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Research Article

Disparities in Hospitalized Chronic Obstructive Pulmonary Disease Exacerbation Between Urban and Rural Residence Patients

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Abstract

Background: The prevalence of chronic obstructive pulmonary disease (COPD) is similar among urban and rural populations, as are diabetes and obesity, which are common COPD comorbidities and the similarity of prevalence of COPD in urban and rural areas may be explain with high number of smokers in both areas. However, the exacerbations of COPD requiring hospitalizations and patient outcomes while exacerbations might be different. We explored the disparities in hospitalized patients with COPD exacerbations accordingly patient outcomes between urban and rural residence patients.

Methods: We retrospectively analyzed COPD hospitalizations from 2011 to 2019 at single pulmonary and critical care medicine department of university hospital. In all patients have investigated clinical symptoms, pulmonary function test, radiographic, biochemistry, and sputum biomarkers at time of hospital admission.

Results: Of 1.926 COPD hospitalizations analyzed, 1.256 (65.2%) were for urban metropolitan (Baku city), 478 (24.8%) were for non-metropolitan urban and 192 (10.0%) for rural residents. Respiratory failure requiring ventilation support and oxygen therapy was commonly applied in patients living in metropolitan urban area (OR 2.14 [0.84 - 5.26] 95% CI; $p < 0.001$), treatment failure related to administration of systematic corticosteroids and antibiotics and progression of disease was significantly higher in patients admitted from metropolitan urban area (OR 1.84 [0.79 - 4.26] 95% CI; $p < 0.01$) need to non- invasive mechanical ventilation (NIV) commonly have found also in patients hospitalized from metropolitan urban area (OR 2.21 [0.89 - 6.14] 95% CI; $p < 0.001$). There were no differences among residents from non-metropolitan urban and rural area in clinical characteristics of patients and also patient outcomes (for all parameters $p > 0.05$). Compared to patients from non-metropolitan urban area and rural area in patients admitted from Baku city re-hospitalization rate was significantly higher (OR 2.41 [0.92 - 6.14] 95% CI; $p < 0.001$). Patients admitted from Baku city were characterized with low pulmonary function (FEV % predicted- 39.7 ± 12.26 vs 50.17 ± 11.92; $p < 0.001$), IL-8 ($p < 0.01$) and MMO- 9 ($p < 0.05$) in induced sputum compared to patients admitted from rural and non- metropolitan urban area. Intensive care admission rate was higher compared to non-metropolitan urban and rural area (OR 3.14 [0.98 - 7.21] 95% CI; $p < 0.001$). Length of hospital stay also was higher in patients hospitalized from Baku city (OR 1.69 [0.72 - 3.14] 95% CI; $p < 0.001$). The number of intubated patients related to hypercapnic respiratory failure with respiratory acidosis was higher compared to rural and non- metropolitan urban area residents (OR 3.74 [1.12 - 8.36] 95% CI; $p < 0.001$). Among hospitalized patients in-hospital mortality was higher in residents from Baku city (168 [13.4%] vs 26 [5.4%] and 10 [5.2%]; $p < 0.001$). Thirty-day mortality was also greater

in patients hospitalized from rural area ($p < 0.001$), but was similar in patients living Baku city and other areas. There was no differences in hospital and thirty-day mortality among hospitalized residents from non-metropolitan urban and rural area ($p > 0.05$).

Conclusion: In this retrospective study conducted between 2012 and 2019 in one Azerbaijan metropolitan region (Baku city), and non-metropolitan urban and rural regions, COPD hospitalizations related to exacerbations of the disease are characterized with different severity of exacerbations and different patients outcomes. More severe course of the disease exacerbations was in patients admitted from metropolitan area and the severity of disease exacerbations were associated with higher rate of ICU admission and higher in-hospital mortality rate. More severe disease exacerbations and poor clinical outcomes for patients admitted from metropolitan area might be explain with high traffic accumulation and high level air pollutions in Baku city. Long-term exposure to ambient air pollution was main source for hospitalized COPD exacerbations with high re- hospitalization rate and poor outcomes for patients.

