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ORIGINAL RESEARCH

Acute Exacerbations of COPD: Delay in Presentation and the Risk of Hospitalization

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ABSTRACT

To determine if a delay in presentation to the emergency department (ED) after the onset of symptoms of an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) increases the risk of hospital admission. A prospective cohort study utilizing data from 396 patient visits to 29 North American EDs. Inclusion criteria were age ≥ 55 years; a diagnosis of COPD; and presentation for treatment of AECOPD, as defined by increasing shortness of breath, worsening cough, or change in sputum production at presentation. The median age was 69 years and 54% were female. Most patients (70%) presented to the ED > 24 hours after symptom onset, and most (61%) were hospitalized. On multivariate logistic regression analysis, after adjusting for 12 potential confounders (including demographics, clinical features, other diagnoses, and bronchodilator use before arrival), a delay in presentation ≥ 24 hours was associated with a over two-fold increase in the odds of admission (odds ratio = 2.2, 95% confidence interval 1.1–4.8). This increase in risk persisted for delay in presentation ≥ 12 hours in place of 24 hours, after restricting the analysis to patients admitted outside the intensive care unit, and to those reporting the ED as their usual site of care. A majority of patients delay presentation to the ED for ≥ 24 hours after symptom onset, and are at higher risk of hospitalization. Early presentation should be emphasized to patients and caregivers to advance efforts to decrease the morbidity, mortality, and costs of AECOPD treatment.

INTRODUCTION

Each year in the United States acute exacerbations of chronic obstructive pulmonary disease (AECOPD) result in 1.5 million patient visits to emergency departments (EDs) and 726,000 hospital admissions (1). The risk of in-hospital death for each admission for AECOPD is about 11% (2, 3).

Among the patients reporting to the ED for AECOPD treatment, some choose to present early after symptom onset (early-presenters) while others wait significantly longer (late-presenters) (4). While prior studies have found that late-presenters have longer exacerbations, it remains unclear if late-presenters are also at higher risk of hospitalization for treatment of the exacerbation (4–7). It is important to know, if by delaying presentation, late-presenters are placing themselves at higher risk of hospitalization, because the sizable morbidity/mortality and cost associated with these hospital admissions may be preventable. Moreover, there are no published studies that have characterized early and late presenters either in terms of demographics, health insurance coverage, or clinical features. Characterizing these patient populations would offer insight into why some patients present early or late after symptom onset.

The aim of this study was to determine if late presentation increases the risk of hospital admission, and to characterize patients presenting early vs. late to the ED for treatment of AECOPD using data gathered from a multicenter prospective cohort

Keywords: admission, chronic obstructive pulmonary disease, emergency department, exacerbation, late presentation, time to presentation.

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study. We hypothesized that patients presenting late would: (1) be at increased risk for admission to the hospital, and (2) present with worse symptoms.

METHODS

We utilized information gathered during the Multicenter Airway Research Collaboration (MARC, a division of the Emergency Medicine Network) study in 2000-01. Details of the study design have been published previously (8) and will be repeated here only in brief.

Study population

Patients were recruited via interview with research staff after arrival in either of 29 EDs in 15 US states and 3 Canadian provinces. Investigators at each ED provided 24-hour/day coverage for a median of 2 weeks under a standardized research protocol. Inclusion criteria were age ≥ 55 years; a diagnosis of COPD; and presentation for treatment of AECOPD, as defined by increasing shortness of breath, worsening cough, or change in sputum production at presentation (9, 10). Some studies on outpatients with COPD have required that these symptoms be present for at least 24 or 48 hours before AECOPD is diagnosed. We did not implement such a time requirement, because unlike the studies performed on outpatients, the symptoms in our patients were already severe enough to warrant ED presentation. The cohort was restricted to those older than 55 years in age to minimize inclusion of patients with only asthma and not COPD. Exclusion criteria were the inability to give informed consent and repeat visits by individual patients.

