

Review began 10/01/2026

Review ended 10/12/2026

Published 10/18/2026

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DOI: 10.7759/cureus.118091

Hospital-Recorded Maintenance Inhaler Coverage, Capsule-Based Dry-Powder Inhaler Technique Errors, and Prior-Year Chronic Obstructive Pulmonary Disease (COPD) Burden in Rural Nepal: A Retrospective Linked-Record Observational Study

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) remains a substantial clinical burden in Nepal. Effective inhaled maintenance therapy depends on consistent medication availability and correct inhaler technique. This study examined hospital-recorded maintenance inhaler coverage, capsule-based dry-powder inhaler technique errors, and their associations with prior-year COPD-related clinical burden in rural Nepal.

Materials and methods

This retrospective linked-record observational study included 208 adults aged ≥ 40 years with physician-confirmed COPD supported by previously documented post-bronchodilator spirometry. Hospital-recorded maintenance inhaler coverage, measured using the proportion of days covered (PDC), and COPD-related clinical outcomes were assessed over the same 365-day period preceding the index visit. Inhaler technique was evaluated once at the index visit using a standardized 10-step observational checklist before corrective retraining. Primary multivariable logistic regression analyses examined associations with frequent exacerbations, emergency department (ED) attendance, and hospitalization. Nested sensitivity analyses among 188 participants with index-date spirometry distinguished the effects of sample restriction from additional adjustment for forced expiratory volume in one second (FEV₁) percent predicted.

Results

Median hospital-recorded PDC was 76.7% (interquartile range (IQR), 59.2-89.0%), and 94 participants (45.2%) achieved PDC $\geq 80\%$. Completely correct inhaler technique was observed in 114 (54.8%) participants, while 50 (24.0%) demonstrated at least one critical technique error. Frequent exacerbations occurred in 78 (37.5%) participants, COPD-related ED attendance in 55 (26.4%), and COPD-related hospitalization in 38 (18.3%). In the primary adjusted analyses, each 10-percentage-point increase in PDC was associated with lower odds of frequent exacerbations (adjusted odds ratio (aOR) 0.77, 95% confidence interval (CI) 0.65-0.92; $p = 0.003$) and ED attendance (aOR 0.81, 95% CI 0.68-0.97; $p = 0.024$), but not hospitalization. Critical technique errors were not independently significant in the primary adjusted models. The PDC-ED association was attenuated after restriction to participants with available spirometry (aOR 0.87, 95% CI 0.72-1.05; $p = 0.152$) and changed minimally after FEV₁ adjustment (aOR 0.88, 95% CI 0.73-1.07; $p = 0.195$). In spirometry-restricted analyses, critical technique errors were associated with frequent exacerbations, although these exploratory findings differed from the primary full-cohort results.

Conclusions

Higher hospital-recorded maintenance inhaler coverage was associated with a lower prior-year frequent-exacerbation burden. The association with ED attendance was less consistent across sensitivity analyses, with attenuation occurring after sample restriction rather than additional FEV₁ adjustment. Critical inhaler-technique errors were not independently significant in the primary adjusted models, although associations were observed in restricted-sample analyses. Because medication coverage and clinical outcomes were assessed over the same retrospective period and inhaler technique was measured only at the index visit, temporal and causal relationships cannot be established. Hospital-recorded PDC reflects medication availability rather than confirmed inhaler use. Prospective studies are needed to clarify these associations

How to cite this article

K C A, Dangal B, Mahaseth A, et al. (October 18, 2026) Hospital-Recorded Maintenance Inhaler Coverage, Capsule-Based Dry-Powder Inhaler Technique Errors, and Prior-Year Chronic Obstructive Pulmonary Disease (COPD) Burden in Rural Nepal: A Retrospective Linked-Record Observational Study. Cureus 18(10): e118091. DOI 10.7759/cureus.118091

and their clinical implications.

Categories: Pulmonology, Epidemiology/Public Health, Internal Medicine

Keywords: chronic obstructive pulmonary disease, copd exacerbation, dry-powder inhaler, emergency department, hospitalization, inhaler technique, medication coverage, rural nepal

Introduction

Chronic obstructive pulmonary disease (COPD) remains a major cause of morbidity, mortality, disability, and healthcare utilization worldwide. Estimates from the Global Burden of Disease Study 2021 indicate a substantial and persistent COPD burden across 204 countries and territories, with marked geographic and socioeconomic inequalities in mortality and disability [1]. Nepal is particularly affected: a nationally representative population-based study reported a spirometry-defined COPD prevalence of 11.7%, with older age, lower educational attainment, heavy smoking, low body mass index, and geographic variation among the associated factors [2]. Contemporary Global Initiative for Chronic Obstructive Lung Disease guidance emphasizes both symptom reduction and prevention of future adverse events, particularly exacerbations [3].

Inhaled maintenance therapy is central to COPD management, but prescription alone does not guarantee effective pulmonary drug delivery. Two related but distinct processes matter: whether maintenance medication is consistently available over time and whether the patient uses the inhaler correctly. Pharmacy- or hospital-record-based measures such as the proportion of days covered (PDC) quantify medication availability but cannot establish whether doses were actually inhaled. In a large administrative claims study of 55,076 patients with COPD, higher PDC was associated with lower subsequent inpatient and emergency healthcare utilization [4]. Incorrect inhaler handling is another major barrier; a systematic review found that critical inhaler errors are associated with exacerbations, poorer disease outcomes, and greater healthcare-resource use [5]. These two dimensions of inhaled therapy should be evaluated separately because medication availability does not necessarily indicate correct administration, while technically correct inhaler use cannot compensate for periods when prescribed maintenance medication is unavailable.

The problem is especially relevant in Nepal and South Asia. In a regional Nepalese hospital, only 3.9% of patients with COPD performed all assessed dry-powder inhaler (DPI) steps correctly, although 77.5% correctly completed the critical steps; literacy and practical demonstration were associated with better technique [6]. At Chitwan Medical College, only 5.7% of patients with asthma or COPD demonstrated completely correct Rotahaler technique before intervention, increasing to 67.1% after pharmacist-led training [7]. A separate Nepalese COPD study showed that face-to-face training plus telephone reminders corrected inhaler technique in 90% of initially incorrect users [8], while a more recent pharmacist-led intervention at Dhulikhel Hospital improved both inhaler adherence and technique [9]. Medication adherence also remains suboptimal: a Patan Hospital study reported high adherence in only about one-third of COPD outpatients [10]. Although these studies highlight important deficiencies in inhaler use and demonstrate the potential value of patient education, they provide limited information on how objectively documented medication coverage and directly observed device-specific technique relate to COPD-related clinical burden.

Regional and international data reinforce the importance of training and technique. In India, correct inhaler use increased from 52.1% before training to 79.2% after structured instruction [11]. In contrast, a Pakistani COPD cohort admitted with exacerbations showed very low rates of entirely correct inhaler use [12]. Contemporary primary-care data from Sweden found that 45% of patients with spirometry-confirmed COPD made at least one inhaler error [13], and a large systematic review found correct technique in only about one-third of inhaler users overall [14]. Despite these findings, relatively little work in Nepal has evaluated hospital-recorded medication coverage and device technique together in relation to exacerbations, emergency care, and hospitalization. This evidence gap matters especially in rural healthcare settings, where hospital dispensing records and routine clinical assessments may complement each other in describing maintenance treatment. However, interpretation requires careful distinction between recorded medication availability, observed inhaler technique at a single clinical encounter, and clinical events occurring during an earlier observation period.

This study aimed to evaluate associations between hospital-recorded maintenance inhaler coverage, measured using the proportion of days covered (PDC), index-date capsule-based DPI technique errors, and COPD-related clinical burden among adults in rural Nepal. The principal clinical outcomes were frequent exacerbations, COPD-related emergency department (ED) attendance, and COPD-related hospitalization documented during the 365 days preceding the index visit. Hospital-recorded medication coverage was measured over the same retrospective period, whereas inhaler technique was assessed once at the index visit. Secondary and exploratory objectives evaluated a combined coverage-technique phenotype and tested whether inadequate prior-year PDC and an index-date critical technique error were associated with greater prior-year clinical burden. Additional sensitivity analyses examined the robustness of the observed associations, including the influence of restricting analyses to participants with index-date spirometry and subsequently adjusting for forced expiratory volume in one second (FEV₁) percent predicted. Because medication coverage and clinical outcomes were measured over the same retrospective period and inhaler

technique was assessed only at the index visit, the analyses were intended to describe associations rather than establish temporal, predictive, or causal relationships.

Materials And Methods

Study design and setting

This hospital-based retrospective analytical study used pre-existing patient-level records from Tsho-Rolpa General Hospital, Dolakha, Nepal. The hospital previously collected the source data as part of a COPD awareness and clinical assessment initiative conducted between Jestha 1, 2082 BS, and Poush 30, 2082 BS (May 15, 2025 to January 14, 2026). These data had been recorded in the hospital system before the present study was conceived.