Keywords: *Chronic Obstructive Pulmonary Disease Exacerbations; Hospitalizations; Metropolitan and Non-Metropolitan Urban Area; Mortality Rate*

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide and most of this mortality related to COPD exacerbations requiring hospitalizations [1,2]. Patients with COPD experience exacerbations of the disease, defined as worsening of their symptoms, high occur more often as the disease progresses. Severe COPD exacerbations requiring admission to the hospital are associated with increased mortality [3-7] and are responsible for 70% of the direct health care costs of the disease [10].

The prevalence of COPD is approximately 8% and 5% in adults living in rural and urban areas, respectively according to a Center of Disease Control (CDC) report [11]. In 2015, rural residency patients experience 27% more exacerbations and more deaths than urban patients [12].

Rural residence is an independent risk factor is for 30-day mortality in patients with COPD exacerbations after adjusting for patient and hospital- level characteristics [13]. Rural patients hospitalized with COPD exacerbations have higher 30-day mortality relative to urban patients [13] which may result from suboptimal care prior to during or after hospitalization. Suboptimal care prior to COPD hospitalization or delay to receive appropriate care due to poor access may result in increased mortality among rural patients [14]. However ambient air pollution is a major risk factor for poor health worldwide [15]. The relationship of air pollution exposures with respiratory morbidity and mortality has been documented in the short-term [16] and by a more limited number of prospective cohorts, in the long-term [17,18]. There is elevated risk of death associated with Ozone (O_3) and fine particulate matter less than 2.5 microns in aerodynamic diameter ($PM_{2.5}$) exposure in patients with COPD [17] and a faster decline in lung function associated with long-term exposure to traffic-related air pollution in healthy populations [19]. No studies accordingly differences in hospitalized COPD exacerbations in metropolitan urban area, non-metropolitan urban area and rural areas in term on assessment of risk factors for disease exacerbations.

This retrospective study examined the disparities in hospitalized COPD exacerbations between metropolitan urban area, other urban areas and rural areas.

Materials and Methods

Azerbaijan Medical University (AMU) is the largest academic center and major transfer center in Azerbaijan and has the country largest intensive care unit (ICU). The study population included living metropolitan urban area (1.256), non-metropolitan urban areas

(478) and rural areas (192), men and women ages 18 and older who were hospitalized for COPD exacerbations between January 2011 and December 2019 at university hospital. Patients were included if they were discharged from the university hospital or died during hospitalization with a diagnosis of COPD, defined by International Classification of Disease 10th revision (ICD-10) and were treated for COPD- related acute events such as worsening shortness of breath and acute respiratory failure.

To account for strong temporal in some air pollutions and the knowledge that their exposure can exacerbated COPD and can alter ventilator function (as seen with smoking) [20]. Air pollution in urban and rural areas has been assessed by checking of baseline exposure, and air pollutions as $PM_{2.5}$, black carbon (CO), NO_x and SO_2 concentrations were assessed for the year of the baseline examination each year from 2011 to 2019. In all patients regardless of living in urban or rural areas main risk factor for COPD was exposure and smoking status was similar (> 30 pack-year).

The COPD health outcome variables include hospital length of stay (LOS) (from the day of death), ICU days, need to non-invasive mechanical ventilator use, supplement oxygen use on discharge, 30-day readmission, and death.

Comorbidities included cardiovascular disease, metabolic disease (DM and dyslipidemia), pulmonary and sleep disorders (asthma, bronchiectasis, lung cancer and obstructive sleep apnoea) and others (obesity, osteoporosis, depression, GERD, chronic kidney disease and anemia).

Continuous variables are expressed as mean ± SD, or median (interquartile range [IQR]), while categorical variables are shown as percentages. Chi-square test was used to evaluate the relationship between categorical variables if we did not have sparse cells. Fishers exact test was used for sparse cells. A2-tailed P value < 0.05 was considered statistically significant.

Liner regression model analysis was performed to determine the association between continuous health outcomes me variables (hospital LOS, ICU days, and mechanical ventilator support days) and predictors (e.g. race, age, gender, smoking history, DM, obesity, number of comorbidities, number of COPD re-hospitalizations). Logistic regression model analysis was performed to determine the association between categorical health outcome variables (history non-invasive and invasive mechanical ventilators use, supplemental oxygen use and 30-days readmission), and predictors (including outdoor air pollution concentrations level).

