to increased rates of respiratory failure (25.6% vs. 8.8%, $p = 0.018$) and mortality (14.6% vs. 0%, $p < 0.001$).

Conclusion: Neither inhaler type was independently associated with an increased risk of exacerbation. Key risk factors for severe exacerbations included a history of multiple prior exacerbations and LAMA use. DPI use was associated with fewer severe complications and resulted in 13% lower total healthcare costs compared to pMDI use.

Keywords: COPD, inhaler devices, exacerbations, risk factors

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) ranks among Thailand's most devastating non-communicable diseases (NCDs), with a mortality rate of 9.12 deaths per 100,000 population in 2020.[1] The disease manifests as a destructive cycle: 40% of patients suffer at least one exacerbation annually, with each episode increasing the risk of future events and progressively impairing lung function. This accounts for repeated hospitalizations, significant productivity losses, and premature mortality.[2] COPD exacerbations are frequently triggered by respiratory infections and environmental exposures, particularly airborne pollutants like smoke and fine particulate matter (PM2.5). This health threat is especially pronounced in Chiang Mai's Hangdong district, where consistently high PM2.5 levels create significant risks for pulmonary health.[3-4]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), Long-acting muscarinic antagonist/ long-active beta-adrenergic agonist combination (LAMA/LABA) dual therapy remains the cornerstone of COPD treatment for most patients, offering bronchodilation and exacerbation reduction with minimal pneumonia risk. Inhaled corticosteroid/long-acting beta-adrenergic agonist (ICS/LABA) is now reserved for specific phenotypes: those with blood eosinophils at least 300 cells/μL or asthma-COPD overlap (ACO), where targeted anti-inflammatory effects reduce exacerbations. [5] For high-risk patients (Group D) who continue to experience exacerbations despite LAMA/LABA therapy, triple therapy (ICS/LAMA/LABA) may be considered. However, regular re-evaluation is recommended to justify continued ICS use.

Despite GOLD recommendations, ICS/LABA continues to dominate COPD treatment in Thailand, prescribed for about 60% of GOLD B-D patients versus only 30% receiving LAMA. This disparity persists due to: (1) earlier inclusion of ICS/LABA in Thailand’s National List of Essential Medicines (NLEM), (2) limited access to LAMA/LABA single-device combinations until 2024, and (3) clinical inertia favoring established ICS/LABA regimens. While LAMA use is rising post-NLEM updates, ICS/LABA remains entrenched as the default therapy, even among severe (GOLD D) patients, where 53% received it alone compared to 33% on triple therapy[6].

Inhaler selection significantly impacts COPD outcomes. The pMDIs offer rapid, consistent dosing through hydrofluoroalkane (HFA) propellants that optimize lung deposition via finer aerosols but demand precise coordination - spacers mitigate this but compromise portability and lose medication to electrostatic charge.[7-9] Dry powder inhalers (DPIs), in contrast, eliminate the need for coordination but require sufficient inspiratory flow, making

them suitable for patients with preserved lung effort but poor coordination or timing.[7-9] This fundamental trade-off between coordination and inspiratory flow highlights the need for patient-specific device selection. Studies have shown that ICS/LABA or short-acting beta-adrenergic agonist (SABA) delivered via pMDIs carry a 0.7–2.7-fold greater risk of exacerbation compared to DPIs,[10-11] while other reports suggest pMDIs are linked to fewer moderate-to-severe exacerbations and lower post-discharge costs.[12-13] Systematic reviews in asthma and COPD reveal no clear superiority between devices, with pMDIs often recommended first-line due to comparable efficacy and lower cost.[11,14-15] However, this equivalence depends entirely on correct technique—a significant challenge given that mishandling occurs in up to 50% of patients[12,15-21], doubling mortality risk [18]. pMDIs exhibit higher error rates (80% overall, 47% critical) versus DPIs like the Accuhaler (7–30%, 21% critical)[18,21], primarily due to coordination demands [22]. For DPIs, most COPD patients maintain adequate inspiratory flow (≥30 L/min) even post-hospitalization.[23] Thus, device selection should prioritize patient-specific factors: coordination ability, learning capacity, and inspiratory flow. [24]

Given Thailand's unique prescribing patterns, cost constraints, and device-specific challenges, this study evaluates the real-world effectiveness and costs of Salmeterol/Fluticasone (pMDI vs DPI) at Hangdong Hospital.

Objectives

This study aimed to compare the effectiveness and cost of Salmeterol/ Fluticasone administered via pressurized metered-dose inhaler (pMDI) versus dry powder inhaler (DPI) and identify risk factors associated with exacerbations and compare clinical outcomes.

Methods

Study design and Participant

This retrospective cohort study evaluated COPD patients on regular Salmeterol/Fluticasone treatment at Hangdong Hospital during Jan 1st to Dec 31st, 2023. Due to missing pulmonary function tests (PFTs) in some patients (often elderly or from minority groups), eligibility was based on clinical symptoms, risk factors, and chest radiographs at diagnosis. This approach may have missed asthma or overlap syndrome cases. Exclusions included patients with only a single symptom episode, irregular follow-up, or LAMA monotherapy. Device switches were categorized by the most recent inhaler used.