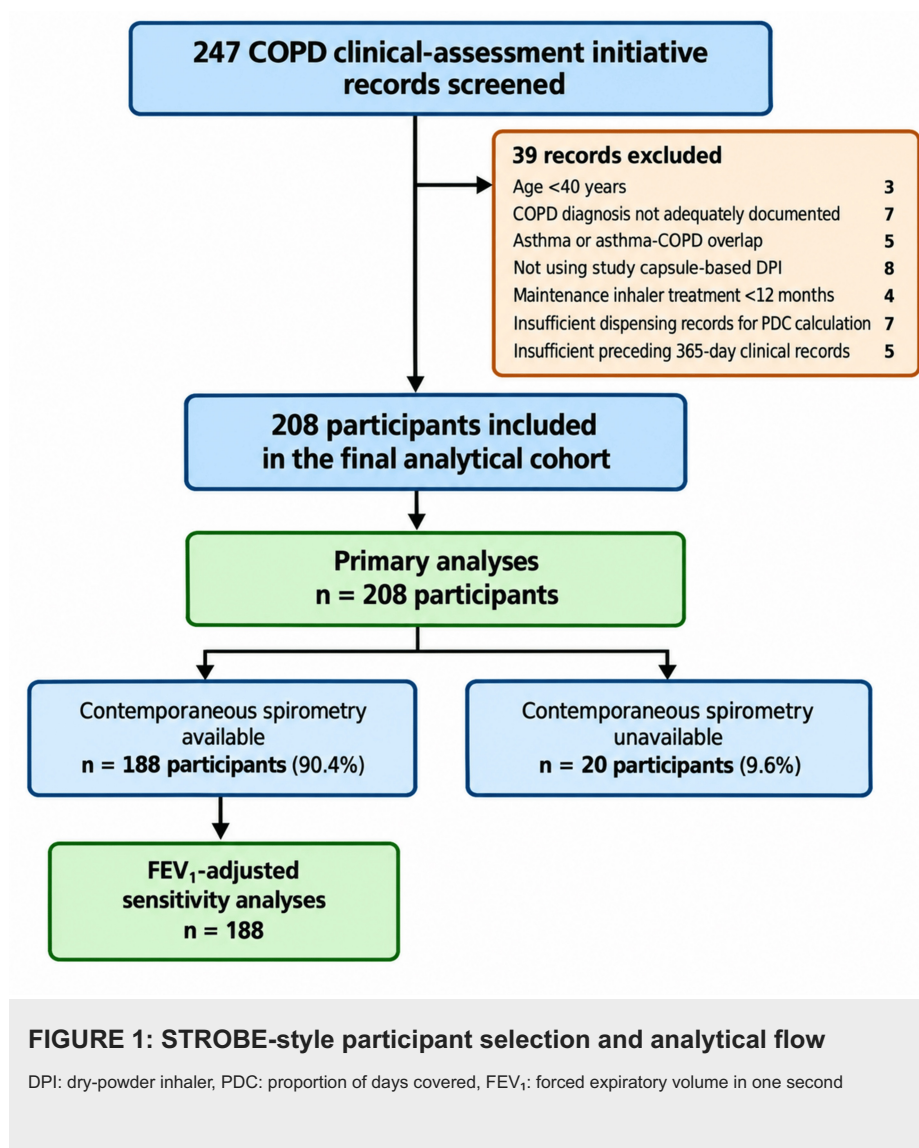
For the present study, no new participant recruitment, interview, clinical examination, inhaler demonstration, intervention, or prospective follow-up was undertaken. Following approval from the Ethical Review Board of the Nepal Health Research Council (NHRC), the investigators retrospectively extracted and analyzed the relevant pre-existing hospital records. All eligible records meeting the predefined study criteria during the source clinical-assessment period were included. The original clinical-assessment initiative and the subsequent retrospective research analysis were distinct activities.

Participants and eligibility criteria

Adults attending the COPD clinical-assessment initiative at Tsho-Rolpa General Hospital during the predefined study period were screened for eligibility. Participants were eligible if they were aged 40 years or older, had an established physician diagnosis of COPD, had been receiving maintenance inhaled treatment through a capsule-based DPI for at least 12 months before the index date, and had sufficient hospital dispensing and clinical records covering the complete 365-day period preceding the index assessment.

Patients were excluded if they were younger than 40 years, did not have adequate documentation supporting the diagnosis of COPD, had asthma without COPD or documented asthma-COPD overlap, were using only a non-capsule inhaler device, had received maintenance inhaler therapy for less than 12 months, lacked sufficient dispensing information to calculate the PDC, or did not have adequate clinical records for ascertainment of outcomes during the preceding 365 days. Patients using pressurized metered-dose inhalers, soft-mist inhalers, or other devices without concurrent use of the capsule-based DPI evaluated in the study were excluded because the inhaler-technique checklist was specific to the capsule-based DPI.

A total of 247 patient records from the COPD clinical-assessment initiative were screened. Thirty-nine records were excluded: three because the patients were younger than 40 years, seven because the COPD diagnosis was not adequately supported by the available records, five because asthma or asthma-COPD overlap was documented, eight because the patients were not using the capsule-based DPI evaluated in the study, four because maintenance inhaler therapy had been used for less than 12 months, seven because dispensing records were insufficient for calculation of PDC, and five because the preceding 365-day clinical record was insufficient for reliable outcome ascertainment. The remaining 208 participants constituted the final analytical cohort (Figure 1).



COPD diagnosis and eligibility confirmation

COPD eligibility required a previously documented physician diagnosis of COPD supported by evidence of persistent airflow obstruction on post-bronchodilator spirometry, defined as an FEV₁/FVC ratio <0.70. The diagnosis was verified from the existing hospital record before inclusion in the analytical cohort. Patients with asthma without COPD and those with a documented diagnosis of asthma-COPD overlap were excluded.

All 208 participants therefore had an established diagnosis of COPD before entry into the present retrospective analysis. Index-date spirometric measurements were available for 188 participants (90.4%). The remaining 20 participants did not have index-date spirometric measurements available but had previously documented physician-confirmed COPD supported by qualifying spirometry in their medical records. These participants remained eligible for the primary analyses, whereas analyses incorporating FEV₁ percent predicted were restricted to the 188 participants with index-date spirometric data. Thus, the absence of index-date spirometry did not indicate an absence of prior diagnostic spirometric confirmation.

Index date and retrospective observation window

For each participant, the index date was defined as the date of the COPD clinical-assessment initiative visit. Hospital-recorded maintenance inhaler coverage and clinical outcomes were ascertained for the 365 days immediately preceding the index date. PDC therefore represented medication coverage during the same retrospective 12-month period in which exacerbations, COPD-related ED visits, and hospitalizations were recorded. Inhaler technique was assessed once at the index visit and was not measured repeatedly during the preceding observation period.

Because medication coverage and clinical outcomes were measured over the same retrospective period, the study could not establish whether changes in medication coverage preceded or followed individual clinical events. Similarly, index-date inhaler technique could not be assumed to represent technique throughout the

preceding year. Accordingly, the analyses examined associations with prior-year clinical burden rather than establishing temporal, predictive, or causal relationships.

Data sources and study variables

Variables included age, sex, educational status, smoking status and pack-years, COPD duration, comorbidities, maintenance inhaler regimen, duration of maintenance inhaler use, prior inhaler-technique training, hospital-recorded medication coverage, device-specific inhaler technique, COPD exacerbations during the preceding 12 months, ED visits, hospitalization, intensive care admission, systemic steroid- and antibiotic-treated exacerbations, home oxygen use, peripheral oxygen saturation, and spirometric measures when available.

Spirometric variables included FEV₁ in liters, FEV₁ percent predicted, and the FEV₁/forced vital capacity ratio. Index-date spirometry was available for 188 of 208 participants; the remaining 20 were eligible because their medical records included qualifying prior spirometry documenting COPD.

Participant-level dispensing, clinical, spirometry, and inhaler-technique information were linked within the existing hospital record before the creation of the de-identified analytical dataset. The analysis was limited to information documented in the available records and did not infer undocumented medication acquisition or clinical events. No additional participant assessment or prospective data collection was undertaken for the present research.

Hospital-recorded maintenance inhaler coverage

Maintenance inhaler coverage was determined from hospital dispensing records during the 365 days immediately preceding the index date. For each maintenance inhaler, covered treatment days associated with each dispensing episode were calculated from the quantity dispensed and the prescribed daily dosing frequency. For example, dispensing 30 capsules for a once-daily maintenance inhaler contributed 30 covered days.

When a maintenance inhaler was refilled before the previous supply was expected to be exhausted, the remaining supply was carried forward so overlapping refills did not double-count covered days. Therefore, each calendar day could contribute no more than one covered day for a given prescribed component. When the prescribed maintenance regimen changed during the observation period, coverage for the previous regimen was counted up to the documented treatment-switch date, and subsequent coverage was calculated according to the new regimen. Temporary changes in brand or formulation were considered continuous treatment when they represented the same intended maintenance pharmacological component.

For participants prescribed more than one maintenance inhaler, a calendar day was considered fully covered only when all components of the prescribed maintenance regimen required on that day were available according to the hospital dispensing record. All included participants had received maintenance inhaler treatment for at least 12 months before the index date and had sufficient dispensing records to assess the full 365-day observation period. The PDC denominator was therefore 365 eligible observation days for each participant. PDC reflected coverage of the full prescribed maintenance regimen, not only the capsule-based DPI used for the technique demonstration.

PDC was calculated as the number of covered days during the preceding 365 days divided by 365 and multiplied by 100. Values were capped at 100%, so accumulated or early refills could not produce coverage greater than 100%. PDC was analyzed continuously per 10-percentage-point increase in the primary regression models and categorized as <50%, 50–79%, and ≥80% for descriptive and secondary analyses. PDC ≥80% was considered adequate hospital-recorded coverage.

Days spent in hospital were retained within the 365-day denominator because the analysis characterized medication availability over the complete observation period rather than self-administered inhaler use exclusively outside the hospital. Medication dispensed or supplied outside Tsho-Rolpa General Hospital could not be systematically captured and therefore did not contribute to the calculated PDC.

Hospital-recorded PDC was interpreted as an indirect measure of prescribed maintenance medication availability rather than confirmed adherence, medication consumption, or effective inhalation. Lower recorded coverage could reflect medication acquisition outside the study hospital rather than actual interruption of treatment. Because medication coverage and clinical events were assessed over the same retrospective period, the possibility of changes in dispensing patterns following acute clinical events could not be excluded.

Inhaler-technique assessment

Inhaler technique was assessed at the index visit using the participant's usual Respirer single-dose capsule-based DPI, in which a capsule is inserted into the device, pierced or activated, and subsequently inhaled forcefully through the device. All participants included in the technique analysis were regular users of this

device class. The source initiative identified the inhaler at the Respirer capsule-DPI level; exact submodel details were not retained in the analytical dataset. The device-specific technique analysis excluded patients using only pressurized metered-dose inhalers, soft-mist inhalers, or other non-capsule inhaler devices.

Participants were asked to demonstrate how they normally used their inhaler, using their own device whenever available. When needed, the participant used a demonstration capsule without active medication to complete the full sequence, including capsule insertion, piercing, inhalation, checking for residual powder, and repeat inhalation when appropriate. Each participant completed one uninterrupted demonstration while the assessor observed and recorded each step as correct or incorrect.

The clinical team at Tsho-Rolpa General Hospital developed a standardized 10-step direct-observation checklist before the COPD clinical-assessment initiative to evaluate inhaler technique. The checklist assessed the essential procedural steps for correct operation of the Respirer capsule-based DPI. The 10 assessed steps were device preparation/opening, capsule insertion, capsule piercing/activation, exhalation before inhalation, avoidance of exhalation into the device, adequate lip seal, forceful/deep inhalation, breath-holding after inhalation, checking for residual powder, and repeating inhalation when residual powder remained. Completely correct inhaler technique required correct performance of all 10 steps. The checklist was established before the present retrospective analysis and was not modified after examination of clinical outcomes.

For the final checklist item, repeating inhalation when necessary was scored as correct when the participant repeated inhalation appropriately if residual powder remained in the capsule or when repeat inhalation was unnecessary because no residual powder remained. Failure to repeat inhalation despite residual powder being present, or incorrect performance of a required repeat inhalation, was scored as incorrect. This conditional scoring convention was applied consistently to all participants.