Results

Of 1.926 total admission for COPD exacerbations to therapeutic and education hospital of university the study period included in the analysis, 1.256 were from metropolitan urban (Baku city with four million people, 65.2%), 487 (24.8%) from non-metropolitan urban (Ganja and Mingechaur cities with 700.00 people together) and 192 (100%) from rural areas. Table 1 shows the characteristics of study cohort, stratified residence location.

Variables	Baku (n = 1.256)	Non-metropolitan (n = 478)	Rural (n = 192)	P-value
Age, years, mean ± SD	62.5 (8.4)	64.1 (8.6)	65.1(10.7)	.072
Male, n (%)	1058 (84.2)	396 (82.8)	162 (84.3)	.121
Smoking status former	684 (54.8)	251 (53.7)	109 (567)	.214
Current	567 (45.2)	227 (47.3)	83 (43.3)	.195
Back-years of smoking, median (SD)	42 (16)	41 (17)	43 (10)	.099
BMI > 30, n (%)	526 (41.8)	127 (26.6)	39 (20.3)	.003
Diabetes	328 (28.5)	74 (15.5)	22 (11.4)	.01
Heart failure	211 (16.8)	79 (16.6)	31 (16.1)	.42

Coronary artery disease	163 (12.9)	61 (12.7)	26 (13.5)	.088
Chronic Kidney Disease	141 (11.2)	38 (7.9)	13 (6.8)	.02
Pneumonia	432 (34.4)	80 (16.7)	33 (17.2)	< .001
Lung cancer	128 (10.3)	25 (5.2)	11 (5.7)	.001
Bronchiectasis	291 (23.2)	63 (13.2)	29 (15.1)	.01
Hypertension	243 (19.3)	101 (21.1)	42 (21.8)	.21
Air pollution over follow up, mean (SD)				
$PM_{2.5}$ 2.5, kg/m^3	28 (2.9)	10 (0.8)	3 (0.4)	< .001
NO_x, ppb	98.4 (8.4)	16.5 (6.2)	2 (0.2)	< .001
Black carbon, kg/m^3	1.9 (0.2)	0.5 (0.1)	0.1 (0.0)	< .001
O_3, ppb	30.7 (2.1)	11 (1.6)	4 (1.1)	.001
Airflow obstruction (FEV1), median (SD)	39 (12)	49 (13)	50 (11)	< .001
Presence of pan-lobular emphysema, n (%)	568 (45.2)	101 (1.4)	45 (23.4)	.004
AAT concentration, mean (SD)	139 (16.5)	131 (14.2)	130 (16.5)	.214
Hypercapnic respiratory failure	687 (54.7)	157 (32.8)	79 (41.1)	.001
Oxygen therapy, n (%)	1045 (83.2)	288 (60.2)	121 (63.0)	< .001
Need to intubation, %	211 (16.8)	49 (10.2)	22 (11.5)	.001
Length of Hospital stay, days, median (SD)	14 (3)	9 (3)	10 (2)	.001
Need to non-invasive ventilation, %	526 (41.4)	127 (26.6)	60 (31.2)	.001
ICU admission, n (%)	412 (32.8)	103 (21.5)	41 (21.4)	.01
In-hospital mortality, n (%)	168 (13.4)	26 (5.4%)	10 (5.2%)	< .001
Re-hospitalization, n (%)	771 (61.3)	120 (25.1)	58 (30.2)	< _.001

Table 1: *Characteristics of patients admitted with a COPD hospitalization by residence location an unadjusted by air pollution.*