The following question was asked to determine the presence of COPD: "Has a doctor ever said that you have asthma? COPD? emphysema? or chronic bronchitis?" COPD was said to be present if patients reported COPD, emphysema, or chronic bronchitis. To exclude diagnostic misclassification a validation study was performed in a subset of the study population ($n = 60$) (11). Spirometry results, medical records, chest radiology reports, and arterial blood gas measurements were requested and reviewed for each patient in this validation cohort. Spirometry results were interpreted using the Global Initiative on Chronic Obstructive Lung Disease (GOLD) criteria (12) with documentation of $FEV_1/FVC \geq 0.70$ or $FEV_1 \geq 80\%$ predicted excluding a diagnosis of COPD. A physician diagnosis of COPD was present in the medical records for 97% of patients, and using a combination of spirometry, medical record review, chest radiology, and arterial blood gas measurement, COPD was diagnosed in 98% (11). Radiology or arterial blood gas results were not used as a standalone criteria to diagnose COPD in any patient. Spirometry results met the GOLD criterion for COPD (available in 42 patients) in 93%.

Then, 584 patients presented to the ED with an acute exacerbation of COPD during the study period. Of these, 397 (68%) were enrolled and consented to an ED interview. Compared to enrolled patients, non-enrolled patients were older (69 vs. 73 years, $p < 0.001$), more likely to be intubated in the past (14%

vs. 33%, $p < 0.001$), and more likely to be admitted (61% vs. 74%, $p = 0.003$). As a result of their increased acuity, non-enrolled patients were less able to undergo data collection. We further excluded one patient with missing data on duration of symptoms, leaving 396 patients for the current analysis.

Data collection and processing

Trained research personnel performed the ED interview to collect information on each patient's demographic and baseline clinical characteristics, COPD history, and details of the current exacerbation. This information was collected within the first hour of presentation when most patients were unaware of the decision to admit or discharge them.

Patients were asked the following question to determine the time elapsed between symptom onset and ED presentation: "How long ago did your current COPD attack begin?" Given the absence of a standardized definition, we defined "early-presenters" as those presenting within 24 hours of symptom onset, and "late-presenters" as those presenting ≥ 24 hours after symptom onset. We thought that a one day cutoff between early and late presentation would be easy for both patients and care givers to remember.

Patients were asked to self-report the frequency, severity, and activity limitation for the exacerbation. For example, to determine symptom frequency patients were asked: "Over the last 24 hours, how often did you experience COPD symptoms?" Response was coded as: none/some/most/all of the time. Patients were also asked an exploratory question to identify precipitating causes for the exacerbation: "Do you think that this COPD attack was triggered by a respiratory infection?"

Median family income was estimated using patients' home postal codes (13, 14). Insurance status was categorized as private (commercial or private), Medicaid, other public (all Canadian and Medicare), or none. Admission to the hospital was defined as admission to the intensive care unit (ICU), the medical floor, or to observation. Data on ED management and disposition were obtained from chart review. All patients were managed at the discretion of the treating physician.

Relapse was defined as a worsening of respiratory symptoms that led to an urgent unscheduled clinic visit or ED visit for further care during the 2-week follow-up period. Follow-up data were collected by telephone interview 2 weeks later. All forms were reviewed by site investigators before submission to the EMNet Coordinating Center in Boston, MA, where they underwent further review by trained personnel and then double data entry.

Statistical analysis

Summary statistics are presented as proportions with 95% confidence intervals (CI), or medians with interquartile range (IQR). For categorical variables, the association with time to presentation was examined using chi-square or Fisher's exact tests, as appropriate. For continuous variables, the t-test or Mann-Whitney test was used after assessing the data for normality.