Four steps were designated as critical based on their potential to substantially compromise pulmonary drug delivery if performed incorrectly: capsule piercing/activation, avoidance of exhalation into the device, adequate lip seal, and forceful/deep inhalation. A critical inhaler-technique error was defined as incorrect performance of at least one of these four steps. The original clinical-assessment initiative established the critical-step classification and did not determine it retrospectively based on associations with clinical outcomes.

Before the initiative, clinical staff received standardized instruction on device operation and checklist-based assessment, and the same checklist and assessment criteria were applied to all participants. The technique was scored before any corrective instruction, demonstration, or retraining at the index visit. After completing and recording the initial assessment, participants with technique errors received appropriate education and demonstration as part of routine clinical care.

The locally developed checklist had not undergone separate formal validation. Adequacy of forceful/deep inhalation was judged through clinical observation rather than objective peak inspiratory-flow measurement. Formal inter-rater reliability testing and objective inspiratory-flow measurement were not documented in the available retrospective records. These limitations were considered when interpreting associations between technique errors and clinical outcomes.

Assessors conducted routine clinical assessments and may have been aware of aspects of participants' medical histories. Formal blinding to previous exacerbations, emergency visits, or COPD-related hospitalizations was therefore not guaranteed. However, assessors completed the technique assessments before the present retrospective analysis was conceived, and analytical classifications were based on scores already documented in hospital records. Observer-related measurement bias could not be excluded.

Because technique was assessed only once at the index visit, it was treated as a contemporaneously documented clinical characteristic rather than a measure of technique over the preceding 365 days. Associations with prior-year clinical events were not interpreted as evidence that the observed errors preceded or caused those events.

For participants prescribed multiple maintenance inhalers, the technique classification referred only to the Respirer capsule-based DPI demonstrated at the index visit. It did not characterize technique for additional inhaler devices that might have formed part of the prescribed maintenance regimen. Thus, PDC represented availability of all prescribed maintenance components, whereas the observed technique measure was device-specific.

Exploratory combined coverage-technique phenotype

As an exploratory analysis, participants were classified into four mutually exclusive groups: adequate PDC with no critical error, adequate PDC with a critical error, inadequate PDC with no critical error, and inadequate PDC with a critical error. The first group was used as the reference category in phenotype-based regression models.

The combined phenotype characterized the coexistence of prior-year medication coverage and index-date inhaler-technique status. Because these measurements represented different time frames and some groups were small, the analyses were interpreted as exploratory descriptions of prior-year clinical burden rather than as validated risk stratification or prediction of future outcomes. Associations between phenotype groups and clinical outcomes were considered hypothesis-generating and were not interpreted as evidence of a causal relationship.

Outcomes

The principal outcomes were ascertained during the 365 days immediately preceding the index date and included frequent COPD exacerbations (defined as at least two separately recorded exacerbation episodes during that period), at least one COPD-related ED visit, and at least one COPD-related hospitalization.

For record abstraction, a COPD exacerbation was defined as a separately dated episode documented by the treating clinical team as an acute COPD exacerbation or acute COPD-related respiratory worsening. ED visits and hospitalizations were classified as COPD-related when the corresponding encounter or admission documentation identified COPD exacerbation or COPD-related respiratory deterioration as the reason for acute care. Multiple entries referring to the same continuous clinical episode, emergency encounter, or hospital admission were treated as a single event to avoid duplicate counting.

Outcome classification relied on the treating clinical team's documented assessment and the corresponding hospital encounter or admission records. The available retrospective analytical records documented no separate, independent outcome-adjudication procedure. Therefore, outcome classification accuracy depended on the completeness and reliability of the original clinical documentation.

Outcome ascertainment relied on available Tsho-Rolpa General Hospital records. Events occurring at another healthcare facility could be included only if the study hospital subsequently documented them. Events managed elsewhere and never recorded in the available hospital system could not be captured. Accordingly, the recorded event frequencies represented hospital-documented clinical burden and may have underestimated the total number of clinical events occurring during the observation period.

Additional descriptive outcomes included any exacerbation, exacerbation count, ED visit count, hospitalization count, intensive care admission, systemic steroid-treated exacerbation, antibiotic-treated exacerbation, home oxygen use, peripheral oxygen saturation, and spirometric indices.

Statistical analysis

Continuous variables were assessed for normality using the Shapiro-Wilk test together with review of their distributions within the relevant comparison groups, where group-specific output was available. Normally distributed variables were summarized as mean $\pm$ standard deviation and compared using the independent-samples t-test or Welch t-test, as appropriate. Non-normally distributed variables were summarized as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Comparisons involving more than two groups were performed using one-way analysis of variance or the Kruskal-Wallis test according to the underlying distribution. Categorical variables were summarized as frequencies and percentages and compared using the Pearson chi-square test or Fisher exact test when expected cell counts were small. Corresponding numerical test statistics were reported for inferential comparisons, including t, U, χ^2 , or F statistics, as applicable.

Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for key binary associations. Multivariable logistic regression models were constructed for inadequate hospital-recorded coverage, critical inhaler-technique error, frequent exacerbation, COPD-related ED attendance, and COPD-related hospitalization.

The primary clinical-outcome models used the same clinically selected adjustment set comprising PDC per 10-percentage-point increase, critical technique error, age, sex, current smoking, COPD duration, and any recorded comorbidity. No data-driven stepwise variable-selection procedure was used. The full-cohort models were considered the primary adjusted analyses, whereas spirometry-restricted models, categorical PDC comparisons, interaction analyses, and combined-phenotype models were considered secondary or exploratory.

All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistically significant p-values were denoted by an asterisk in the relevant tables. No formal adjustment for multiple comparisons was performed. Secondary and exploratory analyses were interpreted primarily using effect estimates, CIs, subgroup sizes, and consistency with the primary models rather than statistical significance alone. All analyses were performed using SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY).

Additional sensitivity analyses compared participants with and without index-date spirometry. Continuous

or ordinal variables were compared using independent-samples t-tests or Mann-Whitney U tests, as appropriate, whereas categorical variables were compared using Pearson chi-square or Fisher exact tests.

Because only 20 participants lacked index-date spirometry, univariable logistic regression was used to explore characteristics associated with spirometry unavailability rather than fitting a high-dimensional missingness model. Potential effect modification by spirometry availability was explored using PDC-by-spirometry-availability and critical-error-by-spirometry-availability interaction terms. These analyses were considered exploratory because the small spirometry-unavailable subgroup limited the precision and stability of interaction estimates.

To assess the robustness of the assumed linear PDC effect, the principal outcome models were repeated using categorized PDC values of <50%, 50–79%, and ≥80%, with ≥80% as the reference category and the same clinical adjustment set used in the primary models. These analyses aimed to assess the consistency of the continuous PDC findings rather than establish validated medication-coverage thresholds.

Study size, missing data, linkage, and model diagnostics

All eligible records meeting the predefined study criteria during the source clinical-assessment period were included. No a priori sample-size calculation was performed because the study used the complete set of available eligible records. The sample size was therefore determined by the number of records satisfying the eligibility criteria rather than a prospectively specified statistical power requirement.

Variables included in the primary models were complete for all 208 participants. Index-date spirometry was unavailable for 20 participants. No imputation was performed, and analyses incorporating FEV₁ percent predicted were restricted to complete cases comprising 188 participants.

To distinguish the effect of restricting the analysis to participants with available spirometry from that of additional adjustment for lung function, sensitivity analyses involving the 188 participants with index-date spirometry were performed in two nested stages. Model B repeated the primary covariate set in the restricted sample without adjustment for FEV₁ percent predicted. Model C then added FEV₁ percent predicted to the same model.

Comparison of the primary full-cohort model with Model B was used to evaluate the influence of sample restriction, whereas comparison of Models B and C assessed the additional influence of FEV₁ adjustment within an identical analytical sample. Because FEV₁ was measured at the index assessment after the retrospective 365-day outcome window, it was treated as a contemporaneous marker of disease severity rather than as a strictly pre-outcome confounder.

Multicollinearity was assessed among predictors included in the primary models. Variance-inflation factors ranged from 1.04 to 1.11, indicating no important multicollinearity in the analytical dataset. The primary and prespecified nested logistic regression models converged without complete separation.

Because only 38 participants experienced COPD-related hospitalization, the number of events was limited relative to the number of parameters estimated in the full multivariable model. Consequently, the hospitalization model was considered potentially vulnerable to overfitting, sparse-data bias, and imprecise effect estimation. A reduced hospitalization sensitivity model retaining PDC, critical technique error, age, and current smoking was examined to assess the qualitative stability of the associations.

Hospitalization-related adjusted findings, including the exploratory combined-phenotype analysis, were therefore interpreted cautiously rather than as definitive evidence of independent effects.

One exploratory PDC-by-spirometry-availability interaction model for ED attendance did not converge and was not interpreted. Penalized or exact logistic regression was not used in the available analytical workflow. Failure of the exploratory model to converge was considered a limitation of estimation rather than evidence of the absence of an interaction.

Because PDC and the principal clinical outcomes were measured over the same retrospective 365-day period, while inhaler technique was assessed only at the index visit, all regression estimates were interpreted as associations with prior-year clinical burden rather than prospective or causal risk estimates.

Ethical considerations

This study involved human participants through retrospective secondary analysis of pre-existing hospital records. The Ethical Review Board of the NHRC, Government of Nepal, reviewed and approved the protocol through the expedited review process (Protocol Registration No. 263_2026; Ref. No. 2033; approval date: June 15, 2026; valid through June 14, 2027).

Tsho-Rolpa General Hospital previously collected and recorded the source data as part of a COPD awareness

and clinical assessment initiative, and the data were already in the hospital system before the present study began. This study involved only a retrospective analysis of these existing records, with no new participant recruitment, interviews, examinations, inhaler-technique demonstrations, interventions, or prospective follow-up.

The analytical dataset was de-identified before analysis, and results were reported only in aggregate form. The NHRC Ethical Review Board waived the requirement for individual informed consent for this retrospective analysis because the study used pre-existing, de-identified records and involved no additional participant contact.

Results

Participant characteristics

A total of 247 COPD clinical-assessment initiative records were screened; 39 were excluded according to the prespecified eligibility criteria, leaving 208 participants in the final analytical cohort. The mean age was 66.4 ± 9.3 years, 128 (61.5%) participants were male, and 124 (59.6%) had at least one recorded comorbidity. Former smokers accounted for 95 participants (45.7%) and current smokers for 76 (36.5%). Median COPD duration was 5.5 years (IQR 3.0–9.0 years). Index-date spirometry was available for 188 (90.4%) participants; mean FEV₁ was 1.22 ± 0.28 L, mean FEV₁ percent predicted was $57.4 \pm 8.8\%$, and median FEV₁/FVC was 0.65 (IQR 0.63–0.67). Table 1 summarizes baseline demographic, clinical, and spirometric characteristics.

