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ORIGINAL ARTICLE

Evidence of the association between adherence to treatment and mortality among patients with COPD monitored at a public disease management program in Brazil

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ABSTRACT

Objective: To evaluate the association between adherence to treatment and mortality among Chronic Obstructive Pulmonary Disease (COPD) patients treated in the Brazilian public health system. **Methods:** This is cohort study of moderate-to-severe COPD patients monitored in a public pharmaceutical care-based Disease Management Program (DMP). All subjects who died one year after the beginning of the cohort were age-matched with those who remained alive at the end of the cohort period. Treatment adherence was measured through pharmacy records. Patients who received at least 90% of the prescribed doses were considered adherent to treatment. **Results:** Of the 333 patients (52.8% age ≥ 65 years, 67.9% male), 67.3% were adherent to treatment (adherence rate, 87.2%). Mortality was associated with lack of adherence (p = 0.04), presence of symptoms (mMRC ≥ 2) and COPD treatment use. The death was associated with non-adherence, presence of symptoms and previous hospitalization. After adjustment, non-adherent patients to treatment were almost twice times likely to die compared to those adherents (Hazard Ratio (HR) 1.86; CI 1.16-2.98, p = 0.01). **Conclusion:** Non-adherence to treatment was associated with higher mortality among moderate-to-severe COPD patients treated in the Brazilian public health system. Strategies to monitor and optimize adherence should be strengthened to reduce COPD-related mortality.

Keywords: COPD; Treatment adherence; Mortality; Pharmaceutical care.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease which is characterized by persistent limitation in the airflow.[1] Currently, it is the main cause of morbimortality around the world, which results in a significant and growing economic and social burden.[1] In Brazil, only three conditions have a higher mortality. Additionally, it was the main cause of death from pulmonary disease in 2017.[2]

Adherence to drug treatment is one of the most important factors for disease management and its failure should be considered the main cause for inadequate treatment response.[1] Unsatisfactory adherence can lead to unfavorable disease outcome, including hospitalization and poor quality of life. Koehorst-Ter and collaborators,[3] using data from the COMIC study, found out that low adherence to inhaled corticosteroids (ICS) and tiotropium was associated with a greater risk of mortality in individuals with COPD.[4]

COPD treatment adherence rates are being reported in real-world studies between 16.0% and 67.0%.[5-9] In fact, the causes associated with the lack of adherence are being more commonly reported as level of schooling, pulmonary function, severity of disease and the presence of symptoms. However, few studies have explored the association between adherence to treatment in COPD patients and mortality.

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Despite the free access to medication policy for the COPD treatment within the Brazilian public health system,[10] recent studies have shown high frequency of undertreatment.[11,12] Furthermore, there are limited data concerning adherence and risk factors for that. This study aimed to evaluate the association between adherence to treatment and mortality among patients with COPD monitored at a public disease management program in the Brazilian public health system.

METHODS

This is a cohort study involving patients previously diagnosed with COPD and referred from the public health care network to the referral outpatient clinic of the pharmaceutical care-based Disease Management Program (DMP) at Octávio Mangabeira Specialized Hospital in Salvador, in the state of Bahia, Northeast of Brazil. The objective of the program was associated with the improvement regarding clinical management and capacity for decision making for respiratory diseases (COPD, asthma, tuberculosis, acute respiratory infection, and lung cancer) within the scope of the public health system in the state of Bahia. The program activities could include medical and pharmaceutical care with free and continuous drug dispensing.

Patients

The present study selected individuals with COPD admitted to the DMP between June 2011 and January 2012 who were 40 years old or more, presenting a disease severity as Global Initiative for Chronic Obstructive Lung Disease II (GOLD II) (moderate), GOLD III (severe) or GOLD IV (very severe)[13] and a post-bronchodilator Forced Expiratory Volume$_1$/Forced Vital Capacity (FEV_1/FVC) ratio < 0.7 and post-bronchodilator FEV_1 < 80% of predicted, as measured by spirometry. Individuals with either (1) asthma, (2) refused to participate in the study or (3) could not provide written Informed Consent Form (ICF) were excluded from study.