Data Collection

Demographic characteristics, comorbidities, and COPD treatment regimens (1-month pre-study) were extracted electronic medical records (EMRs). Data including prior PFT results (if available), outpatient (OPD) visits, emergency department (ED) visits, and hospitalizations during study period were also retrieved. For referred

patients, clinical outcomes (vital status, hospital transfers, and treatment modifications) were obtained through provincial referral networks, with cost data sourced from reimbursement offices. Lost-to-follow-up patients were tracked through EMRs, referrals, and census data; those alive without events were considered exacerbation-free. Person-time was censored at death, last follow-up, or device discontinuation. Seasonal changes and pollution were obtained from the Air Quality and Noise Management Bureau, Pollution Control Department. Months with PM2.5 levels exceeding 75 parts per million (PPM) for more than half the month were classified as PM seasons.

Outcomes

Moderate (ED visit) and severe (hospitalization) COPD exacerbations between pMDI and DPI Salmeterol /Fluticasone users were assessed as the primary outcome. Secondary outcomes included respiratory failure incidence, mortality, and their associations with clinical factors such as prior exacerbations, COPD Assessment Test (CAT) scores, modified Medical Research Council (mMRC) scores, absolute eosinophil counts (AEC), and treatments. Total costs of care during admission were used for the inpatient (IPD) setting, while only COPD-related medication and treatment costs were used for the outpatient/emergency department (OPD/ED). Additionally, data on seasonal changes and PM2.5 levels were included to explore their relationship with exacerbations and air pollution as an exploratory outcome.

Statistical analysis

This study used descriptive statistics (proportions for categorical variables; mean with standard deviation [SD] or median with interquartile range [IQR] for continuous variables) and comparative tests (Chi-square/Fisher's exact for categorical; t-test/Wilcoxon for continuous, with Shapiro-Wilk normality testing). The required sample size was 279 patients, calculated based on an assumed 40% annual exacerbation rate and 1.7-fold increased risk with pMDIs (α=0.05, power=80%). Predictive factors were analyzed using stepwise logistic regression, with variables showing p-value <0.1 in univariate analysis included in multivariate models (significance at p-value <0.05). All analyses were performed using STATA version 17.0 (StataCorp LLC, College Station, TX).

Results

Participants

In 2023, 361 COPD patients were presented to Hangdong Hospital. After excluding 35 patients (8 with insufficient follow-up, 27 on LAMA monotherapy), 326 were analyzed (215 pMDI, 111 DPI), including 16 reclassified from pMDI to DPI due to device switching. Follow-up verification revealed 12.6% of DPI users (14/111) and 17.7% of pMDI users (38/215) initially lost to follow-up were subsequently confirmed

stable—alive without exacerbations or documented costs (absolute difference 5.1%, 95% CI: -2.2% to 12.3%; p-value =0.174). These patients were retained in final analyses with censored time. pMDI users were older (75±9.4 vs 69±8.3 years, p-value <0.001), more often female (52.1% vs 29.7%, p-value <0.001), and had lower BMI (20±4.7 vs 20.9±4.5 kg/m², p-value =0.03) but higher smoking rates (14.9% vs 8.2%, p-value =0.016). DPI users showed greater LAMA utilization (42.3% vs 16.7%, p-value <0.001). Comorbidities, vaccination rates, and ICS doses were comparable. A significantly higher proportion of GOLD stage E patients was observed in the DPI group (34.2% vs 18.6%, p-value =0.002). DPI users had significantly more exacerbations in the preceding year compared to pMDI users. While mMRC scores were comparable, CAT scores showed a non-significant trend towards higher scores in the DPI users (median 4 points [IQR 3-5] in pMDI vs median 4 points [IQR 3.5-6.5] in DPI, p-value =0.057). There were no significant differences between the groups in eosinophil counts or technical errors or PFT results

Table 1 Patient characteristics based on devices.

Patient characteristics based on devices.	pMDI (n= 215)	DPI (n= 111)	All	p-value
Age (mean, SD)	74.94 (9.37)	69.48 (8.27)	73.09 (9.36)	< 0.001*
Female (N, %)	112 (52.09)	33 (29.73)	145 (44.48)	< 0.001*
BMI (mean, SD)	20 (4.69)	20.85 (4.50)	20.29 (4.64)	0.030*
Comorbidities				
Cardiovascular conditions (N, %)	26 (12.09)	13 (11.82)	39 (12.00)	1.000
Hypertension (N, %)	122 (56.74)	60 (54.55)	182 (56.00)	0.724
Cerebrovascular disease (N, %)	18 (8.37)	4 (3.64)	22 (6.77)	0.160
Diabetes mellitus (N, %)	57 (26.51)	36 (32.73)	93 (28.62)	0.246
Chronic kidney disease (N, %)	34 (15.81)	16 (14.55)	50 (15.36)	0.871
Psychological conditions (N, %)	15 (6.98)	10 (9.01)	25 (7.67)	0.516
Influenza vaccination (N, %)	148 (68.84)	81 (72.97)	229 (70.25)	0.523
Smoking				
None (N, %)	19 (8.84)	3 (2.73)	22 (6.77)	
Ex-smoker or Occupational exposure (N, %)	164 (76.28)	98 (89.09)	262 (80.62)	
Active (N, %)	32 (14.88)	9 (8.18)	41 (12.62)	0.016*
GOLD Stage				
A (N, %)	171 (79.53)	69 (62.16)	240 (73.62)	
B (N, %)	4 (1.86)	4 (3.60)	8 (2.45)	
E (N, %)	40 (18.60)	38 (34.23)	78 (23.93)	0.002*
Pulmonary function test (overall N=85) (N, %)	59 (27.44)	26 (23.42)	85 (26.07)	0.434
FEV1/FVC (mean, SD)	64.1 (14.33)	60.62 (16.54)	63.04 (15.02)	0.336
FEV1 (mean, SD)	62.78 (17.83)	57.42 (24.48)	61.14 (20.10)	0.145
FEV1 above 80% (N)	10	5	15	0.767
FEV1 50-80% (N)	34	9	43	0.058
FEV1 30-50% (N)	15	11	26	0.391
FEV1 below 30% (N)	0	1	1	0.306
mMRC score (points, IQR)	0 (0-1)	0 (0-1)	0 (0-1)	0.966
CAT score (points, IQR)	4 (3-5)	4 (3.5-6.5)	4 (3-6)	0.057

Table 1 Patient characteristics based on devices. (Cont.)