Characteristic	Category	Result
Age group	40-59 years	48 (23.1%)
	60-69 years	83 (39.9%)
	70-79 years	61 (29.3%)
	≥80 years	16 (7.7%)
Sex	Male	128 (61.5%)
	Female	80 (38.5%)
Education	No formal education	68 (32.7%)
	Primary education	86 (41.3%)
	Secondary or higher	54 (26.0%)
Smoking status	Never smoker	37 (17.8%)
	Former smoker	95 (45.7%)
	Current smoker	76 (36.5%)
Hypertension	Yes	61 (29.3%)
Diabetes mellitus	Yes	38 (18.3%)
Cardiovascular disease	Yes	38 (18.3%)
Previous pulmonary tuberculosis	Yes	23 (11.1%)
Any recorded comorbidity	Yes	124 (59.6%)
Age, years	-	66.4 ± 9.3
Pack-years	-	22.5 (10.0-32.0)
COPD duration, years	-	5.5 (3.0-9.0)
SpO ₂ , %	-	94.6 ± 1.2
FEV ₁ , L	-	1.22 ± 0.28
FEV ₁ , % predicted	-	57.4 ± 8.8
FEV ₁ /FVC ratio	-	0.65 (0.63-0.67)

TABLE 1: Baseline demographic, clinical, and spirometric characteristics

Data are n (%) unless otherwise stated. Normally distributed continuous variables are summarized as mean ± SD and non-normally distributed variables as median (IQR). Spirometric variables are based on the 188 participants with index-date spirometry; all other characteristics are based on n = 208.

FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, SpO₂: peripheral oxygen saturation, SD: standard deviation, IQR: interquartile range

Maintenance inhaler coverage and inhaler technique

LABA + LAMA was the most frequently recorded maintenance regimen, used by 80 (38.5%) participants, followed by LABA + LAMA + ICS in 48 (23.1%). Previous inhaler-technique training was documented in 143 (68.8%) participants. Median hospital-recorded PDC was 76.7% (IQR 59.2-89.0%), and 94 (45.2%) participants had PDC ≥80%. Completely correct inhaler technique was observed in 114 (54.8%) participants, whereas 94 (45.2%) made at least one technique error and 50 (24.0%) made at least one critical technique error. The most frequent individual errors were forceful/deep inhalation in 25 (12.0%) participants, repeating inhalation when needed in 23 (11.1%), exhalation before inhalation in 20 (9.6%), and checking for residual powder in 20 (9.6%). Table 2 presents findings on maintenance treatment, coverage, and inhaler technique.

Variable	Category	Result
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Maintenance regimen	LAMA	40 (19.2%)
	LABA + LAMA	80 (38.5%)
	LABA + ICS	35 (16.8%)
	LABA + LAMA + ICS	48 (23.1%)
	Other	5 (2.4%)
PDC category	<50%	22 (10.6%)
	50-79%	92 (44.2%)
	≥80%	94 (45.2%)
Multiple maintenance inhalers	Yes	53 (25.5%)
Previous inhaler-technique training	Yes	143 (68.8%)
Adequate PDC ≥80%	Yes	94 (45.2%)
Maintenance inhaler duration, months	-	30.0 (18.0-42.2)
Hospital-recorded PDC, %	-	76.7 (59.2-89.0)
Device preparation/opening	Correct	196 (94.2%)
	Incorrect	12 (5.8%)
Capsule insertion	Correct	201 (96.6%)
	Incorrect	7 (3.4%)
Capsule piercing/activation	Correct	198 (95.2%)
	Incorrect	10 (4.8%)
Exhalation before inhalation	Correct	188 (90.4%)
	Incorrect	20 (9.6%)
Avoided exhalation into device	Correct	197 (94.7%)
	Incorrect	11 (5.3%)
Adequate lip seal	Correct	197 (94.7%)
	Incorrect	11 (5.3%)
Forceful/deep inhalation	Correct	183 (88.0%)
	Incorrect	25 (12.0%)
Breath hold after inhalation	Correct	191 (91.8%)
	Incorrect	17 (8.2%)
Checked residual powder	Correct	188 (90.4%)
	Incorrect	20 (9.6%)
Repeated inhalation if needed	Correct	185 (88.9%)
	Incorrect	23 (11.1%)
Completely correct inhaler technique	Correct	114 (54.8%)
	Incorrect	94 (45.2%)
Any technique error	Present	94 (45.2%)
Any critical technique error	Present	50 (24.0%)
Number of technique errors	Median, IQR	0.0 (0.0-1.0)

TABLE 2: Maintenance inhaler treatment, hospital-recorded coverage, and inhaler technique

Hospital-recorded PDC represents medication coverage recorded by the hospital and not confirmed medication use.

PDC: proportion of days covered, LAMA: long-acting muscarinic antagonist, LABA: long-acting beta2-agonist, ICS: inhaled corticosteroid, IQR: interquartile range

Clinical outcomes

During the 365-day retrospective outcome window preceding the index date, 132 (63.5%) participants had at least one exacerbation and 78 (37.5%) had frequent exacerbations, defined as two or more events. COPD-related ED attendance occurred in 55 (26.4%) participants, COPD-related hospitalization in 38 (18.3%), and ICU admission in eight (3.8%). Systemic steroid-treated exacerbations occurred in 95 (45.7%) participants and antibiotic-treated exacerbations in 62 (29.8%). Table 3 summarizes these outcomes.

Outcome	Result
Any exacerbation	132 (63.5%)
Frequent exacerbation ≥2	78 (37.5%)
COPD-related ED visit	55 (26.4%)
COPD-related hospitalization	38 (18.3%)
ICU admission	8 (3.8%)
Systemic steroid-treated exacerbation	95 (45.7%)
Antibiotic-treated exacerbation	62 (29.8%)
Home oxygen use	6 (2.9%)
Spirometry available	188 (90.4%)
COPD exacerbations in the previous 12 months	1.0 (0.0-2.0)
COPD-related ED visits in the previous 12 months	0.0 (0.0-1.0)
COPD-related hospitalizations in the previous 12 months	0.0 (0.0-0.0)

TABLE 3: Clinical outcomes during the preceding 12 months

Count variables are presented as the median (IQR).

ED: emergency department, ICU: intensive care unit, IQR: interquartile range

Unadjusted associations of coverage and technique with outcomes

Adequate PDC (≥80%) was associated with lower odds of frequent exacerbations during the same preceding 12-month period (OR 0.50, 95% CI 0.28-0.89; p = 0.018). Associations with ED attendance (OR 0.55, 95% CI 0.29-1.04; p = 0.064) and hospitalization (OR 0.66, 95% CI 0.32-1.35; p = 0.253) were not statistically significant.

An index-date critical technique error was associated with frequent exacerbations (OR 2.46, 95% CI 1.29-4.71; p = 0.006), ED attendance (OR 2.34, 95% CI 1.19-4.62; p = 0.013), and hospitalization (OR 2.52, 95% CI 1.19-5.32; p = 0.014). Critical technique errors occurred in 16 of 94 (17.0%) participants with adequate PDC compared with 34 of 114 (29.8%) participants with inadequate PDC (OR 0.48, 95% CI 0.25-0.94; p = 0.032). Table 4 presents these associations.

Exposure	Outcome	Exposure absent	Exposure present	OR (95% CI)	p-value
Adequate PDC ≥80%	Frequent exacerbation	51 (44.7%)	27 (28.7%)	0.50 (0.28-0.89)	0.018*
Adequate PDC ≥80%	ED visit	36 (31.6%)	19 (20.2%)	0.55 (0.29-1.04)	0.064
Adequate PDC ≥80%	Hospitalization	24 (21.1%)	14 (14.9%)	0.66 (0.32-1.35)	0.253
Critical technique error	Frequent exacerbation	51 (32.3%)	27 (54.0%)	2.46 (1.29-4.71)	0.006*
Critical technique error	ED visit	35 (22.2%)	20 (40.0%)	2.34 (1.19-4.62)	0.013*
Critical technique error	Hospitalization	23 (14.6%)	15 (30.0%)	2.52 (1.19-5.32)	0.014*
Adequate PDC ≥80%	Critical technique error	34 (29.8%)	16 (17.0%)	0.48 (0.25-0.94)	0.032*

TABLE 4: Unadjusted associations of adequate coverage and critical technique error with major outcomes

* Statistically significant at $p < 0.05$.

OR: odds ratio, CI: confidence interval, PDC: proportion of days covered, ED: emergency department

Characteristics associated with major clinical outcomes

Participants with frequent exacerbations had a lower median PDC (67.5% versus 80.2%; $p < 0.001$), a higher median technique-error count (1.0 versus 0.0; $p < 0.001$), lower FEV₁ (1.10 versus 1.29 L; $p = 0.008$), and a lower mean FEV₁ percent predicted (54.8% versus 58.9%; $p = 0.005$). Mean SpO₂ was 94.4% versus 94.7% ($p = 0.050$). Table 5 presents detailed comparisons.

Variable	<2 exacerbations	≥2 exacerbations	Statistical test	Test statistic	p-value
Hospital-recorded PDC, %	80.2 (64.1-90.0)	67.5 (51.8-84.0)	Mann-Whitney U	U = 3623.0	<0.001*
Number of inhaler-technique errors	0.0 (0.0-1.0)	1.0 (0.0-2.0)	Mann-Whitney U	U = 3553.5	<0.001*
Age, years	65.6 ± 9.6	67.7 ± 8.8	Independent t-test	t = -1.512	0.132
Pack-years	21.0 (10.0-29.0)	24.0 (10.5-34.0)	Mann-Whitney U	U = 4560.5	0.224
COPD duration, years	5.0 (3.0-8.0)	6.0 (4.0-9.0)	Mann-Whitney U	U = 4531.0	0.198
Maintenance inhaler duration, months	30.5 (17.0-42.8)	29.5 (21.0-41.5)	Mann-Whitney U	U = 5066.0	0.993
SpO ₂ , %	94.7 ± 1.1	94.4 ± 1.3	Independent t-test	t = 1.974	0.050
FEV ₁ , L	1.29 (1.06-1.46)	1.10 (0.97-1.29)	Mann-Whitney U	U = 3104.0	0.008*
FEV ₁ , % predicted	58.9 ± 7.5	54.8 ± 10.1	Welch t-test	t = 2.895	0.005*
FEV ₁ /FVC ratio	0.65 (0.63-0.67)	0.65 (0.62-0.68)	Mann-Whitney U	U = 3788.0	0.455

TABLE 5: Clinical and treatment characteristics according to frequent exacerbation status

* Statistically significant at $p < 0.05$.