Individuals who fulfilled the criteria for eligibility were included in the cohort and their treatment process was monitored for at least 12 months. Within this cohort, the individuals who completed at least one year of exposure to the program alive and during follow-up died before January 31st, 2019 (date set as the end of the cohort follow-up) was age-matched with those who remained alive until January 31st, 2019. Each death was matched with up to three live controls. Mortality was ascertained during active follow-up or through the Brazilian Ministry of Health's Mortality Information System. COPD-related deaths were defined according to the codes J40 - J44 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization (WHO).[14]

Procedures

Enrollment and monitoring procedures details of the participants cohort were specified in a previous study.[11] In synthesis, the patients were admitted into the program and interviewed by two trained pharmacists and a pneumonologist, who used standardized questionnaires to obtain study data. Through these questionnaires, the investigators collected sex, age, self-reported skin color; years of schooling and per capita family income in minimum wages at the time of the study; smoking status, smoking load, duration of COPD in years, number of comorbidities and spirometry results (FEV_1, pre- and post-bronchodilator), emergency department visits/hospitalizations due to COPD in the last year and use of drugs other than for the COPD treatment in the past seven days.

The basal level of dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea scale, those with score of two (2) or more were classified as symptomatic. The COPD spirometric severity classification followed the 2011 GOLD criteria,[13] to which 50% ≤ FEV_1 < 80% was considered as moderate COPD (GOLD II), 30% ≤ FEV_1 < 50% as severe (GOLD III) and FEV_1 < 30% as very severe (GOLD IV). Patients were classified in ABCD in accordance with the GOLD 2011 recommendations.[13] The spirometry (Koko Pneumotach model; PDS Instrumentation Inc., Louisville, CO, USA) was performed in accordance with the American Thoracic Society/European Respiratory Society recommendations.[15] The spirometric variables were expressed in percentage predicted, based on the Brazilian population reference values.[16]

The drugs referred being used as a response to the question "use of some medication for the treatment of COPD", were categorized as short-acting bronchodilators [Short-Acting Muscarinic Antagonists (SAMA), Short-Acting Beta Agonists (SABA) and their combinations]; long-acting bronchodilators [Long-Acting Muscarinic Antagonists (LAMA) and Long-Acting Beta Agonists (LABA), either isolated or combined with ICS]; ICS; and methylxanthines.

While participants were followed in the DMP, the pharmacists dispensed the medications and oriented them for treatment adherence, effectiveness and safety of physician prescribed drugs and the inhaled devices correct management. The drug dispensation occurred monthly, when dates of attendance, amount of medication given were recorded.

Ethical aspects

The study protocol was approved by the Research Ethics Committee of the Bahia State Department of Health (protocol n° CAAE: 17268313.8.0000.5030). All patients signed an ICF.

Sample size calculation

The sample size was calculated based on the following assumptions, i.e., the total number of the moderate-to-severe COPD patients in the state of

Bahia. Based on data from PLATINO[17] study, it was 45,900 patients; relative error margin of 5%; confidence interval of 95%; estimated adherence prevalence of 80%, considering the disease severity and the availability of free medication to all of the patients treated via the DMP and 20% loss to follow-up. From this rationale, a minimum sample of 294 individuals should be followed in the cohort study, to reach a representative sample of this population.

Statistical analysis

The rate of adherence was estimated using following formula: (ND ÷ NT) X 100**;** where ND = number of doses actually dispensed and NT = number of doses that should have been dispensed in the period. Patients who received at least 90% of the prescribed doses within the initial 12 months after admission to the program were considered adherence to treatment. The reason why this rate was higher than the ones recorded in the literature (80%)[5,7,18,19] was related to the fact that our patients sample presented greater disease severity and had free access to COPD drugs provided by DMP.

To analyze the date, the statistical package of IBM SPSS Software (Statistical Product and Service Solutions - IBM Corporation, Armonk, NY, USA) version 18.0 was used. The frequency of the categorical and nominal variables were calculated to describe the data; average and standard deviation for the continuous variables, or median and interquartile interval, when the variables did not meet normal distribution, was calculated. The Chi-square test was used to verify possible associations between categorical variables. For the continuous variables, the Student's *t* test and Mann-Whitney U-test were used to investigate the association between independent variables and adherence to treatment. Variables with $p \leq 0.10$ were included in an adjusted Cox regression model to evaluate their influence on mortality. In the regression model, the variable of time of duration of COPD was transformed into a logarithmic scale (t-$COPD_{lg}$) to obtain an approximately normal distribution. The Hazard Ratio (HR) was calculated with Confidence Intervals (CI) of 95% (95% CI).

RESULTS

A total of 441 patients were invited to participate in the study. Of these, 333 were included in the cohort to evaluate adherence to treatment and 257 in the matched analysis (Figure 1).