Patient characteristics based on devices.	pMDI (n= 215)	DPI (n= 111)	All	p-value
AEC (median cells/μL, SD)	482.61 (494.14)	564.46 (548.45)	508.07 (511.52)	0.350
AEC > 100 cells/μL (N, %)	196 (91.16)	105 (94.59)	301 (92.33)	0.380
AEC > 300 cells/μL (N, %)	159 (73.95)	84 (75.68)	243 (75.54)	0.789
Inhalation technique error (overall N=73) (N, %)	28 (38.36)	12 (16.44)	40 (54.79)	0.147
Severity				
Any prior exacerbations in previous year (N, %)	50 (23.26)	51 (45.95)	101 (30.98)	< 0.001*
Any prior moderate exacerbations in previous year (N, %)	24 (118.16)	42 (37.84)	66 (20.25)	< 0.001*
Any prior severe exacerbations in previous year (N, %)	37 (17.21)	27 (24.32)	64 (19.63)	0.142
Prior severe exacerbations > 1 in previous year (N, %)	9 (4.19)	12 (10.81)	21 (6.44)	0.030*
LAMA use (N, %)	36 (16.74)	47 (42.34)	83 (25.46)	< 0.001*
Lost follow-up (N, %)	14 (12.6)	38 (17.7)	52 (15.95)	0.174

ICS/LABA Inhaled Corticosteroid/Long-acting Beta-agonist, pMDI pressurized Metered-Dose Inhaler, DPI Dry Powder Inhaler, SD Standard Deviation, BMI Body Mass Index, FEV1 Forced Expiratory Volume (1 sec), FVC Forced Vital Capacity, mMRC modified Medical Research Council, CAT COPD Assessment Test, AEC Absolute Eosinophil Count, LAMA Long-acting Muscarinic Antagonist

Characteristic of pMDI and DPI users were compared using Chi-square test, Wilcoxon rank-sum test or t-test as appropriate

** = significant difference*

Exacerbations

In 2023, a total of 1,844 COPD-related visits were recorded over 3,439 person-months. These included 1,467 follow-up appointments, 181 visits for moderate exacerbations, and 196 visits for severe exacerbations (Table 2). DPI users had significantly more visits for moderate exacerbations compared to pMDI users (0.11 vs 0.03 incidents per person-month, p-value < 0.001). However, there was no significant difference in the rate of severe exacerbations between the two groups (0.08 vs 0.04 incidents per person-month, p-value =0.165). The admission rates due to severe exacerbations were 25.1% for pMDI users and 33.3% for DPI users (p=0.120). Among those admitted, 28.6% of pMDI users developed respiratory failure, compared to 8.8% of DPI users (p=0.018). The in-hospital mortality rate was 14.6% among pMDIs users, while no deaths were recorded in the DPI group (p < 0.001). The length of stay per admission did not differ significantly between groups. Among the 16 patients who switched groups, three patients experienced a total of six exacerbations (four severe and two moderate) while using pMDI. After switching to DPI, only one severe exacerbation was recorded among these 16 patients.

Table 2 Outcomes based on devices.

Outcomes based on devices	pMDI (n= 215)	DPI (n= 111)	p-value
Total OPD visits (visits)	1105	739	< 0.001*
Total moderate exacerbations in this year (visits, %)	64 (5.79)	117 (15.83)	< 0.001*
Total severe exacerbations in this year (visits, %)	105 (9.50)	91 (12.31)	0.111
Total exacerbations in this year (visits, %)	169 (15.29)	208 (28.15)	0.001*
Total FU time (person-month)	2358	1081	
Total moderate exacerbations in this year (incidents per person-month)	0.03	0.11	0.001*
Total severe exacerbations in this year (incidents per person-month)	0.04	0.08	0.165
Total exacerbations in this year (incidents per person-month)	0.07	0.19	0.004*
Admitted cases (N, %)	54 (25.12)	37 (33.33)	0.120
Total respiratory failure			
Cases (N, %)	24 (44.44)	8 (21.62)	0.088
Episodes (Episodes, %)	30 (28.57)	8 (8.79)	0.018*
Total deaths (N, %)	8 (14.55)	0 (0.00)	0.020*
Length of stay, days (median, IQR)	4 (3-7)	4 (2-7)	0.984
Cumulative length of stay, days (median, IQR)	6.5 (4-13)	5 (3-13)	0.868

ICS/LABA Inhaled Corticosteroid/Long-acting Beta-agonist, pMDI pressurized Metered-Dose Inhaler, DPI Dry Powder Inhaler, OPD Outpatient department, IPD Inpatient department, IQR Interquartile range

Characteristic of pMDI and DPI users were compared using Chi-square test, Wilcoxon rank-sum test or t-test as appropriate