PDC: proportion of days covered, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, SpO₂: peripheral oxygen saturation

Participants with COPD-related ED attendance had lower median PDC (68.4% versus 79.0%; $p = 0.010$), a higher median technique-error count (1.0 versus 0.0; $p = 0.002$), lower mean SpO₂ (94.2% versus 94.8%; $p = 0.004$), lower mean FEV₁ (1.14 versus 1.25 L; $p = 0.022$), and lower mean FEV₁ percent predicted (54.3% versus 58.5%; $p = 0.003$). Table 6 presents detailed comparisons.

Variable	No ED visit	ED visit	Statistical test	Test statistic	p-value
Hospital-recorded PDC, %	79.0 (61.7-89.9)	68.4 (53.4-85.2)	Mann-Whitney U	U = 3215.5	0.010*
Number of inhaler-technique errors	0.0 (0.0-1.0)	1.0 (0.0-1.5)	Mann-Whitney U	U = 3142.0	0.002*
COPD exacerbations in previous 12 months	1.0 (0.0-1.0)	3.0 (1.5-3.0)	Mann-Whitney U	U = 1228.5	<0.001*
Age, years	65.7 ± 9.6	68.3 ± 8.4	Independent t-test	t = -1.783	0.076
Pack-years	22.0 (9.0-30.0)	25.0 (12.0-33.5)	Mann-Whitney U	U = 3759.5	0.241
COPD duration, years	5.0 (3.0-9.0)	6.0 (3.0-9.0)	Mann-Whitney U	U = 4101.5	0.782
SpO ₂ , %	94.8 ± 1.1	94.2 ± 1.3	Independent t-test	t = 2.904	0.004*
FEV ₁ , L	1.25 ± 0.29	1.14 ± 0.27	Independent t-test	t = 2.316	0.022*
FEV ₁ , % predicted	58.5 ± 8.0	54.3 ± 10.0	Independent t-test	t = 2.971	0.003*
FEV ₁ /FVC ratio	0.65 (0.63-0.68)	0.65 (0.63-0.67)	Mann-Whitney U	U = 3371.0	0.711

TABLE 6: Clinical and treatment characteristics according to COPD-related ED attendance

* Statistically significant at p < 0.05.

ED: emergency department, PDC: proportion of days covered, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, SpO₂: peripheral oxygen saturation

Hospitalized participants had a lower median PDC (68.2% versus 77.8%; p = 0.013), more technique errors (1.0 versus 0.0; p < 0.001), and were older (69.9 ± 7.4 versus 65.6 ± 9.6 years; p = 0.003). They also had lower mean FEV₁, lower mean FEV₁ percent predicted, and lower median FEV₁/FVC. Mean SpO₂ did not differ significantly between groups. Table 7 presents detailed comparisons. Figure 2 shows the distribution of hospital-recorded PDC across the three major clinical outcomes.

Variable	No hospitalization	Hospitalization	Statistical test	Test statistic	p-value
Hospital-recorded PDC, %	77.8 (61.5-90.0)	68.2 (51.8-81.4)	Mann-Whitney U	U = 2398.5	0.013*
Number of inhaler-technique errors	0.0 (0.0-1.0)	1.0 (0.0-2.8)	Mann-Whitney U	U = 1981.5	<0.001*
COPD exacerbations in previous 12 months	1.0 (0.0-2.0)	3.0 (2.0-4.0)	Mann-Whitney U	U = 840.5	<0.001*
Age, years	65.6 ± 9.6	69.9 ± 7.4	Welch t-test	t = -3.047	0.003*
Pack-years	22.0 (9.2-32.0)	25.5 (12.5-29.8)	Mann-Whitney U	U = 2830.5	0.233
COPD duration, years	5.5 (3.0-8.0)	5.5 (4.0-9.0)	Mann-Whitney U	U = 3014.0	0.519
Maintenance inhaler duration, months	30.0 (18.0-42.8)	28.0 (20.5-41.5)	Mann-Whitney U	U = 3183.5	0.891
SpO ₂ , %	94.7 ± 1.2	94.4 ± 1.3	Independent t-test	t = 1.435	0.153
FEV ₁ , L	1.26 ± 0.28	1.05 ± 0.25	Independent t-test	t = 3.787	<0.001*
FEV ₁ , % predicted	58.8 ± 7.8	50.3 ± 9.8	Independent t-test	t = 5.295	<0.001*
FEV ₁ /FVC ratio	0.66 (0.63-0.68)	0.63 (0.62-0.66)	Mann-Whitney U	U = 1677.0	0.006*

TABLE 7: Clinical and treatment characteristics according to COPD-related hospitalization

* Statistically significant at p < 0.05.

PDC: proportion of days covered, FEV₁: forced expiratory volume in one second, FVC: forced vital capacity, SpO₂: peripheral oxygen saturation

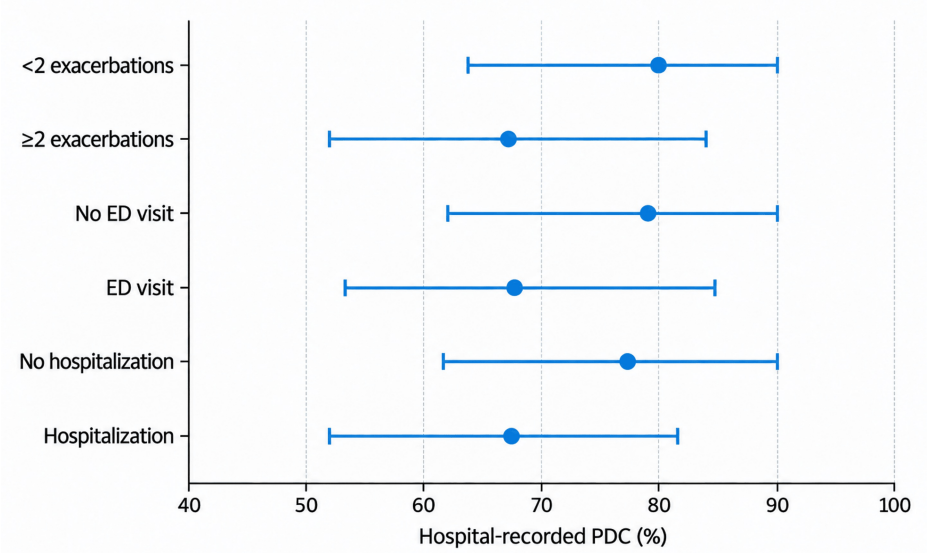


FIGURE 2: Hospital-recorded maintenance inhaler coverage across major clinical outcomes

Points represent the median hospital-recorded PDC, and horizontal error bars represent the IQR for each outcome group.

PDC: proportion of days covered, IQR: interquartile range

Factors associated with inadequate PDC and critical inhaler-technique error

In multivariable analysis, secondary or higher education was associated with lower odds of inadequate PDC (aOR 0.45, 95% CI 0.21-0.98; $p = 0.043$), as was previous inhaler-technique training (aOR 0.39, 95% CI 0.20-0.76; $p = 0.006$). Previous inhaler-technique training was also associated with lower odds of a critical technique error (aOR 0.16, 95% CI 0.08-0.36; $p < 0.001$). Other covariates were not independently significant (Table 8).

Predictor	Inadequate PDC aOR (95% CI)	p-value	Critical error aOR (95% CI)	p-value
Age, per year	0.99 (0.96-1.02)	0.637	1.03 (0.99-1.07)	0.204
Male sex	0.88 (0.48-1.62)	0.686	1.03 (0.48-2.22)	0.946
Former smoker	1.05 (0.47-2.38)	0.899	0.80 (0.28-2.25)	0.670
Current smoker	1.49 (0.62-3.56)	0.368	1.08 (0.37-3.17)	0.882
COPD duration, per year	1.02 (0.96-1.08)	0.534	1.06 (0.98-1.14)	0.146
Primary education	0.82 (0.42-1.63)	0.580	0.60 (0.26-1.35)	0.216
Secondary/higher education	0.45 (0.21-0.98)	0.043*	0.61 (0.24-1.59)	0.312
Multiple maintenance inhalers	1.72 (0.86-3.44)	0.124	0.96 (0.43-2.16)	0.927
Previous inhaler-technique training	0.39 (0.20-0.76)	0.006*	0.16 (0.08-0.36)	<0.001*
Any recorded comorbidity	0.72 (0.40-1.32)	0.292	Not included	-
PDC per 10-percentage-point increase	Not included	-	0.95 (0.77-1.17)	0.618

TABLE 8: Multivariable factors associated with inadequate hospital-recorded coverage and critical inhaler-technique error

Inadequate PDC was defined as <80%. * Statistically significant at $p < 0.05$.

aOR: adjusted odds ratio, CI: confidence interval, PDC: proportion of days covered

Exploratory combined coverage-technique phenotype

Clinical burden during the preceding 12 months differed across the four groups defined by prior-year PDC and index-date inhaler-technique status. Frequent exacerbations occurred in 20 of 78 (25.6%) participants with adequate PDC and no critical error, seven of 16 (43.8%) with adequate PDC and a critical error, 31 of 80 (38.8%) with inadequate PDC and no critical error, and 20 of 34 (58.8%) with both inadequate PDC and a critical error (global $p = 0.009$).

COPD-related ED attendance occurred in 16 of 78 (20.5%), three of 16 (18.8%), 19 of 80 (23.8%), and 17 of 34 (50.0%) participants, respectively (global $p = 0.008$). COPD-related hospitalization occurred in 11 of 78 (14.1%), three of 16 (18.8%), 12 of 80 (15.0%), and 12 of 34 (35.3%) participants, respectively (global $p = 0.044$). Exacerbation counts also differed across groups ($p = 0.025$). Table 9 presents these results.

Phenotype	N	Frequent exacerbation	ED visit	Hospitalization	Exacerbation count
Adequate PDC + no critical error	78	20 (25.6%)	16 (20.5%)	11 (14.1%)	1.0 (0.0-1.8)
Adequate PDC + critical error	16	7 (43.8%)	3 (18.8%)	3 (18.8%)	1.0 (0.0-2.0)
Inadequate PDC + no critical error	80	31 (38.8%)	19 (23.8%)	12 (15.0%)	1.0 (0.0-2.0)
Inadequate PDC + critical error	34	20 (58.8%)	17 (50.0%)	12 (35.3%)	2.0 (0.2-2.8)
Overall p-value	-	0.009*	0.008*	0.044*	0.025*

TABLE 9: Exploratory clinical outcomes across combined coverage-technique phenotypes

These comparisons were exploratory, and no multiplicity adjustment was applied. * Statistically significant at $p < 0.05$.