Most participants from the cohort were male (67.9%), elderly (52.8% ≥ 65 years) and their family income

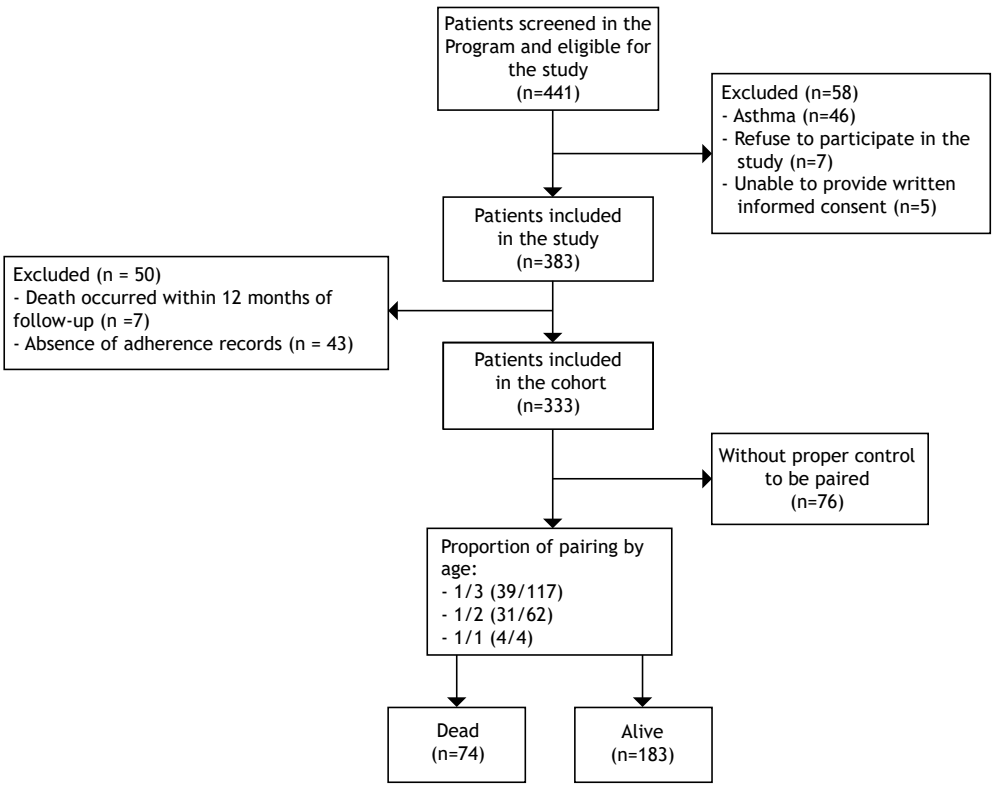

Figure 1. Flowchart of the participants' study.

was less than or equal to a minimum wage (81.7%). Almost half of them (44.7%) belonged to the GOLD D group. The general characteristics of the patients according to the non-adherent and adherent group to treatment are presented in Table 1.

The rate of adherence to treatment was 87.2%. Overall, 224 (67.3%) patients from the cohort were adherence to treatment. Adherence was associated with mMRC dyspnea grade (p = 0.02) and the previous use of some medication to the treatment of COPD (p = 0.03).

It could be noted that those adherent patients to treatment died less than those not adherence (20.1% *versus* 29.4%, p=0.04). Age at the beginning of the cohort was strongly associated with mortality (dead: mean age at the beginning 70.3 (11.7) years; alive: 64.6 (11.2), $p < 0.0001$). According to this result and in order to minimize the effect of age on mortality, matched by age was performed. The individuals more symptomatic (mMRC ≥ 2) (p = 0.03) and who were hospitalized (p= 0.02) died in greater proportion after a year of study monitoring (Table 2). The participants who had the disease for a greater length of time (p = 0.01) remained alive until the end of the monitoring period.

After adjustment, the likely of being dead at the end of the cohort's monitoring period was almost two times greater for those who did not adhere to treatment in the first 12 months (adjusted HR 1.86; CI 1.16-2.98, p = 0.01) (Table 3). After the first year of the monitoring, the survival mean time, in years, was greater within those who adhered to treatment (7.0 *versus* 6.4 years, p = 0.02). Figure 2 shows survival curves of mortality for adherent and non-adherent patients to treatment.