** = significant difference*

The IPD group exhibited distinct clinical characteristics compared to the OPD group, including a lower prevalence of hypertension (44.4% vs. 60.4%, p-value =0.012) but higher rates of psychological disorders (13.2% vs. 5.5%, p-value =0.034) and lower influenza vaccination coverage (60.4% vs. 74.0%, p-value =0.021) (Table 3). Disease severity was markedly greater in the IPD cohort, evidenced by a higher proportion of GOLD stage E (41.8% vs 17.0%, p-value < 0.001), higher mMRC scores (median 0 points [IQR 0-1] vs median 0 points [IQR 0], p-value < 0.001), and higher CAT scores (median 5.5 points [IQR 4-9] vs median 4 points [IQR 2-4], p-value < 0.001). Prior exacerbations were more common in the IPD group including any exacerbations (50.6% vs 23.4%, p-value < 0.001), moderate exacerbations (31.9% vs 15.7%, p-value =0.002), severe exacerbations (39.6% vs 11.9%, p-value < 0.001), and more than one severe exacerbation (18.7% vs 1.7%, p-value < 0.001). Although mean absolute eosinophil counts were comparable between groups, fewer IPD patients had AEC above 100 cells/μL (85.7% vs 94.9%, p-value =0.009). Smoking status, pulmonary function test results, and technical errors showed no significant differences between groups.

Table 3 Patient characteristics based on OPD and IPD groups.

Patient characteristics based on OPD and IPD groups	OPD (n= 235)	IPD (n= 91)	p-value
Cases (N, %)	235 (72.09)	91 (27.91)	
Age (mean, SD)	72.79 (9.25)	73.88 (9.67)	0.469
Female (N, %)	107 (45.53)	38 (41.76)	0.619
BMI (mean, SD)	20.48 (4.69)	19.8 (4.48)	0.224
Comorbidities			
Cardiovascular conditions (N, %)	29 (12.34)	10 (11.11)	0.850
Hypertension (N, %)	142 (60.43)	40 (44.44)	0.012*
Cerebrovascular disease (N, %)	17 (7.23)	5 (5.56)	0.805
Diabetes mellitus (N, %)	70 (29.79)	23 (25.56)	0.495
Chronic kidney disease (N, %)	36 (15.32)	14 (15.56)	1.000
Psychological conditions (N, %)	13 (5.53)	12 (13.19)	0.034*
Influenza vaccination (N, %)	174 (74.04)	55 (60.44)	0.021*
Smoking			
None (N, %)	17 (7.23)	5 (5.56)	
Ex-smoker or Occupational exposure (N, %)	188 (80.00)	74 (82.22)	
Active (N, %)	30 (12.77)	11 (12.22)	0.917
GOLD Stage			
A (N, %)	192 (81.70)	48 (52.75)	
B (N, %)	3 (1.28)	5 (5.49)	
E (N, %)	40 (17.02)	38 (41.76)	< 0.001*
Pulmonary function test (overall N=85) (N, %)	63 (26.81)	22 (24.18)	0.675
FEV1/FVC (mean, SD)	63.56 (14.11)	61.55 (17.66)	0.389
FEV1 (mean, SD)	63.73 (20.79)	53.73 (16.21)	0.060
FEV1 above 80% (N)	14	1	0.101
FEV1 50-80% (N)	32	11	0.856
FEV1 30-50% (N)	17	9	0.494
FEV1 below 30% (N)	0	1	0.259
mMRC score (points, IQR)	0 (0-0)	0 (0-1)	< 0.001*
CAT score (points, IQR)	4 (2-4)	5.5 (4-9)	< 0.001*
AEC (cells/μL, SD)	510.79 (524.92)	500.59 (477.95)	0.586
AEC > 100 cells/μL (N, %)	223 (94.89)	78 (85.71)	0.009*
AEC > 300 cells/μL (N, %)	174 (74.04)	69 (75.82)	0.779
Inhalation technique error (overall N=73) (N, %)	22 (52.36)	18 (58.06)	0.644
Severity			
Any prior exacerbations in previous year (N, %)	55 (23.40)	46 (50.55)	< 0.001*
Any prior moderate exacerbations in previous year (N, %)	37 (15.74)	29 (31.87)	0.002*
Any prior severe exacerbations in previous year (N, %)	28 (11.91)	36 (39.56)	< 0.001*
Prior severe exacerbations > 1 in previous year (N, %)	4 (1.70)	17 (18.68)	< 0.001*
DPI use (N, %)	74 (31.49)	37 (40.66)	0.120
LAMA use (N, %)	38 (16.17)	45 (49.45)	< 0.001*

OPD Outpatient department, IPD Inpatient department, SD Standard Deviation, BMI Body Mass Index, FEV1 Forced Expiratory Volume (1 sec), FVC Forced Vital Capacity, mMRC modified Medical Research Council, CAT COPD Assessment Test, AEC Absolute Eosinophil Count, DPI Dry Powder Inhaler, LAMA Long-acting Muscarinic Antagonist

Characteristic of OPD and IPD groups were compared using Chi-square test, Wilcoxon rank-sum test or t-test as appropriate

** = significant difference*

Risk factors for severe exacerbations

The results of the univariate and multivariate analysis of factors associated with severe exacerbations in COPD treated with ICS/LABA combine are shown in Table 4. In univariate analysis, a history of more than one severe exacerbation in the prior year demonstrated the strongest association with severe exacerbation risk (OR 13.27, 95% CI 4.33-40.67, p-value < 0.001), followed by CAT scores ≥10 (OR 8.91, 95% CI 3.54-22.40, p-value < 0.001). Significant risk elevations were also observed for LAMA use (OR 5.07, 95% CI 2.96-8.69, p-value < 0.001), montelukast use (OR 2.34, 95% CI 1.42-3.87, p-value = 0.001), and psychological disorders (OR 2.59, 95% CI 1.14-5.92, p-value = 0.024), while protective effects emerged for AEC above 100 cells/μL (OR 0.27, 95% CI 0.11-0.64, p-value =0.003), and hypertension (OR 0.52, 95% CI 0.32-0.86, p-value =0.010). DPI use showed no significant association (OR 1.49, 95% CI 0.90-2.46, p-value = 0.118).