PDC: proportion of days covered, ED: emergency department

Primary multivariable outcome models

In the primary adjusted model, each 10-percentage-point increase in prior-year PDC was associated with

lower odds of frequent exacerbation (aOR 0.77, 95% CI 0.65-0.92; $p = 0.003$). Critical technique error was not independently significant (aOR 1.87, 95% CI 0.94-3.72; $p = 0.077$).

For ED attendance, increasing PDC was associated with lower odds (aOR 0.81, 95% CI 0.68-0.97; $p = 0.024$), whereas critical technique error was not independently significant (aOR 1.78, 95% CI 0.87-3.65; $p = 0.116$).

For hospitalization, PDC and critical technique error were not independently significant. Increasing age (aOR 1.06 per year, 95% CI 1.02-1.11; $p = 0.008$) and current smoking (aOR 2.43, 95% CI 1.09-5.39; $p = 0.029$) were associated with higher odds of hospitalization. Because only 38 (18.3%) participants were hospitalized, we considered this model exploratory. The primary adjusted models are presented in Table 10. Although critical inhaler-technique errors were associated with major clinical outcomes in the unadjusted analyses, these associations did not reach statistical significance after adjustment for the prespecified covariates in the primary full-cohort models.

Outcome	Predictor	aOR (95% CI)	p-value
Frequent exacerbation	PDC per 10-percentage-point increase	0.77 (0.65-0.92)	0.003*
	Critical technique error	1.87 (0.94-3.72)	0.077
	Age, per year	1.02 (0.99-1.06)	0.223
	Male sex	1.13 (0.60-2.10)	0.711
	Current smoker	1.63 (0.86-3.08)	0.135
	COPD duration, per year	1.03 (0.97-1.10)	0.372
	Any recorded comorbidity	0.92 (0.49-1.71)	0.788
ED visit	PDC per 10-percentage-point increase	0.81 (0.68-0.97)	0.024*
	Critical technique error	1.78 (0.87-3.65)	0.116
	Age, per year	1.03 (0.99-1.06)	0.176
	Male sex	1.06 (0.54-2.09)	0.865
	Current smoker	1.44 (0.72-2.88)	0.3
	COPD duration, per year	1.01 (0.95-1.08)	0.734
	Any recorded comorbidity	1.21 (0.61-2.40)	0.583
Hospitalization	PDC per 10-percentage-point increase	0.83 (0.67-1.02)	0.073
	Critical technique error	1.84 (0.82-4.10)	0.138
	Age, per year	1.06 (1.02-1.11)	0.008*
	Male sex	0.77 (0.35-1.69)	0.519
	Current smoker	2.43 (1.09-5.39)	0.029*
	COPD duration, per year	1.00 (0.93-1.08)	0.91
	Any recorded comorbidity	0.62 (0.28-1.38)	0.245

TABLE 10: Primary multivariable logistic regression models for frequent exacerbation, ED visit, and hospitalization

Each outcome was modeled separately. * Statistically significant at $p < 0.05$.

aOR: adjusted odds ratio, CI: confidence interval, PDC: proportion of days covered, ED: emergency department

A reduced four-variable hospitalization sensitivity model produced similar estimates for PDC (aOR 0.84, 95% CI 0.68-1.02; $p = 0.081$), critical technique error (aOR 1.79, 95% CI 0.81-3.99; $p = 0.151$), age (aOR 1.06, 95% CI 1.01-1.10; $p = 0.013$), and current smoking (aOR 2.21, 95% CI 1.03-4.73; $p = 0.042$).

Nested sensitivity analyses including lung function

Among the 188 (90.4%) participants with index-date spirometry, nested models separated the effect of sample restriction from the effect of adding FEV₁ percent predicted. For frequent exacerbation, the spirometry-restricted model without FEV₁ adjustment showed lower odds with increasing PDC and higher odds with critical technique error. Additional adjustment for FEV₁ produced little change in either estimate. Higher FEV₁ percent predicted was associated with lower odds of frequent exacerbation.

For ED attendance, the PDC association was already attenuated after restricting the analysis to participants with available index-date spirometry, and additional adjustment for FEV₁ produced little further change. For COPD-related hospitalization, FEV₁ percent predicted was associated with lower odds after adjustment. These nested sensitivity analyses are presented in Table 11.

Outcome	Predictor	Model B, n = 188, aOR (95% CI)	Model B p-value	Model C, n = 188, aOR (95% CI)	Model C p-value
Frequent exacerbation	PDC per 10-percentage-point increase	0.75 (0.62-0.90)	0.002*	0.74 (0.62-0.90)	0.002*
	Critical technique error	2.22 (1.04-4.71)	0.038*	2.28 (1.05-4.95)	0.036*
	FEV ₁ , % predicted	Not included	-	0.95 (0.91-0.99)	0.016*
ED visit	PDC per 10-percentage-point increase	0.87 (0.72-1.05)	0.152	0.88 (0.73-1.07)	0.195
	Critical technique error	2.08 (0.98-4.42)	0.057	2.14 (0.98-4.64)	0.055
	FEV ₁ , % predicted	Not included	-	0.95 (0.91-0.99)	0.013*
Hospitalization	PDC per 10-percentage-point increase	0.85 (0.68-1.06)	0.151	0.88 (0.68-1.12)	0.298
	Critical technique error	2.03 (0.84-4.88)	0.113	2.33 (0.88-6.19)	0.09
	FEV ₁ , % predicted	Not included	-	0.89 (0.84-0.94)	<0.001*

TABLE 11: Same-sample nested sensitivity models among participants with index-date spirometry

Model B repeated the primary covariate set in the 188 participants with available spirometry without FEV₁ adjustment. Model C used the same participants and additionally adjusted for FEV₁ percent predicted. * Statistically significant at p < 0.05.

aOR: adjusted odds ratio, CI: confidence interval, PDC: proportion of days covered, FEV₁: forced expiratory volume in one second

For frequent exacerbations, critical technique error was not independently significant in the primary full-cohort model (aOR 1.87, 95% CI 0.94-3.72; p = 0.077), whereas statistically significant associations were observed in the spirometry-restricted models both before (aOR 2.22, 95% CI 1.04-4.71; p = 0.038) and after adjustment for FEV₁ percent predicted (aOR 2.28, 95% CI 1.05-4.95; p = 0.036). For ED attendance, the association with PDC was attenuated following restriction to the 188 participants with available index-date spirometry before additional adjustment for FEV₁ percent predicted. These findings show differences between the analytical samples and sensitivity models but do not explain the reasons for those differences.

Additional sensitivity analyses of spirometry availability and PDC categorization

Compared with the 188 participants with index-date spirometry, the 20 without index-date spirometry were older (70.9 ± 7.5 versus 65.9 ± 9.4 years; p = 0.023) and were less likely to have received previous inhaler-technique training (eight of 20 (40.0%) versus 135 of 188 (71.8%); p = 0.004). Educational distribution also differed (p = 0.023). Hospital-recorded PDC was similar between groups. Prior-year hospitalization occurred in seven of 20 (35.0%) participants without index-date spirometry and 31 of 188 (16.5%) with available spirometry (Fisher exact p = 0.063). Table 12 presents the additional comparisons.

Characteristic	Spirometry unavailable, n = 20	Spirometry available, n = 188	p-value
Age, years	70.9 ± 7.5	65.9 ± 9.4	0.023*
Hospital-recorded PDC, median %	75.7	76.7	0.893
Adequate PDC ≥80%	9 (45.0%)	85 (45.2%)	0.985
Critical technique error	8 (40.0%)	42 (22.3%)	0.098
Frequent exacerbation	11 (55.0%)	67 (35.6%)	0.089
COPD-related ED visit	4 (20.0%)	51 (27.1%)	0.492
COPD-related hospitalization	7 (35.0%)	31 (16.5%)	0.063
Previous inhaler-technique training	8 (40.0%)	135 (71.8%)	0.004*
Multiple maintenance inhalers	8 (40.0%)	45 (23.9%)	0.117
Male sex	13 (65.0%)	115 (61.2%)	0.738
Smoking, never/former/current	2/14/4 (10.0%/70.0%/20.0%)	35/81/72 (18.6%/43.1%/38.3%)	0.071
Education, none/primary/secondary+	3/14/3 (15.0%/70.0%/15.0%)	65/72/51 (34.6%/38.3%/27.1%)	0.023*
Maintenance regimen, LAMA/LABA + LAMA/LABA + ICS/triple/other	2/9/1/8/0	38/71/34/40/5	0.175

TABLE 12: Characteristics according to availability of index-date spirometry

Fisher exact test was used when required because of small expected cell counts. * Statistically significant at $p < 0.05$.

PDC: proportion of days covered, ED: emergency department, LAMA: long-acting muscarinic antagonist, LABA: long-acting beta₂-agonist, ICS: inhaled corticosteroid

In exploratory univariable models, older age (OR 1.06 per year, 95% CI 1.01-1.12; $p = 0.025$) and prior-year hospitalization (OR 2.73, 95% CI 1.01-7.39; $p = 0.048$) were associated with the unavailability of index-date spirometry, whereas PDC was not. Table 13 presents these analyses.

Predictor	OR (95% CI)	p-value
PDC per 10-percentage-point increase	0.98 (0.76-1.27)	0.887
Critical technique error	2.32 (0.89-6.04)	0.086
Frequent exacerbation	2.21 (0.87-5.60)	0.095
COPD-related ED visit	0.67 (0.21-2.10)	0.494
COPD-related hospitalization	2.73 (1.01-7.39)	0.048*
Age, per year	1.06 (1.01-1.12)	0.025*
Male sex	1.18 (0.45-3.09)	0.738
Current smoking	0.40 (0.13-1.25)	0.116
COPD duration, per year	1.02 (0.94-1.12)	0.608
Any recorded comorbidity	0.65 (0.26-1.64)	0.359

TABLE 13: Univariable factors associated with unavailable index-date spirometry

Outcome was index-date spirometry unavailable. These models were exploratory and univariable because only 20 participants lacked index-date spirometry. * Statistically significant at $p < 0.05$.

OR: odds ratio, CI: confidence interval, PDC: proportion of days covered, ED: emergency department

The critical-error-by-spirometry-availability interaction for frequent exacerbation was not statistically significant (OR 5.13, 95% CI 0.65-40.16; $p = 0.120$). The planned PDC-by-spirometry-availability interaction model for ED attendance did not converge and was not interpreted.

In categorical-PDC sensitivity analyses, compared with PDC $\geq 80\%$, PDC $< 50\%$ was associated with higher odds of frequent exacerbation (aOR 3.65, 95% CI 1.32-10.09; $p = 0.013$) and ED attendance (aOR 3.20, 95% CI 1.17-8.80; $p = 0.024$), but not hospitalization. PDC of 50-79% was not significantly different from PDC $\geq 80\%$ for any major outcome. Table 14 shows the results.