DISCUSSION

The rate of adherence to treatment of the cohort (87.2%) was greater than those observed in previous studies in the real world, in which values varied from 16.0% - 67.0%.[3,5,6,20,21] These results could be

Table 1. Comparison of the general characteristics of adherent (≥ 90%) and non-adherent (< 90%) patients to treatment in the cohort (n = 333).

Characteristics	Non-adherent (n=109)	Adherent (n=224)	*p*-value*
Male	67 (61.5%)	159 (71.0%)	0.05
Age ≥ 65 years	60 (55.0%)	116 (53.8%)	0.33
Age at cohort entry[a]	66.2 (11.1)	65.8 (11.8)	0.76
Less than nine years of schooling	92 (84.4%)	180 (80.4%)	0.23
One or less NMW per capita of family income	88 (80.7%)	184 (82.1%)	0.43
Pack-years smoking history[b]	30.0 (15.0-54.0)	30.0 (15.0-50.5)	0.90
Smoking status			
Never smoked	91 (83.5%)	199 (88.8%)	0.06
Former smoker	14 (12.8%)	11 (4.9%)	
Smoker	2 (1.8%)	9 (4.0%)	
COPD duration in years[b]	6.0 (3.0-14.0)	7.0 (3.0-10.0)	0.76
Five or more comorbidities	5 (4.6%)	17 (7.6%)	0.22
Pre-bronchodilator FEV_1 (% predicted)[a]	39.21 (±14.47)	36.56 (±12.90)	0.14
Post-bronchodilator FEV_1 (% predicted)[a]	42.41 (±15.66)	39.46 (±13.42)	0.15
mMRC dyspnea grade, ≥ 2	79 (72.5%)	186 (83%)	0.02
Mortality	32 (29.4%)	45 (20.1%)	0.04
Spirometric severity			0.21
Moderate	34 (31.2%)	51 (22.8%)	
Severe	46 (42.2%)	113 (50.4%)	
Very severe	29 (26.6%)	60 (26.8%)	
GOLD group			
A	9 (8.3%)	10 (4.5%)	0.16
B	8 (7.3%)	19 (8.5%)	
C	21 (19.3%)	28 (12.5%)	
D	71 (65.1%)	167 (74.6%)	
Emergency department visit	60 (55.0%)	116 (51.8%)	0.36
Hospitalization	25 (22.9%)	56 (25%)	0.39
Use of any previous medication to treat COPD	71 (65.1%)	170 (75.9%)	0.03

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced Expiratory Volume in the first second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; NMW: National Minimum Wage. Statistical analysis: Chi-square test. [a]student *t* Test: mean (standard deviation); [b]Mann-Whitney test: median (interquartile range); *A p-value < 0.05 was defined as statistically significant.

Table 2. Demographic clinical and functional characteristics of dead and alive individuals until January 31st, 2019.

Characteristics	Dead (n = 74)	Alive (n = 183)	*p*-value*
Male	51 (68.9%)	123 (67.2%)	0.46
65 or more years of age	53 (71.6%)	117 (63.9%)	0.15
Age at the beginning of the study[a]	69.4 (11.0)	67.4 (11.2)	0.19
Less than nine years of schooling	66 (89.2%)	146 (79.8%)	0.05
One or less NMW per capita of family income	61 (82.4%)	148 (80.9%)	0.46
Pack-years smoking history[b]	27.8 (9.5-59.3)	30 (15.00-51.5)	0.73
Smoking status			
Never smoked	4 (5.4%)	6 (3.2%)	0.73
Former smoker	63 (85.1%)	162 (88.5%)	
Smoker	7 (9.5%)	14 (7.6%)	
COPD duration in years[b]	5.0 (2.0-10.0)	8.0 (3.0-14.0)	0.01
Five or more comorbidities	5 (6.8%)	12 (6.6%)	0.57
Pre-bronchodilator FEV_1 (% predicted)[a]	35.6 (±14.9)	38.2 (±13.1)	0.18
Post-bronchodilator FEV_1 (% predicted)[a]	38.0 (15.1)	41.1 (±13.8)	0.11
mMRC dyspnea grade, ≥ 2	65 (87.8%)	141 (77.0%)	0.03
Adherence to treatment	43 (58.1%)	127 (69.4%)	0.06
Spirometric severity			0.31
Moderate	17 (23.0%)	51 (27.9%)	
Severe	31 (41.9%)	85 (46.4%)	
Very severe	26 (35.1%)	47 (25.7%)	
GOLD group			
A	2 (2.7%)	12 (6.6%)	0.24
B	6 (8.1%)	16 (8.7%)	
C	7 (9.5%)	30 (16.4%)	
D	59 (79.7%)	125 (68.3%)	
Emergency department visit	45 (60.8%)	92 (50.3%)	0.08
Hospitalization	27 (36.5%)	42 (23.0%)	0.02
Use of any previous medication to treat COPD	51 (68.9%)	130 (71.0%)	0.42

