Medication Adherence Assessment and Cost Analysis of COPD Treatment Under Out-Patient Clinic in Vietnam

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ABSTRACT: Chronic obstructive pulmonary disease (COPD) out-patient clinic is for stable patients but it requires patient's adherence to medicine and medical checkups. Our study aimed to assess COPD out-patient clinics management efficacy with respect to medication adherence and treatment costs at 3 out-patient clinics. Data were collected through 514 patient interviews and from medical records for statistical analysis. The most common comorbidity was hypertension (28.8%), and 52.9% of patients had experienced exacerbations in the past year requiring 75.7% of them to be hospitalized. According to the Morisky scale, 78.8% had high adherence and 82.9% were using inhaled corticosteroids regimens. The mean cost per year among different cohorts varied, with the out-patient cohort at $305.93, the acute exacerbations of COPD non-hospital cohort at $247.39, the standard admission cohort at $1275.3, and the emergency department cohort at $2132.5. Patients with low medication adherence had significantly lower annual costs ($238.25 vs $325.04, $P = .001$). In Vietnam, economic constraints have made Inhaled corticosteroids/ Long-acting β-2 agonists the main mode of treatment. However, the exclusion of Long-acting β-2 agonists/Long-acting anti-muscarinic antagonists drugs from health insurance coverage poses a challenge to Global Initiative for Chronic Obstructive Lung Disease-based prescription practices and increases the importance of monitoring medication adherence, particularly in patients with higher COPD Assessment Test scores.

KEYWORDS: Cost analysis of COPD treatment, medication adherence, acute exacerbation, out-patient management efficacy

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is highly prevalent worldwide and the prevalence of COPD in Europe and the United States ranges from 3.4% to 13.4%. According to the World Health Organization, COPD is one of the leading causes of morbidity and mortality globally. COPD causes 3.23 million deaths in 2019. More than 90% of COPD deaths occur in Low Middle-Income Country (LMIC).[1] In Asia, this COPD percentage ranges from 3.5% to 19.1%.[2] In Vietnam, COPD prevalence is between 7%and 10% and is commonly undiagnosed.[3]

COPD management efficacy is still facing the issues of medication non-adherence leading to high treatment costs. And the Morisky Medication Adherence Scale (MMAS) is an empirically validated assessment tool for gauging non-adherence in various patient groups. A high level of adherence was given an MMAS-8 score of 8, moderate adherence received a score between 6 and 8, and poor adherence received a score less than 6. Patients with poor levels of adherence were regarded as not taking their medications as prescribed. This tool has been supported by numerous studies worldwide, featuring 110 versions and 80 translations.[4] The MMAS uses a series of brief behavioral questions aimed at avoiding "yes-saying" bias often observed in patients with chronic conditions. COPD treatment adherence assessed by MMAS were reported in many previous studies, with rates ranging from 38.3% to 83.4%.[5-10] The variation in medication adherence observed in previous studies indicates that it is difficult for people with common chronic diseases to follow their medication schedules. Therefore, an evaluation tool is needed to gain a comprehensive understanding of the situation. Evaluating adherence can also help determine whether separate clinics for managing COPD are more effective than general internal medicine clinics.

Treatment costs were found to be directly related to disease severity categorized by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) basing on disease symptoms and risk of acquisition. The GOLD has 4 groups as A, B, C, and D classification is more closely associated with treatment costs and health-related quality of life.[11] In Europe, the annual cost for GOLD-A COPD patients was $429, increasing to $5677 for GOLD-D COPD patients. The direct cost per COPD patient in 2014 in the US was $11 232. Exacerbation treatment costs account for a high proportion of direct treatment costs. In the United States, annual direct costs for COPD without exacerbations increased from $1425 to $12 765 dollars for patients with 2 or more exacerbations. Overall, in Asian countries, high hospitalization rates are strongly associated

with exacerbation severity. The average cost per hospitalized patient increased from $951 in the general ward to $2660 in the intensive care unit (ICU). However, the published data appears to be missing costs related to health insurance and self-financing.[2] In Vietnam, the relation of COPD medication adherence and the treatment cost with out-patient clinic has not been evaluated. Thus, this study aimed to analyze the direct costs of all COPD visits (ranging from regular to severe cases) in relation to medication adherence assessment as it is a crucial factor in assuring the quality of COPD out-patientclinic management.