Outcome	PDC category versus $\geq 80\%$	aOR (95% CI)	p-value
Frequent exacerbation	$< 50\%$	3.65 (1.32-10.09)	0.013*
Frequent exacerbation	50-79%	1.48 (0.78-2.80)	0.229
COPD-related ED visit	$< 50\%$	3.20 (1.17-8.80)	0.024*
COPD-related ED visit	50-79%	1.38 (0.68-2.80)	0.378
COPD-related hospitalization	$< 50\%$	1.70 (0.53-5.48)	0.377
COPD-related hospitalization	50-79%	1.24 (0.55-2.82)	0.607

TABLE 14: Adjusted categorical PDC sensitivity analyses

Models were adjusted for critical technique error, age, sex, current smoking, COPD duration, and any recorded comorbidity. PDC $\geq 80\%$ was the reference category. Only 22 participants had PDC $< 50\%$; these analyses were therefore considered secondary sensitivity analyses. * Statistically significant at $p < 0.05$.

aOR: adjusted odds ratio, CI: confidence interval, PDC: proportion of days covered

Exploratory adjusted phenotype models and interaction analysis

In exploratory adjusted phenotype models using adequate prior-year PDC with no index-date critical error as the reference category, inadequate PDC combined with a critical technique error was associated with frequent exacerbation (aOR 3.45, 95% CI 1.43-8.29; $p = 0.006$) and yielded an imprecise association with hospitalization (aOR 2.79, 95% CI 1.02-7.64; $p = 0.045$). Increasing age and current smoking were also

associated with hospitalization. Table 15 presents these findings. These phenotype-based associations were exploratory, and the hospitalization estimate was imprecise because of the limited number of events and relatively small phenotype subgroups. The findings should therefore be interpreted cautiously.

Outcome	Predictor	aOR (95% CI)	p-value
Frequent exacerbation	Adequate coverage + critical error	2.11 (0.67-6.66)	0.203
	Inadequate coverage + no critical error	1.81 (0.91-3.62)	0.093
	Inadequate coverage + critical error	3.45 (1.43-8.29)	0.006*
	Age, per year	1.02 (0.99-1.06)	0.166
	Male sex	1.10 (0.59-2.03)	0.764
	Current smoker	1.74 (0.93-3.27)	0.084
	COPD duration, per year	1.03 (0.96-1.09)	0.431
	Any recorded comorbidity	0.96 (0.52-1.78)	0.897
Hospitalization	Adequate coverage + critical error	0.95 (0.21-4.24)	0.948
	Inadequate coverage + no critical error	0.98 (0.39-2.47)	0.967
	Inadequate coverage + critical error	2.79 (1.02-7.64)	0.045*
	Age, per year	1.07 (1.02-1.12)	0.005*
	Male sex	0.75 (0.34-1.63)	0.464
	Current smoker	2.51 (1.14-5.54)	0.022*
	COPD duration, per year	0.99 (0.92-1.07)	0.891
	Any recorded comorbidity	0.61 (0.27-1.37)	0.231

TABLE 15: Exploratory adjusted outcome models using the combined coverage-technique phenotype

Adequate PDC plus no critical technique error was the reference phenotype. These models were exploratory, and hospitalization estimates should be interpreted cautiously because of the limited event count and small phenotype cells. * Statistically significant at p < 0.05.
aOR: adjusted odds ratio, CI: confidence interval, PDC: proportion of days covered

In a separate frequent-exacerbation interaction model, the PDC-by-critical-error interaction was not statistically significant (aOR 0.96, 95% CI 0.65-1.40; p = 0.817), providing no evidence of multiplicative interaction.

Discussion

Principal findings

In this analytical cohort of 208 adults with COPD, approximately half achieved adequate hospital-recorded maintenance inhaler coverage during the preceding 12 months and just over half performed all 10 assessed inhaler steps correctly at the index assessment. Critical technique errors were present in about one-quarter of participants. Higher PDC was associated with lower odds of frequent exacerbation and ED attendance in the full-cohort primary models. Although critical technique errors were associated with adverse clinical outcomes in the unadjusted analyses, these associations did not reach statistical significance in the primary full-cohort adjusted models. The nested analyses involving 188 participants showed that the PDC-ED association had already attenuated when the analysis was restricted to participants with index-date spirometry and changed little after additional adjustment for FEV1. Similarly, the stronger critical-error estimate for frequent exacerbation was already present in the spirometry-restricted sample before FEV1 adjustment.
Additional analyses showed that the 20 participants excluded by the spirometry restriction were older, were less likely to have received previous inhaler-technique training, and had a higher observed proportion of participants with prior-year COPD-related hospitalization. However, the hospitalization difference was not

statistically significant, while their PDC was essentially unchanged. These findings suggest that differences in analytical sample composition, rather than additional FEV₁ adjustment alone, drove the changes observed in the restricted-sample estimates. However, the available analyses cannot establish the precise mechanisms underlying these differences, and residual confounding or selection effects cannot be excluded.

The categorical sensitivity analysis further suggested that the strongest PDC associations were concentrated among participants with very low coverage (<50%), although this subgroup was small. Higher FEV₁ percent predicted was consistently associated with lower prior-year clinical burden. Exploratory combined coverage-technique phenotype analyses identified the group with inadequate PDC and a critical technique error as having the highest observed event burden, but the hospitalization estimate was imprecise and should not be treated as a stable predictive effect. Because of the retrospective temporal structure, all findings are associations with prior-year clinical burden rather than prospective risk estimates.

Inhaler technique in relation to Nepalese, South Asian, and international studies

The observed prevalence of completely correct inhaler technique was substantially higher than that reported in several older Nepalese studies. Baral reported completely correct DPI technique in only 3.9% of 204 Nepalese patients with COPD, although 77.5% performed the critical steps correctly [6]. Poudel et al. found that only 5.7% used the correct Rotahaler technique before intervention, increasing to 67.1% after pharmacist-led training [7]. In another Nepalese COPD study, only one-third were correct at baseline, but face-to-face training and telephone reminders corrected technique in 90% of initially incorrect users [8]. The higher overall accuracy in the present analysis is therefore plausible in a population where inhaler-technique training was common, but it also highlights how strongly prevalence estimates depend on the checklist used, patient setting, device type, and prior education.

The present estimate aligns more closely with contemporary regional and international observations. Nitya et al. reported correct inhaler technique in 52.1% of Indian outpatients before training and 79.2% after training [11], while Lindh et al. found that 45% of Swedish primary-care COPD patients made at least one inhaler error, almost identical to the proportion with any error in the present dataset [13]. Conversely, Sanaullah et al. reported very poor technique among Pakistani patients admitted with COPD exacerbations [12]. A systematic review spanning four decades found overall correct technique in only about 31% of inhaler users and identified pre-inhalation exhalation and breath-holding among common DPI problems [14]. These differences argue against treating any single percentage of “correct technique” as universal; device-specific definitions and prior training exposure must be considered.

Another consideration is that the present study assessed inhaler technique using a locally developed, standardized 10-step observational checklist established by the clinical team at Tsho-Rolpa General Hospital before the COPD clinical-assessment initiative. Although the checklist covered essential procedural steps relevant to the Respirer capsule-based DPI, it had not undergone separate formal validation, and inter-rater reliability testing was not documented. Differences in checklist structure, critical-error definitions, and assessment procedures may therefore contribute to variation in reported technique accuracy across studies. Consequently, direct comparisons of the prevalence of completely correct inhaler technique should be interpreted cautiously.

Training, education, and inhaler behavior

Previous inhaler-technique training was strongly associated with lower odds of both inadequate coverage and critical technique error in this analysis. That direction is consistent with Nepalese intervention studies showing substantial improvement after pharmacist instruction, face-to-face demonstration, and reinforcement [7-9]. Bhattarai et al. demonstrated significant improvements in inhaler adherence and inhalation technique after pharmacist-led intervention. They found that better adherence and technique were associated with lower COPD Assessment Test scores [9]. Indian data likewise support structured retraining: Nitya et al. observed marked improvement in correct technique after instruction [11], and Khurana et al. showed improvement in COPD Assessment Test scores after technique correction even though short-term FEV₁ change in COPD was not significant [15]. Higher education and better medication coverage may be linked through health literacy and treatment navigation, although this relationship is not universal; an Indian tertiary-center study of adult asthma patients using pressurized metered-dose inhalers found no significant difference in inhaler-technique scores across educational strata [16].

Critical technique errors and clinical outcomes

International COPD literature has reported the relationship between critical errors and adverse outcomes. In a real-world study of 2,935 patients, Molimard et al. found device-specific critical errors common and associated with severe exacerbations requiring emergency care or hospitalization [17]. Ahn et al. reported that any critical inhaler-technique error independently predicted frequent exacerbation, with an odds ratio of approximately 2.0 [18], similar in magnitude to the present unadjusted and spirometry-adjusted estimates. Melani et al. also linked inhaler mishandling to hospitalization, emergency visits, oral corticosteroid use, antimicrobial treatment, and poorer disease control [19].

In the present study, critical technique errors were associated with frequent exacerbations, ED attendance, and hospitalization in unadjusted analyses. However, none of these associations reached statistical significance in the primary full-cohort adjusted models. For frequent exacerbations, the aOR was 1.87 (95% CI 0.94-3.72; $p = 0.077$). Statistically significant associations were observed in the spirometry-restricted sensitivity models both before (aOR 2.22, 95% CI 1.04-4.71; $p = 0.038$) and after adjustment for FEV₁ percent predicted (aOR 2.28, 95% CI 1.05-4.95; $p = 0.036$). These associations were already present in the spirometry-restricted sample and should not be interpreted as overriding the primary full-cohort findings. The differences between models highlight the potential influence of analytical sample composition and reinforce the need for cautious interpretation.

Inhaler technique was measured only at the index visit, after ascertainment of the preceding 12-month outcomes. The observed associations therefore indicate that index-date technique status was related to prior clinical burden; they do not demonstrate that the measured technique error preceded or caused those events. The technique may also have changed during the prior year or after healthcare encounters and retraining. The attenuation of associations in some adjusted models further suggests that technique may be correlated with disease severity, education, treatment behavior, and other determinants of clinical outcomes.

Hospital-recorded coverage and outcomes

The association between higher PDC and lower odds of frequent exacerbations or ED attendance in the full cohort is directionally consistent with findings from several large studies. Toy et al. used PDC in more than 55,000 patients with COPD and found that greater coverage was associated with fewer inpatient and emergency visits [4]. In the TORCH trial, good inhaled-therapy adherence was associated with lower mortality and fewer hospital admissions for COPD exacerbation, independent of randomized treatment assignment [20].