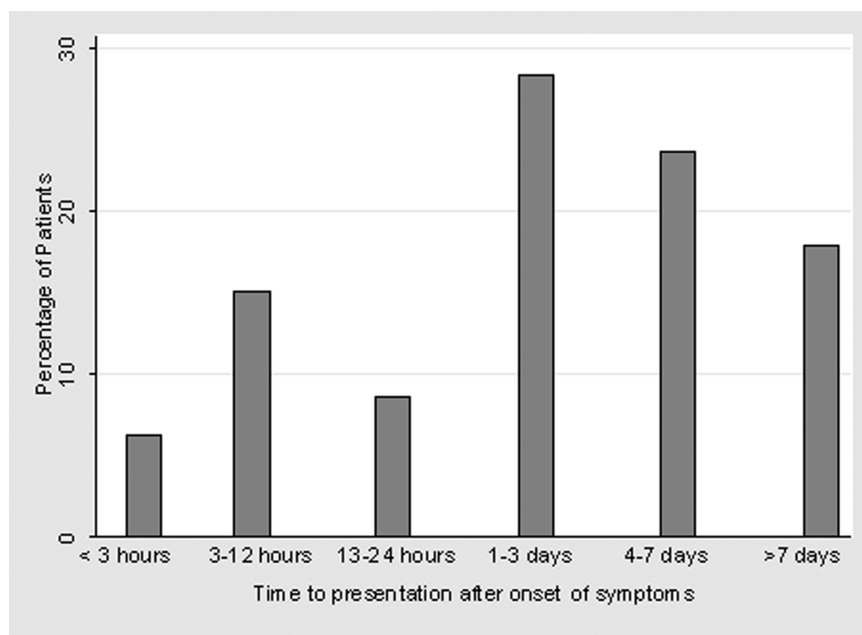


Figure 1. Percentage of patients with acute exacerbation of chronic obstructive pulmonary disease presenting to the emergency department after varying amounts of time from symptom onset.

A multivariate logistic regression model, with admission to the hospital as the outcome variable, was created using variables associated with admission at $p < 0.10$ on univariate analysis. Age, gender, race, and inhaled beta-agonist use in the 6 hours before presentation were included throughout the model-building process because of their potential clinical significance. We excluded statistically significant variables that occurred more than 60 minutes after ED presentation because they may have been influenced by the decision to admit, and variables with substantial missing data (i.e., PaO_2 and PaCO_2). The area under the receiver-operating-characteristic (ROC) curve was used to assess discrimination, while the Hosmer-Lemeshow test was used to assess goodness-of-fit. Interaction terms were generated to test for significant interactions.

A sensitivity analysis was performed by excluding patients admitted to the ICU because these patients had severe exacerbations and were thus likely to have been admitted irrespective of time to presentation. To determine the relationship between time to presentation and risk of admission for frequent ED users, we also performed a sensitivity analysis restricted to only those patients who reported that the ED was their usual site for COPD care. Finally, to determine how the results would change with a reduction in delay in presentation, we repeated the analysis using 12 hours as the cutoff for defining early vs. late presentation (in place of 24 hours). All analyses were performed using Stata 9.0 (StataCorp, College Station, TX). All p -values are two-tailed, with $p < 0.05$ considered statistically significant. The institutional review boards at each of the 29 participating hospitals approved the study, and informed consent was obtained from all participants.

RESULTS

The median age of the cohort ($n = 396$) was 69 years (IQR 62–76 years) and 54% were women. Figure 1 displays the percentage of patients presenting after varying amounts of time from symptom onset. In our cohort, 70% of patients were late-presenters (95% CI 65–74%). The demographic and baseline clinical characteristics for early and late-presenters are summarized in Table 1. Late-presenters tended to include more White patients, have higher income, and have more private insurance, though these differences were not statistically significant. Compared to early-presenters, late-presenters had higher BMI, were significantly less likely to be male, report that the ED was their usual site for COPD care, have been intubated in the past, admitted with COPD, have presented to the ED during the preceding year, and to have used inhaled β -agonists during the last four weeks.

Presentation and course in the ED

Data on presenting symptoms and ED management and clinical course – for early and late-presenters – are shown in Table 2. Late-presenters reported more symptoms than early-presenters, including more frequency and severity, more activity limitation, and more cough and sputum production. Late-presenters were more likely to report that a respiratory infection triggered their acute exacerbation. Late-presenters also reported less β -agonist use in the 6 hours before ED presentation, and were less likely to present after hours. Late-presenters were more likely to be admitted compared to early-presenters.

Table 1. Demographic and baseline clinical characteristics of patients presenting to the emergency department with an acute exacerbation of chronic obstructive pulmonary disease, according to duration of symptoms