Methods

This is a cross-sectional, non-interventional, descriptive observational study that was done from August 2020 to April 2021 at 3 COPD out-patient clinics in the North of Vietnam: Dong Da General Hospital, Thanh Hoa Lung Hospital, and Hai Phong Tuberculosis and Lung Disease Hospital.

Patients were selected when they met certain criteria such as being a confirmed COPD patient age 40 or older who had been an out-patient since January 1, 2018 and had signed the study written consent. Pregnant or breastfeeding individuals, those with other respiratory diseases, pneumonia, acute bronchitis, or participating in other studies were excluded.

Our study observed patients and grouped them into 4 categories based on their symptom conditions when they came to the hospital—whether it was because of their serious symptoms or a scheduled follow-up visit. Sorting patients this way helped us see how much it cost to treat different types of acute hospitalization, and normal visits. Patients were divided into 4 groups based on the most intensive type of COPD-related care they received during the study period.

- Group 1 (Out Patient): Patients had no evidence of exacerbations in the previous year.
- Group 2 (Acute Exacerbation—AE COPD non-hospitalization): Patients had exacerbations only requiring out-patient treatment.
- Group 3 (Standard Admission): Patients had acute exacerbations resulting in general department admission.
- Group 4 (Emergency Department—ED cohort): Patients had at least one emergency admission in the past year.

We used 3 different tools for medication adherence assessment and clinical classification data through the quantitative questionnaire on adherence that was administered to patients, clinical examination, and patients' record as follows[12]:

(1) Morisky Medication Adherence Scale (MMAS) is an empirically validated assessment tool for gauging non-adherence in various patient groups. A high level of adherence was given an MMAS-8 score of 8, moderate adherence received a score between 6 and 8, and poor adherence received a score less than 6. Patients with poor levels of adherence were regarded as not taking their medications as prescribed.

(2) Modified Medical Research Council (mMRC) Dyspnea Scale is used to assess the degree of baseline functional disability due to dyspnea. It is useful in characterizing baseline dyspnea in patients with respiratory disease such as COPD. The mMRC dyspnea score is a 5-point (0-4) scale based on the severity of dyspnea.

(3) COPD Assessment Test (CAT) is a patient-completed instrument to assess and quantify health-related quality of life and symptom burden in COPD patients. It comprises 8 questions, each is presented as a semantic 6-point (0-5) differential scale, providing a total score out of 40. Scores of 0-10, 11-20, 21-30, 31-40 represent mild, moderate, severe or very severe clinical impact, respectively

(4) The secondary tool Global initiative for Chronic Obstructive Lung Disease (GOLD) is used to determine COPD disease severity (A, B, C, or D) basing on the use of CAT or mMRC questionnaires.

Treatment costs were divided into 2 categories: costs covered by health insurance and costs paid by the patient. Cost calculations were based on totals paid in 2020-2021 and adjusted to US dollars in 2020 (exchange rate was 23 236.21 Vietnam dong = 1 USD).

Statistical analysis

Descriptive statistics were used to describe qualitative and quantitative variables and analytical statistics (Chi-square test, *t*-test, and Kruskal-Wallis test) were used to determine the relationship between independent variables (clinical data such as smoking status, comorbidities, respiratory treatments, exacerbations, socio demographic factors such as age, sex, distance from home to clinic) and the mediation adherence variable with statistically significant by value $P < .05$. And logistic regression analysis was utilized to identify potential factors associated with the outcomes, and to calculate the corresponding odds ratios (ORs).

The study was ethically approved by the Vietnam National Biomedical Research Ethics Council under No. 05/CN-HDDD dated January 14, 2020 and all patients signed the consent forms as their agreement to join the study voluntarily before we interviewed them.

Results

The study included 514 patients, of which most of the patients were male (85.8%), aged 60 to 79 years (75.5%), and 20.8% were current smokers. Co-morbidities with the highest rates were hypertension (28.8%), gastroesophageal reflux disease (12.6%), and allergic rhinitis (9.7%). Treatment regimens with

Table 1. Characteristics of COPD Patients (n = 514).