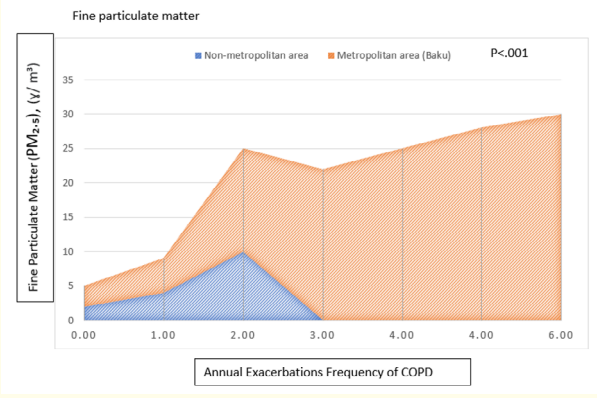
Median pack- years of smoking was similar in all residents (p = .099), however l, BMI was higher in patients from Baku city (p = .003). The prevalence of comorbidities such as diabetes (p = .01), chronic kidney diseases (p = .02), bronchiectasis (p = .01) was higher in patients hospitalized from Baku city. Higher prevalence of lung cancer and pneumonia among hospitalized patients from Baku area was related to impact of environmental factors (high level of ambient air pollution) as potential causes of observed metropolitan urban-non-metropolitan urban-rural disparities (p < .001 for both analysis).

Greater exposures to O_3, $PM_{2.5}$, NO_x and black carbon averaged through 2011 to 2019 were significantly associated with an increased hospitalization related to COPD exacerbations in residents from Baku city (Figure 1).

In this analysis of air pollution over follow up, the long-term exposure of high-concentration of $PM_{2.5}$ was significantly associated with an increased hospitalized exacerbation rate (p < .001).

The long-term exposure of black carbon (CO) concentrations was also significantly associated with increased exacerbations frequency in patients (OR 2.57, 95% CI; 0.92 - 6.24; p < .001).

Most important predictors for frequent re-hospitalizations were long-term exposure of BC and high O_3 concentrations in Baku city. Further analysis of these patients has been shown the prevalence of emphysema changes and low pulmonary function compared to non-metropolitan urban and rural areas (p = .004 and < .01; respectively).



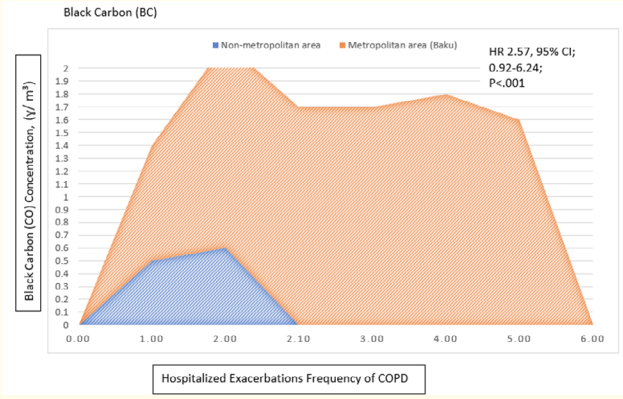


Figure 1: *Annual mean air pollution concentrations per year and risk of hospitalized exacerbations of COPD.*

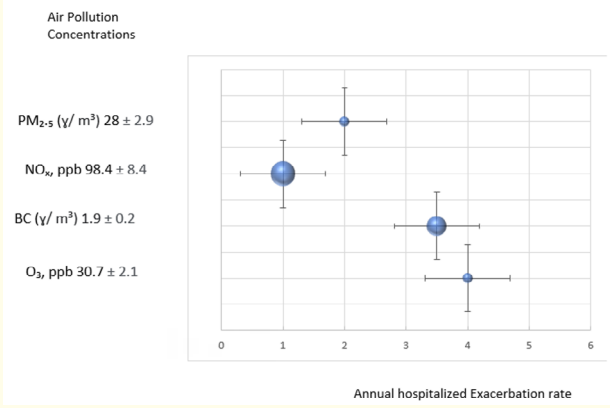


Figure 2: *The relationship between air pollutions and hospitalized exacerbations frequency, in Baku city.*

Long-term air pollution was associated with more severe hospitalized COPD exacerbations. Acute hypercapnic respiratory failure (AH RF) was commonly in patients hospitalized from Baku area (p = .001), which was associated with administration of non-invasive (NIV) and invasive mechanical ventilation (IMV) (p < .001 for both).

Median length of hospital stay was higher in patients from Baku area (p = .001) and the prolonged time of hospital stay was related to higher rate for ICU admission and intubation rate (p = .01 and .001; respectively).