Characteristic	Symptoms <24 h (n = 119)	Symptoms ≥ 24h (n = 277)	p-value
Demographic factors			
Age, median (IQR), years	70 (62–77)	69 (62–75)	0.52
Female sex, %	43	56	0.02
Race, %			0.12
White	66	72	
Black	21	21	
Hispanic	12	5	
Other	2	1	
Body mass index, median (IQR), kg/m ²	23.8 (20.5–27.9)	25.6 (21.5–30.2)	0.02
High school graduate, %	50	56	0.29
Household income, median (IQR), \$	36,698 (23,050–45,691)	38,630 (29,530–47,694)	0.07
Healthcare-related factors			
Insurance status, %			0.06
Private	22	26	
Medicaid	22	12	
Other public	50	50	
None	7	12	
Has primary care provider, %	88	91	0.40
ED usual site for problem COPD care, %	63	48	0.007
ED usual site for COPD prescriptions, %	18	14	0.29
Smoking related factors			
Smoking status, %			0.83
Never smoker	8	9	
Current smoker	30	30	
Past smoker	62	60	
Pack-years of smoking, median (IQR)	53 (35–80)	51 (29–79)	0.38
Diagnosis, %			0.38
COPD only	53	57	
Mixed COPD and asthma	47	42	
Severity of chronic COPD			
Duration of COPD history, median (IQR), years	6 (3–19)	9 (4–19)	0.24
Breathing between COPD exacerbation, %			0.18
No symptoms	18	20	
Some symptoms on some days	36	26	
Some symptoms on most days	19	24	
Symptoms most of the time	28	31	
Ever admission for COPD, %	69	64	0.33
Ever intubation for COPD, %	19	12	0.046
Ever taken corticosteroid for COPD, %	65	65	0.96
Admissions for COPD in past year, median (IQR)	0 (0–3)	0 (0–1)	0.01
Urgent clinic visits in past year, median (IQR)	0 (0–1)	0 (0–2)	0.12
Number of ED visits in past year, median (IQR)	2 (0–5)	1 (0–3)	<0.001
COPD medications in past 4 weeks, %			
Inhaled β -agonists	89	80	0.04
Inhaled anticholinergics	70	61	0.08
Inhaled corticosteroid	49	49	0.95
Systemic corticosteroid	35	37	0.72
Methylxanthine	20	16	0.39
Antibiotics	15	19	0.39
Comorbidity, %			
Coronary artery disease	18	24	0.17
Congestive heart failure	13	21	0.06
History of arrhythmia	10	13	0.36
Depression	10	13	0.42

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; IQR, interquartile range.

Table 2. Emergency department presentation, course, disposition, and relapse in patients with an acute exacerbation of chronic obstructive pulmonary disease, according to duration of symptoms

Characteristic	Symptoms <24 h (n = 119)	Symptoms ≥ 24h (n = 277)	p-value
Symptoms and pre-ED arrival treatment			
Severity of exacerbation in past 24 hrs, median (IQR)			
Frequency of COPD symptoms*	3 (2–3)	3 (3–4)	<0.001
Severity of COPD symptoms†	3 (3–4)	4 (3–4)	0.002
Activity limitations‡	3 (3–4)	4 (3–4)	0.001
Triggered by respiratory infection	37	65	<0.001
Airway symptoms§			
More short of breath than usual	87	92	0.37
Coughing more than usual	51	74	0.01
Bringing up more sputum	35	62	0.006
Change in sputum color	29	41	0.24
No. of β-agonist puffs within 6 hours of ED, median (IQR)	6 (2–12)	4 (0–8)	0.009
No. of anticholinergic puffs within 6 hours of ED, median (IQR)	0 (0–4.5)	0 (0–4)	0.78
ED presentation			
ED triage time, %			0.02
Midnight to 7:59 AM	21	12	
8:00 AM to 3:59 PM	50	64	
4:00 PM to 11:59 PM	29	24	
Respiratory rate, median (IQR), breaths/min	24 (22–28)	24 (20–28)	0.17
O ₂ saturation in room air, median (IQR), %§	94 (89–97)	93 (7)	0.20
Arterial blood gas, median (IQR)			
pO ₂ , mmHg	68 (56–107)	64 (54–78)	0.22
pCO ₂ , mmHg	45 (41–56)	48 (38–61)	0.52
Concomitant diagnosis, %			
Pneumonia	17	16	0.79
Congestive heart failure	10	13	0.39
Arrhythmia	0.8	4	0.09
Pneumothorax	0.8	0.0	0.13
ED course			
No. of inhaled β-agonist treatments in first hour, median (IQR) ¶	1 (1–2)	1 (0–2)	0.002
No. of inhaled β-agonist treatments over ED stay, median (IQR) ¶	3 (2–4)	3 (1–3)	0.04
No. of inhaled anticholinergic treatments in first hour, median (IQR) ¶	1 (0–1)	0 (0–1)	0.08
No. of inhaled anticholinergic treatments over ED stay, median (IQR) ¶	1 (1–3)	1 (1–2)	0.35
Received systemic corticosteroids in ED, %	63	61.5	0.77
Received antibiotics in ED, %	23	30.7	0.11
Received NIPPV, %	3	3.2	0.95
Received intubation in ED, %	0.8	0.3	0.55
ED outcomes			
ED length of stay, median (IQR), minutes	295 (196–415)	314 (230–484)	0.10
ED disposition, %			0.02
Sent home	46	35	
Observation	0.9	2	
Hospital admission	42	57	
Intensive care unit admission	8	6	
Others	3	0.4	
Discharge medications, % **			
Sent home on systemic corticosteroids	60	57	0.68
Post-ED follow-up, % ††			
Relapse event at 48 h	5	2	0.18
Relapse event at 2 wks	19	17	0.65

Abbreviations: COPD, chronic obstructive pulmonary disease; ED, emergency department; IQR, interquartile range; and NIPPV, noninvasive positive pressure ventilation.