The multivariate model confirmed persistent independent associations for prior severe exacerbations (OR 6.70, 95% CI 1.17-38.32, p-value = 0.033) and LAMA use (OR 4.71, 95% CI 2.08-10.70, p-value < 0.001), while AEC above 100 cells/μL remained the sole protective factor (OR 0.20, 95% CI 0.08-0.51, p-value = 0.001).

Table 4 Factors associated with severe exacerbations in COPD treated ICS/LABA combine—univariable and multivariable logistic regression

Risk for severe exacerbation	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
Age	1.01	0.986 – 1.039	0.349			
low BMI (<18.5 kg/m^2)	1.25	0.766 – 2.049	0.369			
Female Sex	0.86	0.526 – 1.399	0.539			
Any prior severe exacerbation	4.84	2.719 -8.612	< 0.001*			
More than 1 severe exacerbation	13.27	4.328 – 40.670	< 0.001*	6.70	1.170 – 38.3.17	0.033*
Any prior exacerbation	3.35	2.009 – 5.571	< 0.001*	1.21	0.408 – 3.604	0.729
Any prior moderate exacerbation	2.50	1.427 – 4.398	0.001*	-	-	-
LAMA use	5.07	2.961 – 8.686	< 0.001*	4.71	2.076 – 10.702	< 0.001*
ICS/LABA with DPI use	1.49	0.904 – 2.460	0.118			
Theophylline use	1.64	0.890 – 3.035	0.113			
Montelukast use	2.34	1.415 – 3.870	0.001*	0.764	0.289 – 2.020	0.588
Active smoking status	0.95	0.454 – 1.990	0.895			
AEC > 300 cells/μL	1.02	0.523 – 1.970	0.964			
AEC > 100 cells/μL	0.27	0.113 – 0.643	0.003*	0.20	0.078 – 0.514	0.001*
mMRC ≥ 2 points	1.65	0.914 – 2.989	0.096	0.838	0.024 - 29.764	0.923
CAT ≥ 10 points	8.91	3.542 – 22.404	< 0.001*	2.632	0.412 – 16.828	0.307
Inhalation technique error	1.26	0.494 – 3.209	0.630			
Cardiovascular conditions	0.89	0.414 – 1.906	0.760			
Hypertension	0.52	0.321 – 0.856	0.010*	0.471	0.219 - 1.012	0.054
Cerebrovascular disease	0.75	0.270 – 2.109	0.591			
Diabetes mellitus	0.81	0.467 – 1.403	0.451			

Table 4 Factors associated with severe exacerbations in COPD treated ICS/LABA combine—univariable and multivariable logistic regression (Cont.)

Risk for severe exacerbation	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
Chronic kidney disease	1.02	0.520 – 1.993	0.958			
Psychological conditions	2.59	1.136 – 5.992	0.024*	2.96	0.925 – 9.495	0.067

OR Odd ratio, CI Confidence Interval, BMI Body Mass Index, LAMA Long-acting Muscarinic Antagonist, DPI Dry Powder Inhaler, AEC Absolute Eosinophil Count, FEV1 Forced Expiratory Volume (1 sec)

** = significant association*

Risk factors for moderate exacerbations

In univariate analysis (Table 5), history of any exacerbations, LAMA use, DPI use, montelukast use, and CAT scores of 10 points or more were associated with an increased risk of moderate exacerbations. Conversely, advanced age, female sex, and hypertension were protective factors.

However, in multivariate analysis, only a history of any exacerbations and CAT scores of 10 points or more remained significantly associated with an increased risk (OR 4.41, 95% CI 2.40 – 8.12, p-value < 0.001, and OR 4.03, 95% CI 1.51-10.76, p-value = 0.005, respectively). Advanced age was the only protective factor (OR 0.94, 95% CI 0.91 – 0.97, p-value < 0.001), while hypertension showed a non-significant trend towards protection. Notably, DPI use lost its significant association with exacerbation risk in the multivariate model.

Table 5 Factors associated with moderate exacerbations in COPD treated ICS/LABA combine—univariable and multivariable logistic regression.

Risk for moderate exacerbation	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
Age	0.962	0.936 – 0.989	0.006*	0.940	0.909 – 9.73	< 0.001*
low BMI (<18.5 kg/m^2)	0.943	0.569 – 1.562	0.819			
Female Sex	0.649	0.392 – 1.074	0.093*	0.650	0.347 – 1.216	0.178
Any prior severe exacerbation	2.676	1.509 – 4.745	0.001*			
More than 1 severe exacerbation	6.356	2.471 – 16.347	< 0.001*	2.31	0.720 – 7.400	0.160
Any prior exacerbation	4.637	2.748 – 7.826	< 0.001*	4.41	2.399 – 8.118	< 0.001*
Any prior moderate exacerbation	5.359	3.013 – 9.529	< 0.001*	-	-	-
LAMA use	2.884	1.693 – 4.912	< 0.001*	1.24	0.615 – 2.499	0.549
ICS/LABA with DPI use	2.627	1.583 – 4.358	< 0.001*	1.69	0.897 – 3.193	0.105
Theophylline use	1.147	0.637 -2.065	0.648			
Montelukast use	2.278	1.370 – 3.790	0.002*	0.862	0.412 – 1.801	0.692
Active smoking status	1.318	0.648 – 2.678	0.446			
AEC > 300 cells/μL	1.113	0.582 – 2.127	0.747			
AEC > 100 cells/μL	0.558	0.232 – 1.337	0.191			
mMRC ≥ 2 points	1.224	0.661 – 2.267	0.521			
CAT ≥ 10 points	1.888	1.090 – 3.273	0.023*	4.03	1.506 – 10.759	0.005*
Inhalation technique error	0.512	0.198 – 1.324	0.167			
Cardiovascular conditions	0.563	0.239 – 1.328	0.190			