In the present analysis, however, PDC and clinical events were measured over the same preceding 365-day window, so temporal order cannot be established. The nested same-sample analysis showed that the PDC-ED association was already attenuated when the analysis was restricted to participants with index-date spirometry, before additional adjustment for FEV₁. The 20 participants excluded by this restriction were older and had a higher observed proportion of prior-year hospitalizations, although the hospitalization difference was not statistically significant. Hospital-recorded PDC was similar between groups. These differences suggest that analytical sample composition may have attenuated the PDC-ED association, whereas additional adjustment for FEV₁ percent predicted produced little change.

In a secondary categorical analysis, the clearest associations were observed in the PDC <50% group. Compared with PDC ≥80%, adjusted odds were higher for frequent exacerbation and ED attendance, whereas the intermediate 50-79% group was not significantly different. This pattern suggests a non-linear relationship or a threshold concentrated at very low coverage, but the <50% group included only 22 participants, and the estimates were imprecise; therefore, the continuous PDC analysis remained the primary approach.

However, the literature examining associations between medication coverage, adherence, and clinical outcomes is not uniform. In a large Ontario cohort using time-varying PDC and methods intended to account for time-varying confounding, Weir et al. found a non-linear pattern in which the highest recent adherence category was associated with increased emergency visits and hospitalizations compared with zero recent adherence [21]. The authors emphasized confounding by disease severity, perceived need for treatment, and residual confounding. This is an important counterpoint to the present same-window analysis because patients with more severe or unstable COPD may take medications more consistently due to greater disease severity or more frequent healthcare contact; conversely, clinical deterioration or barriers to healthcare access could reduce medication coverage. Reverse causation and confounding by disease severity therefore cannot be excluded. Moreover, PDC should not be interpreted as confirmed medication use. Hesso et al. found median refill-based PDC of 97.8% but electronically measured actual adherence of only 42.7%, illustrating the potential divergence between medication availability and correct real-world use [22]. The terminology “hospital-recorded coverage” is therefore preferable to “adherence” for the present exposure.

Lung function, age, smoking, and hospitalization

The strong relationship between lower FEV₁ percent predicted and adverse clinical burden is biologically and epidemiologically coherent. In the ECLIPSE cohort, exacerbations became progressively more frequent as airflow limitation worsened, while a history of exacerbations identified a stable frequent-exacerbator phenotype across severity strata [23]. Miravittles et al. found that higher FEV₁ percent predicted was independently associated with lower odds of both frequent exacerbations and hospital admission [24]. In ECLIPSE, hospitalized exacerbations were also associated with more severe airflow limitation and older age [25]. In the present nested sensitivity models, higher index-date FEV₁ percent predicted was associated with lower odds of frequent exacerbation, ED attendance, and hospitalization during the preceding 12 months. Because FEV₁ was measured at the index assessment after that event window, it should be viewed as a

contemporaneous severity marker rather than as a strictly pre-outcome confounder.

The primary hospitalization model also found older age and current smoking to be associated with higher odds of hospitalization, and a reduced four-variable model yielded similar directions. Older age is supported by ECLIPSE and other observational cohorts [25,26]. Evidence for current smoking is more mixed. A large Scottish linked-record cohort found current smoking associated with greater risk of a first COPD hospitalization after diagnosis [26]. In contrast, smoking status was not among the dominant independent determinants of the frequent-exacerbator phenotype in ECLIPSE [23]. In the same 188 participants, current smoking was associated with hospitalization before FEV₁ was added (aOR 2.39; *p* = 0.048) but attenuated after addition of FEV₁ percent predicted (aOR 1.80; *p* = 0.211), a pattern that may reflect the contribution of contemporaneous lung-function differences to the observed association. However, this change alone does not establish confounding by disease severity. These hospitalization estimates nevertheless remain exploratory because only 38 events occurred.

Combined coverage-technique phenotype

The exploratory combined phenotype analysis extends the separate coverage and technique findings. Participants with both inadequate prior-year PDC and an index-date critical technique error had the highest observed proportions of frequent exacerbations, ED attendance, and hospitalization during the preceding 12 months. Conceptually, medication availability and device execution represent different stages in the pathway from prescription to effective pulmonary drug delivery. Objective monitoring studies have shown that refill measures and actual inhaler use can diverge substantially [22]. Nevertheless, the smallest phenotype group included only 16 participants, only 38 participants experienced hospitalization overall, and the adjusted hospitalization estimate had a wide CI. Because technique was assessed at the index visit and clinical events were retrospective, the four-group phenotype should therefore be regarded as an exploratory clinical-burden construct rather than a validated predictive phenotype. The absence of a statistically significant multiplicative PDC-by-critical-error interaction further argues against interpreting the joint category as evidence of biological synergy. Prospective external validation would be required.

Clinical implications

The findings reinforce several practical priorities. First, inhaler technique should be demonstrated and reassessed rather than assumed, consistent with current COPD management recommendations [3]. Second, refill or hospital-dispensing data can help identify patients with low medication coverage but should not substitute for direct assessment of actual use. Third, technique and coverage should be evaluated separately because a patient may have adequate medication availability but ineffective inhalation or good technique but insufficient medication coverage. Nepalese and Indian intervention studies suggest that structured demonstration, pharmacist involvement, and repeated reinforcement can improve these behaviors [7-9,11,15].

Strengths and limitations

This study has several methodological strengths, including separate assessment of medication coverage and inhaler technique, use of a standardized locally developed observational checklist with four critical steps established before the retrospective research analysis, use of clinically meaningful record-based outcomes, nested same-sample sensitivity analysis for lung function, direct examination of the spirometry-missing subgroup, and explicit separation of medication availability from confirmed inhaler use. The exploratory combined phenotype also provides an intuitive framework for considering two distinct treatment-process dimensions simultaneously.

Several limitations should be considered. The retrospective observational design cannot establish causality and is susceptible to residual confounding by disease severity, health literacy, socioeconomic factors, access to care, treatment behavior, and prior exacerbation history. The temporal relationship between exposures and outcomes warrants particular caution: hospital-recorded PDC and clinical events were assessed over the same preceding 365-day period, while inhaler technique and FEV₁ were documented at the index assessment after the retrospective event window. Thus, neither index-date technique nor index-date lung function is a strictly pre-outcome exposure or confounder, and reverse causation is possible. Days spent in hospital remained in the PDC denominator, and we lacked separate inpatient-day medication-coverage data; therefore, hospitalization itself could influence measured outpatient dispensing coverage. Hospital-recorded PDC may also underestimate total medication availability if participants obtained inhalers from outside pharmacies, while ED visits, hospitalizations, or exacerbations managed elsewhere could be missed if they were never documented in the available Tsho-Rolpa record. Because medication coverage and clinical events came largely from the same hospital information system, the study may have jointly under-ascertained outside medication acquisition and outside acute-care use.

As a single-center study based on patients attending a hospital clinical-assessment initiative and meeting device- and record-availability criteria, the study may be subject to selection bias, and generalizability to all patients with COPD in Nepal may be limited. The 20 participants without index-date spirometry differed from the spirometry-complete group in age, previous technique training, education, and the observed

proportion of prior-year hospitalization, indicating that complete-case lung-function analyses were susceptible to sample-composition effects.

Before the original assessment initiative, the hospital's clinical team developed a standardized 10-step observational checklist to assess inhaler technique. Although the instrument included essential procedural steps relevant to capsule-based DPI use, it had not undergone separate formal validation, and the study did not document objective inspiratory-flow measurement or inter-rater reliability testing. Furthermore, the available retrospective records did not document formal assessor blinding or independent adjudication of outcomes. These factors introduce potential measurement and classification bias. Technique assessment was also limited to the Respirer capsule-based device and did not characterize any additional inhaler devices prescribed to participants.

Some combined phenotype groups and the PDC <50% category were small, reducing precision, and hospitalization regression models were vulnerable to sparse-data instability despite qualitative consistency in a reduced model. One exploratory PDC-by-spirometry-availability interaction model for ED attendance did not converge and was not interpreted. Finally, multiple exploratory comparisons increase the likelihood of chance findings; therefore, secondary and phenotype results should be interpreted in the context of effect estimates, CIs, and the primary analyses.

Conclusions

Higher hospital-recorded maintenance inhaler coverage was associated with lower odds of frequent exacerbation during the same preceding 12-month period. The lower odds of ED attendance observed with higher PDC in the full cohort did not persist after restriction to participants with index-date spirometry, and nested same-sample models showed that this change occurred before FEV₁ was added. Additional subgroup analyses showed that participants without index-date spirometry differed in age, previous technique training, education, and the observed proportion of prior-year hospitalization, but not in PDC, suggesting that differences in analytical sample composition may have contributed to the changes in restricted-sample estimates. However, the underlying reasons for these differences could not be established.

Critical inhaler-technique errors documented at the index assessment were associated with greater prior-year clinical burden in unadjusted analyses, but these associations did not reach statistical significance in the primary full-cohort adjusted models. Spirometry-restricted sensitivity analyses showed an association with frequent exacerbation, although these findings require cautious interpretation. The timing of the technique assessment precludes causal or prospective inference.

Higher index-date FEV₁ percent predicted was consistently associated with lower prior-year clinical burden, although it was measured after the retrospective event window and should be interpreted as a contemporaneous severity marker. Secondary categorical analyses suggested that the strongest PDC associations were concentrated among participants with very low coverage, but this subgroup was small. Exploratory combined coverage-technique phenotype analyses suggested that the subgroup with inadequate prior-year coverage and an index-date critical technique error had the greatest observed burden, but hospitalization estimates were imprecise.

In clinical practice, medication coverage and inhaler technique should be assessed as complementary but distinct components of COPD management. Prospective studies with repeated inhaler-technique assessments and more complete medication-dispensing and clinical-event ascertainment are needed to clarify temporal relationships and determine whether these measures predict subsequent clinical outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Ethical Review Board of the Nepal Health Research Council, Government of Nepal issued approval 2033. This study involved human participants through a retrospective secondary analysis of pre-existing hospital records. The requirement for individual informed consent for this retrospective analysis was waived by the Ethical Review Board of the Nepal Health Research Council because the study used pre-existing, de-identified records and involved no additional participant contact. No identifiable patient information is included in the manuscript. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** This study received financial support from M.D.H. Pharmaceuticals Pvt. Ltd., Nepal, for research-related activities. M.D.H. Pharmaceuticals Pvt. Ltd. manufactures the Respirer capsule-based dry powder inhaler evaluated in this study. The funder had no role in the study design, data collection, data cleaning, statistical analysis, interpretation of the findings, manuscript preparation, or decision to submit the manuscript for publication. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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