*On 4-point ordinal scale. (1, none of the time; 2, some of the time; 3, most of the time; 4, all of the time).

†On 4-point ordinal scale. (1, none; 2, mild; 3, moderate; 4, severe).

‡Available for 122 patients.

§Available for 277 patients.

||Available for 112 patients.

¶Each nebulizer treatment was counted as equivalent to six puffs from a metered-dose inhaler.

**Restricted to patients sent home from ED (n = 150).

††Restricted to patients available for follow-up (n = 349).

Table 3. Results from the unadjusted and multivariate logistic regression analysis for the association between duration of symptoms before presentation and risk of hospitalization among patients with acute exacerbation of chronic obstructive pulmonary disease

Duration of symptoms (sample size)	Covariates adjusted for	Odds ratio for admission (95%CI)
≥24 hours vs. <24 hours (n = 396)	Unadjusted	1.63 (1.04–2.54)
≥24 hours vs. <24 hours (n = 396)	Age, sex, race, ED as usual site of care, codiagnosis of asthma, number of ED visits in last 1 year, inhaled steroid use in the 4 weeks prior to presentation, history of cardiac arrhythmia, inhaled beta agonist use in the 6 hours preceding presentation, respiratory rate, oxygen saturation, and presence of pneumonia on the chest x-ray	2.30 (1.11–4.76)
≥12 hours vs. <12 hours (n = 396)	Adjusted for same variables as above	2.33 (1.03–5.28)
≥24 hours vs. <24 hours, excluding ICU admission (n = 365)	Adjusted for same variables as above	2.40 (1.13–5.10)
≥24 hours vs. <24 hours, if ED is usual site of care (n = 203)	Adjusted for same variables as above	4.11 (1.16–14.62)

Abbreviations: ED: Emergency Department, ICU: Intensive Care Unit.

Risk of admission

Late presentation remained a significant predictor of admission to the hospital on multivariate analysis after adjusting for 12 variables (OR 2.2, 95% CI, 1.1–4.7, Table 3). These variables were selected based on criteria discussed above (see methods section). The area under the ROC curve for this logistic regression model—that contained a total of 13 variables—was 0.81 indicating excellent discrimination, and the Hosmer-Lemeshow test was non-significant ($p = 0.57$) indicating good model fit. No statistically significant interactions were detected. Late presentation remained significantly associated with increased hospitalization by reducing late presentation to a 12-hour cut-off in place of 24 hours, after restricting the analysis to patients admitted to non-ICU beds, and those reporting the ED as their usual site of care (Table 3). Further adjustment for respiratory infection as the trigger of exacerbation did not materially change these results (OR 2.08, 95% CI, 0.98–4.41).

DISCUSSION

This prospective cohort study finds that patients with AECOPD who present to the ED more than 24 hours after symptom onset are at increased risk for hospitalization, and that the increase in risk persists after adjusting for a number of potential confounders, by using a different time cutoff for defining early vs. late presentation, and in subgroup analyses. Late-presenters differ from early-presenters in terms of demographics, access to healthcare, stability of disease (frequency of admission for COPD and history of intubation), bronchodilator use, and frequency and severity of symptoms at presentation.

Risk of hospitalization

The increase in risk of hospitalization among late presenters suggests that early treatment may result in reduction in hospitalization rates for AECOPD patients. A potential mechanism for this finding is a differential response to initial medical treatment in early and late-presenters. The response to initial bronchodilator treatment commonly influences the decision to admit patients with COPD exacerbations. It is known that some patients' airways are more responsive to bronchodilators than others (15–17). It is possible that bronchodilator responsiveness may worsen as the exacerbation progresses. It has already been demonstrated that early treatment with systemic steroids and antibiotics reduces the total duration of an exacerbation (4, 5, 10). Because steroids and antibiotics take time to produce effect, it is unlikely that they would act fast enough to influence the decision to admit a patient in the ED in our cohort (18, 19).