Table 5 Factors associated with moderate exacerbations in COPD treated ICS/LABA combine—univariable and multivariable logistic regression. (Cont.)

Risk for moderate exacerbation	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
Hypertension	0.506	0.308 – 0.832	0.007*	0.58	0.318 – 1.041	0.068
Cerebrovascular disease	1.029	0.389 – 2.717	0.956			
Diabetes mellitus	1.263	0.742 – 2.151	0.390			
Chronic kidney disease	0.473	0.212 – 1.052	0.066	0.89	0.341 - 2.325	0.812
Psychological conditions	0.668	0.243 – 1.837	0.434			

OR Odd ratio, CI Confidence Interval, BMI Body Mass Index, LAMA Long-acting Muscarinic Antagonist, DPI Dry Powder Inhaler, AEC Absolute Eosinophil Count, FEV1 Forced Expiratory Volume (1 sec)

** = significant associatio*

Risk factors for respiratory failure and mortality

In univariate analysis, female sex was associated with an increased risk of respiratory failure requiring intubation (OR 2.76, 95% CI 1.23-6.18, p-value =0.014). Conversely, DPI usage was associated with a protective effect against respiratory failure (OR 0.35, 95% CI 0.13-0.89, p-value =0.028). Both AEC thresholds (over 100 cells/μL and 300 cells/μL) were significantly associated with a reduced risk of respiratory failure (OR 0.19, 95% CI 0.05-0.68, p-value =0.011 and OR 0.17, 95% CI 0.05-0.58, p-value =0.005, respectively). The multivariable analysis confirmed these protective associations, with DPI use maintaining a strong inverse relationship with respiratory failure (OR 0.07, 95% CI 0.01-0.71, p-value =0.024). Similarly, AEC above 100 cells/μL remained significantly protective (OR 0.15, 95% CI 0.03-0.74, p-value =0.020) (Table 6).

While univariable analysis revealed mortality trends for age, low BMI, and female sex (with protective trends for DPI use and AEC above 100 cells/μL), none remained significant in the adjusted model.

Table 6 Factors associated with respiratory failure in COPD treated ICS/LABA combine—univariable and multivariable logistic regression.

Risk for respiratory failure	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
Age	1.035	0.994 – 1.007	0.093	0.920	0.816 – 1.039	0.178
low BMI (<18.5 kg/m^2)	2.114	0.953 – 4.692	0.066	2.04	0.411 – 10.094	0.384
Female Sex	2.759	1.232 – 6.179	0.014*	1.39	0.287 – 6.799	0.680
Any prior severe exacerbation	1.917	0.865 – 4.250	0.109			
More than 1 severe exacerbation	1.800	0.698 – 4.642	0.224			
Any prior exacerbation	1.647	0.748 – 3.629	0.216			
Any prior moderate exacerbation	1.045	0.450 – 2.426	0.919			
LAMA use	1.182	0.540 – 2.589	0.675			
ICS/LABA with DPI use	0.345	0.133 – 0.891	0.028*	0.07	0.008 – 0.706	0.024*
Theophylline use	1.132	0.428 – 2.995	0.802			
Montelukast use	1.680	0.762 – 3.703	0.198			
Active smoking status	0.849	0.263 – 2.738	0.784			

Table 6 Factors associated with respiratory failure in COPD treated ICS/LABA combine—univariable and multivariable logistic regression. (Cont.)

Risk for respiratory failure	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	Adj.OR	95% CI	p-value
AEC > 300 cells/μL	0.170	0.050 – 0.581	0.005*			
AEC > 100 cells/μL	0.190	0.053 – 0.681	0.011*	0.15	0.032 – 0.742	0.020*
mMRC ≥ 2 points	1.124	0.482 – 2.624	0.787			
CAT ≥ 10 points	1.101	0.500 -2.426	0.810			
Inhalation technique error	1.250	0.274 -5.705	0.773			
Cardiovascular conditions	1.990	0.618 – 6.411	0.249			
Hypertension	1.013	0.476 – 2.157	0.974			
Cerebrovascular disease	1.605	0.308 – 8.365	0.574			
Diabetes mellitus	0.727	0.279 – 1.895	0.514			
Chronic kidney disease	1.719	0.619 – 4.774	0.299			
Psychological conditions	2.471	0.728 – 8.388	0.147			

*OR Odd ratio, CI Confidence Interval, BMI Body Mass Index, LAMA Long-acting Muscarinic Antagonist, DPI Dry Powder Inhaler, AEC Absolute Eosinophil Count, FEV1 Forced Expiratory Volume (1 sec) * = significant association*