	TOTAL COPD (N = 514)	GOLD A, B (N = 280)	GOLD C, D (N = 234)
Demographics			
Age, years	66.1 (43-93)	66.2 (43-84)	66.0 (43-93)
Male	85.8	86.1	85.5
Smoking status			
No smoking	17.3	18.2	16.2
Used to smoke	61.9	59.6	64.5
Currently smoking	20.8	22.1	19.2
Comorbidities			
Arterial hypertension	28.8	29.6	27.8
Gastroesophageal reflux	12.6	9.6	16.2
Allergic rhinitis	9.7	11.1	10.7
Diabetes	6.4	6.8	6.0
Arrhythmia	5.1	4.3	6.0
Ischemic cardiopathy	2.3	2.9	1.7
Heart failure	1.6	1.8	1.3
Depression	1.6	0.7	2.6
Respiratory treatments			
SABA	17.1	17.1	17.1
ICS+ LABA/SABA	75.9	71.1	81.6
ICS+ LABA	6.2	10.7	0.9
ICS+ LABA+ LAMA/SABA	0.8	1.1	0.4
Number of exacerbations	52.9	15.7	97.4

Abbreviations: LAMA, long-acting anti-muscarinic antagonists; LABA, long-acting β2-agonists; ICS, inhaled corticosteroids; SABA, short acting beta agonist.
Data are presented as mean (95% CI) or %.

Inhaled corticosteroids (ICS)/ Long-acting β-2 agonists (LABA) were most commonly used (82.9%) with only 0.8% of patients using regimens with long-acting anti-muscarnic antagonists (LAMA) only (see Table 1).

The CAT score (cutoff of 10) and MMAS score (cutoff of 6) were found significant difference that the median CAT score of non-adherent patients was higher than the adherent patients (17 ± 8.61vs 15 ± 3.9, $P = .02$) (see Table 2). According to GOLD classification, 24.3%, 30.2%, 17.7%, and 27.8% of the patient population were classified as A, B, C, and D, respectively in adherent patients with high MMAS score (⩾6 points), compared to 31.0%, 24.1%, 13.8%, and 31% in non-adherent patients with low MMAS score (<6 points) (see Table 2).

A higher proportion of patients who lived further away from the clinics demonstrated greater adherence to treatment than those who lived in closer proximity (485 patients, accounting for 94.4%, compared to 29 patients, accounting for 5.6%). The annual treatment cost of non-adherent patients was significantly lower than adherent ones at $238.25 and $325.04 respectively ($P < .0001$).

The annual average out-patient treatment costs by patient groups (1 -4) was $305.9; $208.3; $405.5, and $320.9, respectively. Drugs accounted for a large proportion of costs ($259.08; $178.06; $360.48 and $284.32, respectively). Examination costs and transport expenses accounted for a smaller portion (see Figure 1).

The proportion of patients entitled to 100% health insurance was 40.4%, 40%, 53.1%, and 50.9% for patient groups (1-4), respectively. Of those, 4.3% had insurance that paid less than 60% (see Figure 2).

Table 2. Factors Related to Medication Adherence by MMAS (Cutoff of 6) With OR (Odd ratio) Values.