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced Expiratory Volume in the first second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; NMW: National Minimum Wage. Statistical analysis: Chi-square test. [a]student *t* test: mean (± standard deviation); [b]Mann-Whitney test: median (Q1-Q3); *A *p*-value < 0.05 was defined as statistically significant.

associated with the fact that our sample consisted of mainly severe and symptomatic patients and who participated in a pharmaceutical care-based DMP, in which the interventions included monitoring and optimization of treatment adherence. Recent evidence has shown the benefits of the practice of pharmaceutical care on important outcomes for COPD, including improvement adherence to treatment.[22-29]

Generally, adherence rates near to 80% are found in clinical trials,[19] in which the study conditions are more controlled when compared with studies in the real world. Greater frequency of symptoms (mMRC ≥ 2) and greater disease severity can be associated with adherence to inhaled medications.[30-33]

Association between adherence and mMRC ≥ 2 ($p = 0.02$) was found by Boland and colleagues, in a 2-year cluster randomized trial,[19] showing that more symptomatic patients adhered more to the treatment than less symptomatic patients during the second trial-year. This finding strengthens our hypothesis that more symptomatic patients have a higher need for medication and as a result, they are more likely to be adherence to treatment.

Still with the cohort, the results showed an association between adherence and the previous use of some medication to treat COPD (75.9%, $p = 0.03$), demonstrating that those patients who were using inhaled medications, even if undertreated,[11] had more chances to maintain the therapy after being admitted to the DMP. The results of our analyses are in accordance with the findings of cohort studies which confirm previous adherence as the dominant predictor of future adherence.[5,34] In one of these studies, Ingebrigtsen and colleagues,[5] using an indirect method to estimate the adherence, found that previous adherence (adherence for ICS/LABA, LAMA and LABA during the first year) was associated with the increased adherence in COPD patients.

The association between non-adherence to treatment and increase in mortality evident in the multivariate analysis (adjusted HR 1.86; 95% CI 1.16-2.98, $p = 0.01$) adjusted for schooling, mMRC grade, hospitalization,

Table 3. Multivariate analysis adjusted by Cox regression of the mortality predictor variables.

Variables	*p*-value*	Adjusted Hazard Ratio	95% CI	
			Lower	Upper
Non-adherence to treatment	0.01	1.86	1.16	2.98
Less than nine years of schooling	0.09	1.92	0.92	4.04
Post-bronchodilator FEV_1, % predicted	0.24	0.99	0.97	1.01
mMRC dyspnea grade, ≥ 2	0.06	2.00	0.98	4.11
$t\text{-}COPD_{log}$	0.01	0.54	0.34	0.84
Emergency department visit	0.79	1.07	0.66	1.75
Hospitalization	0.03	1.72	1.06	2.82

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; mMRC: modified Medical Research Council; $t\text{-}COPD_{log}$: log of COPD duration; FEV_1: Forced Expiratory Volume in the first second; *A *p*-value < 0.05 was defined as statistically significant.