Expenses of treatments

In 2023, Hangdong Hospital allocated 5.28 million THB for COPD treatment, comprising 2.59 million THB for OPD care and 2.69 million THB for IPD care (Table 7). The pMDI group incurred significantly higher total IPD costs (1.56 million vs. 1.13 million THB), averaging 14,800 THB per admission compared to 12,400 THB for DPI (p-value =0.045), driven largely by pMDI's greater respiratory failure (RF) incidence – with RF episodes averagely costing nearly double non-RF episodes (22,524.16 vs. 11,445.64 THB, p-value <0.001). Paradoxically, while per-episode RF costs were 146% higher with DPI (42,350 vs. 17,189 THB, p-value =0.028), DPI's 73% reduction in RF frequency (8 vs. 30 episodes, p-value =0.018) yielded 34% lower total RF expenditures (340,244 vs. 515,674 THB). OPD costs favored pMDI, with 13% lower total spending (1.27 vs. 1.32 million THB, p<0.001) and 36% lower per-visit costs (1,150 vs. 1,800 THB). Collectively, DPI demonstrated superior cost-effectiveness through 13% net savings (2.45 vs. 2.83 million THB) and reduced RF burden, supporting its use despite higher per-episode costs in severe cases.

Table 7 Cost based on devices as IPD and OPD

Cost based on ICS/LABA group as IPD and OPD	pMDI	DPI	p-value
OPD cases (326 cases)	215 cases	111 cases	
Total OPD cost (THB)	1,271,044.00	1,323,582.00	
Average cost per case (THB)	5,911.83	11,924.16	
Average cost per visit (THB)	1,150.27	1,791.04	< 0.001*
IPD cases (196 admissions)	05 admissions	91 admissions	
Total IPD cost (THB)	1,558,273.00	1,128,947.00	
Average cost per admission (THB)	14,840.70	12,406.01	0.045*

Table 7 Cost based on devices as IPD and OPD (Cont.)

Cost based on ICS/LABA group as IPD and OPD	pMDI	DPI	p-value
Total respiratory failure cost (THB)	515,674.30	340,243.80	
Average cost per respiratory failure (THB)	17,189.14	42,350.48	0.028*

ICS/LABA Inhaled corticosteroid/Long-acting Beta-agonist, IPD Inpatient department, OPD Outpatient department, pMDI pressurized metered-dose inhaler, DPI dry powder inhaler

** = significant difference*

Association of exacerbations and weather

In 2023, Thailand's seasonal division were: summer (March to May), rainy season (June to October), and winter (November to February). Exacerbation rates were consistent across seasons (28%, 38%, and 33% for summer, rainy season, and winter, respectively). PM2.5 levels remained non-hazardous from June to October, defining this period as the non-PM season; January to May and November to December were classified as the PM season. Among the 326 patients, 130 experienced exacerbations, totaling 377 episodes (196 severe and 181 moderate). PM season accounted for 62% of episodes with p-value <0.001 for across all severity and device groups.

Discussion

Among the 326 COPD patients, 130 experienced 377 exacerbations (196 severe, 181 moderate), yielding a severe exacerbation rate of 0.06 events per person-month (0.68 per person-year). Over 90% of patients reported either smoking or occupational/household exposures. Inhaler technique was formally assessed in 22% of patients, with errors detected in 55% of cases - a finding consistent with prior reports of device misuse.[16-18] Notably, neither specific device type nor technical errors correlated with exacerbation frequency. This study corroborates systematic review findings[11] that prior exacerbation history represents the strongest predictor of future events. Patients with any exacerbation in the preceding year and those with CAT scores of 10 or more demonstrated at least 4-fold increased risk of moderate exacerbations, while those with multiple severe exacerbations faced a nearly 7-fold higher risk of subsequent severe events. Additionally, though not statistically significant, A trend toward increased severe exacerbation risk among patients with psychological disorders was observed, aligning with existing literature.[11]

DPI users were younger with fewer females, and exhibited more severe disease characteristics, including higher LAMA use. Both groups demonstrated comparable mMRC score, CAT score, eosinophil counts, inhalation technique errors, and PFT results. Notably, while DPI users experienced significantly more overall exacerbations (0.19 vs. 0.07 incidents per person-month, p-value =0.004), their hospitalization rates did not differ significantly from pMDI users (0.08 vs 0.04 incidents per person-month, p-value =

0.165). This paradox appears driven by disease severity factors, as DPI users showed significantly higher rates of prior exacerbations in both IPD and OPD settings. Importantly, despite their more severe disease profile, DPI users demonstrated significantly lower respiratory failure rates (8.8% vs 25.6% of hospitalizations, p-value = 0.018) Mortality was higher in pMDI users, though not statistically linked to disease severity or device type. These findings suggest that DPI use may confer protection in severe COPD cases.

LAMA use was associated with increased severe exacerbation risk (OR 4.71, 95% CI 2.08-10.70, p-value < 0.001), likely reflecting prescribing bias toward higher-risk patients (e.g., GOLD E, frequent exacerbators). This aligns with the UPLIFT trial's conclusion that LAMA may not effectively prevent declining in lung function or overcome the treatment ceiling effects.[25] However, we a key modifier was identified: blood eosinophils ≥100 cells/μL were protective against severe exacerbations (OR 0.20, 95% CI 0.08-0.51, p-value = 0.001), suggesting COPD phenotyping matters. These patients may have type 2 inflammation or asthma overlap, explaining their better response to ICS/LABA in GOLD guidelines.[5] For such individuals, LAMA monotherapy might be insufficient, while those with low eosinophils could benefit from LAMA's bronchodilation without added risk.