Another possible explanation could be a difference in the triggers of the exacerbation in early vs. late-presenters. In an exploratory analysis we found that late-presenters were much more likely to report that a respiratory infection had triggered their exacerbation, and inclusion of this variable in our multivariate model made the p -value borderline non-significant. It is also possible that the infection had progressed more in late-presenters, resulting in more severe exacerbations compared to early presenters. Notably, there were no differences in the percentage of patients found to have an infiltrate on the chest X-ray among early vs. late-presenters, indicating that the infection may have involved the upper respiratory tract.

Future studies might explore these possible explanations by conducting patient interviews directed at the decision-making

process regarding time of presentation for treatment. Future studies might explore the role of treatment and infection as possible explanations for the higher risk of hospitalization in late presenters.

Early vs. late presenters

In agreement with our hypothesis late-presenters reported worse respiratory symptoms at presentation. There is very limited published information on the association between time to presentation and severity of symptoms of an exacerbation. In a study on 128 COPD patients, participants were asked to maintain daily diary records of symptoms and to report any changes in symptoms to research staff at the earliest, thus influencing their symptom perception and severely limiting their ability to choose time of presentation. Also, severity of the exacerbation was measured by the self-reported number of respiratory symptoms and not the severity of each symptom as in our study. The investigators found that patients with worse symptoms contacted the research staff early (4).

In terms of what determined time to presentation in our cohort, late-presenters had equal, if not better, access to healthcare and worse symptoms than early-presenters. However, due to their more stable COPD in the past they may have been less familiar with the early symptoms of a COPD exacerbation, or may have chosen a “wait and watch” approach. On the other hand, early-presenters may have been patients who were chronically ill with COPD and thus had heightened awareness of their symptoms resulting in earlier presentation to the ED (20). It has been demonstrated that patients with COPD can have very different understanding of their disease and its symptoms (21–24). Besides the patient’s perception of his/her symptoms, it is also possible that late presenters were less familiar with the nearest ED due to infrequent visits in the past, or may have been hesitant to seek care after hours, resulting in a decision to wait till the next day before presenting.

And, 54% of the patients in our cohort were female. Historically, COPD has been far more frequent in men than in women, related to patterns of smoking and occupational exposures (1). Lately, however, COPD prevalence seems to be becoming equal in men and women from high-income countries such as the United States, where smoking habits are more similar between the sexes (25, 26). Other factors contributing to this increase in COPD prevalence in women may be the higher susceptibility to developing COPD among women who smoke compared to men, or a reduction in the under diagnosis of COPD in women in recent years (27).

Limitations

Our study has potential limitations. The diagnosis of COPD was via validated self-report (11). It is not possible to diagnose COPD using spirometry in patients presenting with AECOPD to the ED. For this reason, we validated the diagnosis in our patients after discharge from the ED.

We were unable to enroll all eligible patients presenting to the ED because some of them were acutely ill. This is not a problem in study design, but a reflection of actual emergency-medicine

practice. Some patients may have contacted their physician prior to presentation or started self-medication. Therefore, we collected data on medications given immediately before ED presentation and included this information in our multivariate analysis. Also, when we restricted our analysis to patients who reported that the ED was their usual site of care, time to presentation remained a strong predictor of hospital admission. We did not use spirometric criteria, such as reduction peak expiratory flow (PEF), to determine the time of onset of the exacerbation because prior research has demonstrated that symptoms worsen before the PEF drops during exacerbation onset (28).

Also, most patients do not use PEF to decide when to present to the ED, thus the results from a study using PEF criteria would have limited utility for clinical practice. The decision to admit was made by individual physicians; however we have demonstrated previously that there is high concordance with GOLD criteria for COPD admission at the EDs located at research centers that participate in the emergency medicine network (29). Finally, the findings of our study are based on COPD patients presenting to urban EDs with acute exacerbations and may not be generalizable to all settings where COPD care is provided.

CONCLUSIONS

Almost two-thirds of patients with AECOPD wait for more than a day after onset of increased symptoms to present to the ED for treatment. At presentation, their symptoms are significantly worse than those of early-presenters, and they are more likely to be admitted to the hospital. Early presentation after symptom onset should be emphasized to patients and caregivers, and future studies should confirm if early therapy reduces the risk of hospitalization for AECOPD.

Declaration of interest

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