	NON-ADHERENCE MMAS < 6 (N = 29)		ADHERENCE MMAS ⩾ 6 (N = 485)		OR (CI 95%)	*P*-VALUE
	N	%	N	%		
Age (years)						
40-59	4	13.8	95	19.6	1	-
60-79	24	82.8	364	75.1	0.91 (0.98-8.53)	.93
⩾80	1	3.4	26	5.4	0.58 (0.07-4.48)	.60
Sex						
Female	6	20.7	67	13.8	1.62 (0.63-4.14)	.28
Male	23	79.3	418	86.2		
Number of co-morbidities						
0	11	37.9	235	48.5	1	-
1	11	37.9	168	34.6	1.82 (0.88-4.86)	.23
⩾2	7	24.1	82	16.9	1.30 (0.48-3.48)	.59
mMRC (Modified Medical Research Council) Dyspnea Scale						
0-1	13	44.8	206	42.1	1.11 (0.52-2.37)	.84
⩾2	16	55.2	279	57.9		
COPD Assessment Test (CAT)						
<10	5	17.2	27	5.6	3.53 (1.25-9.98)	.02
⩾10	24	82.8	458	94.4		
Mean ± SD	17 ± 8.6		15 ± 3.9			
COPD stages						
GOLD A	9	31	118	24.3	-	-
GOLD B	7	24.1	146	30.2	1.59 (0.57-4.39)	.37
GOLD C	4	13.8	86	17.7	1.64 (0.49-5.50)	.42
GOLD D	9	31	135	27.8	1.14 (0.44-2.97)	.78
AECOPD	2.2 ± 2.54		1.5 ± 1.09			.28
Distance[a]	5.4 ± 4.9		12.4 ± 8.2			.001
Annual cost (USD)	238.2 ± 135.2		325.0 ± 137.8			<.0001

Abbreviation: AECOPD, Acute exacerbation of COPD (in the previous year).
[a]Distance from home to hospital (km).

Discussion

Five hundred fourteen COPD patients participated in our trial in the outpatient clinic. Through this study, we found that medication adherence was high (80.4%) assessed by MMAS, and the main treatment drugs were ICS/LABA (82.9%). The average treatment cost was $305.93 and changed regarding to adherence (patients with low medication adherence had significantly lower annual costs). The factor associated with adherence was found to be a high CAT score.

In our study, the medication adherence rate was higher than previous studies which ranged from 65% to 83.4%.[5-10] Various factors such as depression, frequency of COPD medication use, and concerns about adverse events, as mentioned in a study, it was found that the adverse events increased the risk of non-adherence

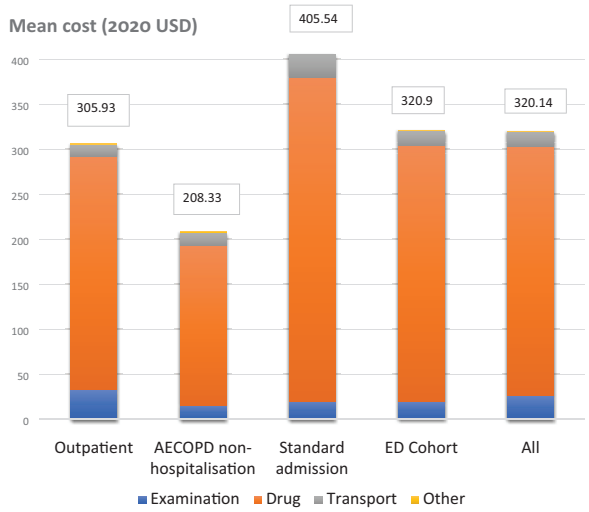

Figure 1. Mean of annual COPD treatment costs by expense and patient groups.

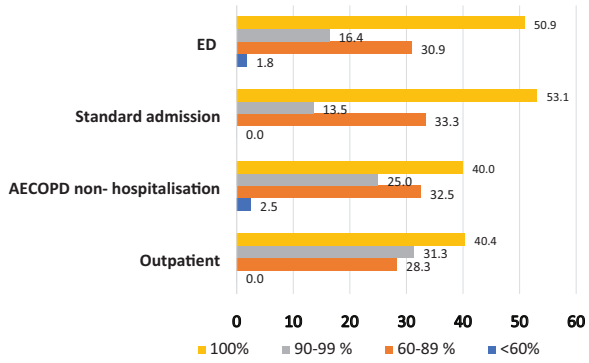

Figure 2. Health insurance benefit rates by patient groups.

by 25% (OR 0.251, CI 0.24-0.76).[10] The association between adherence (as measured by the MMAS score) and lower disease impact (as measured by a CAT score of ⩽15) was reported with OR=0.56 [95% CI: 0.33-0.95, *P*=.03).[13] In our study, the patients with CAT score equal or greater than10 points has the non-compliance rate of 82.8%. It is reported that the high CAT scores are associated with lower adherence and so this group of patients need offering more personalized education, reminders of adherence, and more listening to address their issues.[14] The compliance rate of our study is high due to the collection of data from specialized units managing chronic obstructive pulmonary disease (COPD), rather than general clinics. Within these units, COPD patients are consolidated and administered monthly medication, while being closely monitored by specialized physicians on a monthly basis. Additionally, patients receive guidance on the proper usage of inhalation devices and timely instruction to rectify any errors in their usage.