Influenza vaccination rates were significantly lower in the admitted group, though this did not independently predict exacerbations in adjusted analyses. Nevertheless, vaccination remains vital for preventing severe influenza in this vulnerable population. Inhaler technique assessment was also notably low, with over half of those assessed using inhalers incorrectly. This underscores the importance of regular education, hand-on-training sessions, and reassessments during routine follow-up especially for elderly patients and those with psychiatric conditions.

The economic burden of COPD treatment at Hangdong Hospital is substantial, with over 5 million THB spent annually. DPI users incurred significantly higher outpatient (OPD) expenses than pMDI users. However, this OPD cost disadvantage was offset by DPI's superior performance in inpatient (IPD) settings, where pMDI users had higher costs per admission due to a greater incidence of respiratory failure (RF). When considering total expenditures, pMDIs were 15.3% more costly than DPIs, as their higher IPD burden outweighed OPD savings. This paradox—where DPI has higher per-visit OPD costs but lower overall system costs due to reduced severe complications—highlights the need for a risk-stratified inhaler selection strategy. DPI adoption for high-risk COPD patients (to prevent costly IPD admissions) should be prioritized, while pMDIs remain a viable option for stable, low-risk

patients in OPD settings. This approach balances short-term OPD savings with long-term IPD cost reductions. Additionally, enhanced patient training on proper inhaler use, early exacerbation detection through remote monitoring could further improve outcomes while controlling costs. By integrating these strategies, healthcare providers can minimize the economic burden of COPD while ensuring patient safety and treatment efficacy.

Chiang Mai faces a dual challenge in COPD management: high regional disease prevalence[1] driven by PM2.5 pollution [3], wildfires, industrial emissions, and widespread smoking—particularly hand-rolled cigarettes among the elderly—and elevated healthcare costs linked to exacerbations. This study highlights that 62% of COPD exacerbations occurred during the hazardous PM2.5 season, compared to only 38% in cleaner periods, emphasizing the critical role of environmental control alongside clinical interventions. While seasonal exacerbation rates were statistically similar, the sheer volume of PM2.5-associated cases demands urgent action to reduce air pollution exposure for vulnerable populations.

While pulmonary function tests (PFTs) remain the gold standard for COPD diagnosis[5,26], several important limitations affect their reliability and clinical utility. The ongoing debate about the optimal FEV1/FVC threshold - whether to use the fixed 0.7 ratio or LLN values - remains clinically relevant, as patients falling between these cutoffs still demonstrate significant risks of hospitalization and mortality.[26] Current PFT protocols may fail to identify approximately 10% of COPD cases that show structural changes on CT imaging, particularly in patients with significant FVC-VC gaps where airway collapse can produce misleadingly normal ratios.[26] The diagnostic challenge is further compounded by the dynamic nature of mild-to-moderate obstruction and the difficulty in recognizing certain at-risk conditions like PRISm, pre-COPD.[26-27] Adding to the complexity, about 32% of COPD patients demonstrate bronchodilator responsiveness, a finding traditionally associated with asthma.[26,28] While PFTs effectively establish airflow limitation, they provide limited guidance for treatment decisions as they cannot characterize patient symptoms or disease phenotypes.[5,26] The test's reliability also depends heavily on proper technique and operator experience[29], though when performed correctly, it remains an invaluable diagnostic tool. Emerging multimodal approaches that incorporate risk factors, symptoms, and imaging with spirometry - such as that proposed by Lowe et al.[30] - show promise, potentially increasing diagnostic accuracy by nearly 40% and addressing many of these limitations.

This study reflects the real-world challenges of COPD diagnosis and management in Chiang Mai's municipal hospitals, where PFT utilization remains suboptimal (an average of 22% in new

cases and 53% cumulatively in 2024)[6], despite encouragement. Multiple barriers contribute to this gap: resource limitations (inadequate trained personnel, equipment shortages) and communication difficulties (particularly with elderly patients). Our retrospective design in this resource-constrained setting - limited access to guideline-directed therapies like LABA/LAMA combinations and unavailable statistic supports - inherently carries limitations: potential diagnostic uncertainty without standardized PFTs, possible inclusion of undifferentiated respiratory conditions, and missing data. However, these constraints precisely document the realities of COPD care in provincial Thailand. The study provides crucial insights into: (1) clinical outcomes using Thailand's most accessible inhalers (pMDIs/DPIs), (2) the disproportionate impact of PM2.5 (62% of exacerbations occurring during pollution peaks), and (3) widespread inhaler technique deficiencies (55% error rate among assessed patients) - all under actual practice conditions where ideal diagnostics and treatments are often unavailable. These findings are particularly valuable for improving COPD management in similar resource-limited settings.

Future research is needed to strengthen the evidence base. Larger, well-controlled trials would help better assess inhaler device effectiveness and healthcare system impacts. However, such studies should also account for real-world constraints—such as limited diagnostic resources, variable patient adherence, and environmental factors—to ensure findings remain clinically applicable beyond idealized trial conditions. Bridging the gap between controlled research and actual clinical practice will be essential for optimizing COPD management in resource-limited settings.

Conclusion

Neither device was associated with an increased risk of exacerbations. Risk factors for severe exacerbations included a history of more than one severe exacerbation in the previous year, and LAMA use. The DPI use protect against respiratory failure (8.8% vs 25.6%) and 13% lower total costs than pMDI users. Environmental factors were significant, with 62% of exacerbations occurring during PM2.5 peaks. A tiered approach is recommended: DPIs for high-risk patients, pMDIs for stable cases, plus systemic improvements in training and pollution control.

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