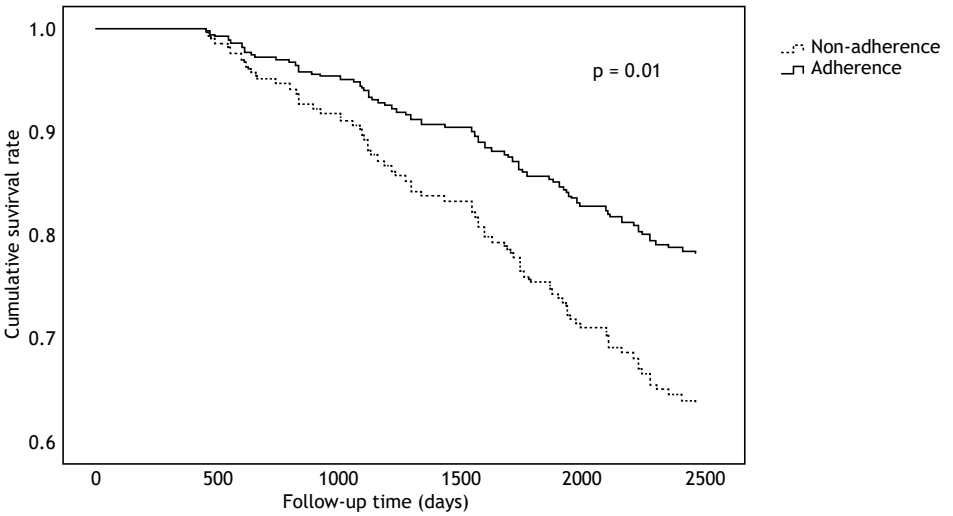

Figure 2. Survival curves of mortality showing a comparison between adherent and non-adherent to patients treatment by multivariate Cox-regression survival analysis.

post-bronchodilator $FEV_{1\%}$ and log of duration of COPD, was consistent with previous studies.[3,19,20] An analysis of the study entitled *Cohort of Mortality and Inflammation in COPD* (COMIC) performed in the Netherlands found an increase in risk of mortality among COPD patients with underuse of ICS and tiotropium compared to those in optimal use, with a HR equal to 5.3 (95% CI 3.3-8.5) *versus* 6.4 (95% CI 3.8-10.8), respectively.[3] A populational-based Italian study[20] involving 12,224 patients with moderate to severe COPD evaluated the impact of adherence to inhaled therapy on a survival period of 5 years; and showed that individuals who regularly used LABA had higher survival rates than those who occasionally used a combination of ICS/LABA (HR = 0.89, 95% CI 0.79-0.99). Further, a secondary analysis of the study *Towards a Revolution in COPD Health* (TORCH), a randomized clinical trial, involving 6,112 patients with moderate to severe COPD with a duration of 3 years,[19] showed an association between adherence and mortality (HR = 0.40, 95% CI 0.35-0.46, $p < 0.001$). Despite the difference in methodologies between the different studies, such findings showed the substantial impact of adherence to treatment on mortality and reinforced the importance of adequate evaluation of adherence to treatment in the daily clinical practices of these patients, with the aim of achieving suitable disease management.

Despite the high rate of adherence found in this study, it was evident that patients with COPD who had a low adherence rate in the first year in the DMP were those who had a higher risk of death after this period. Thus, this finding reinforces the necessity of implementing measures which promote changes in these patients' behavior, ensuring that they adhere to the prescribed treatment in order to achieve positive health results. Therefore, the implementation of initiatives based on pharmaceutical care in which interventions include encouraging consciousness raising about health conditions, including the identification of signals and symptoms to disease control; training about correct inhalation technique, as well as identification, treatment, prevention and monitoring of problems

related to medications. These are the recommended actions which have already had promising results around the world.[26-29]

There were some limitations in this study. The first was inherent to the indirect method of assessment of adherence used. Dispensation may not reflect adherence to the prescribed pharmacotherapy nor exact usage of the dispensed medicine.[35] However, studies showed high consistency between dispensation and consumption by patients.[36-38] Another limitation was that only one method for evaluating adherence was used, whereas recommendation is related to the use of more than one method.[39] However, studies showed that estimates for adherence obtained from records of medicine dispensing were comparable to those provided by direct methods such as electronic measures; therefore, those were a good estimate for adherence.[40]

To our knowledge, this was the first large-scale study carried out in a Brazilian population of COPD patients treated in the public health system that evaluated the adherence to treatment and patient-related determinants. However, new studies, combined with other methods to evaluate adherence using prospective designs, should be considered in order to identify predictive factors for adherence and the relation between adherence and morbidity and mortality related to the disease.

In conclusion, COPD patients monitored in a pharmaceutical care-based DMP of a public health system with free supply of drugs showed a high rate of adherence to treatment. Non-adherent individuals to treatment at the first year of follow-up were almost twice times likely to die compared to those adherents. Strategies to monitor and optimize adherence should be implemented to reduce COPD-related morbidity and mortality.

AUTHOR CONTRIBUTIONS

CRP, ACML, LAC and GSS: contributed to the design and concept of the study. CRP and ATAM: carried out the data collection. EMN and CRP: performed the statistical analyses and data interpretation. ATAM and CRP: drafted the manuscript. EMN, CRP and ACML: checked the final manuscript and revised it critically. All authors read and approved the final manuscript.

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