The findings of the statement contradict popular belief that the adherent group is closer to the out-patient clinics than the non-adherent group. According to a study in Nepal, among 121 COPD patients, those who had access to medical facilities within a 30-minute distance had a higher degree of medication adherence (OR: 0.10; 95% CI: 0.02-0.55).[5] Vietnam has a limited number of management units, particularly in rural areas. However, the government's national program aimed at preventing and controlling COPD has resulted in the establishment of management units that provide low-cost medication, covered by health insurance. This provides an incentive for patients to visit these units, despite potential transport challenges, as they can obtain medication at lower costs or even free of charge. Moreover, patients residing near hospitals in larger cities with better economic conditions may not prioritize health insurance medication, instead relying on nearby healthcare facilities and only seeking treatment when faced with severe breathing difficulties. This can lead to lower medication compliance rates.

It has been found that higher healthcare costs are associated with the treatment of acute exacerbations. In Vietnam, the annual average out-patient treatment costs are much lower than in other countries, at $310.2. In a study in Canada, the mean annual total COPD-related cost per patient was $4147. Both the costs for maintenance therapy and acute treatment increased regarding the COPD severity level.[15]

In our study, the treatment regimens commonly used in our study were ICS/LABA (82.9%) with only 0.8% of patients using regimens with LAMA only. The percentage of patients taking different kinds of medications (ICS/LABA combination, LABA, and long-acting anticholinergic medications) increased as the severity of COPD increased. In moderate to severe COPD patients, 70% of the $2475 per patient was from medication for maintenance treatment.[15] Figure 1 of our study displays data indicating that outpatient COPD patients spent $259.08 on medication, which represents 84.68% of the total cost of $305.93. These results imply that medication expenses remain the primary cost associated with COPD treatment.

In both groups (non-adherence, adherence), the same rate of acute exacerbations (more than one time) in the previous year was found, similar to other studies that showed patients having 1 or 2 acute exacerbations in the previous year.[16,17]

Interestingly, it was found that the annual cost of non-adherent patients was lower significantly to adherent patients. This could be explained by the saving cost of skipping medical checkups as scheduled in non-adherent patients. This issue should be solved by patient education and consultancy in order to reduce the risk of treatment failure due to late detection of symptom progression during COPD out-patient clinic management.

Our study has several strengths, such as a large sample size and well-validated tools (MMAS, mMRC, and CAT) that provides an overview of the current state of COPD management in Vietnam. However, there are some limitations to this study, such as the fact that the study population may not be representative of the entire COPD population in Vietnam, as all 3 study sites were concentrated in the North of the

country. Additionally, data collection and verification were time-consuming.

Conclusion

The use of ICS/LABA as the main mode of treatment in Vietnam persists due to economic constraints. The exclusion of LABA/LAMA drugs from the list of medicines covered by health insurance poses a challenge to GOLD-based prescription practices. Medicinal expenses remain a significant factor in treatment costs. It has been observed that patients with higher CAT scores have lower adherence to medications, necessitating increased vigilance in adherence monitoring to enhance therapeutic outcomes in the management of chronic lung disease.

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Author Contributions

Phan Thanh Thuy: Conceptualization (equal); Methodology (equal); Data curation (lead); Investigation (equal); Validation (lead); Writing-original draft (equal).

Vu Van Giap: Conceptualization (equal); Methodology (supporting); Data analysis (lead); Writing-review & editing (equal); Le Thi Tuyet Lan: Methodology (equal); Writing-review & editing (equal) Nguyen Viet Nhung: Methodology (equal); Writing-review & editing (equal) Ngo Quy Chau: Methodology (lead); Writing-review & editing (lead).

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