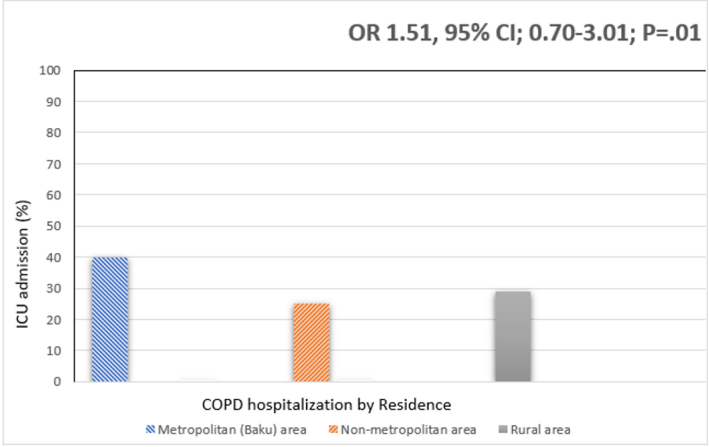


Figure 3: *ICU admission frequency and COPD hospitalization by residence location.*

As shown in table 1 long-term exposure of air pollutions was associated with an increased in-hospital mortality (OR 2.64, 95% CI; 0.72 - 6.14; p < .001).

Multivariable logistic regression model for in-hospital mortality has shown in figure 4.

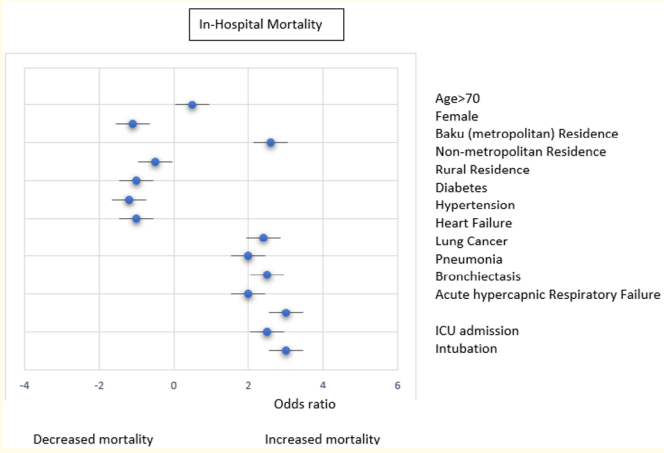


Figure 4: *Multivariable logistic regression analysis in-hospital mortality in hospitalized COPD patients by residence location.*

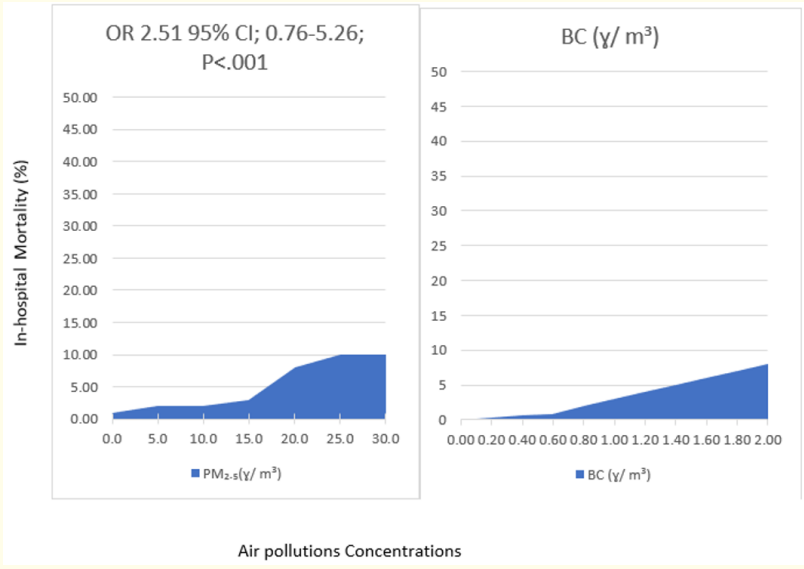


Figure 5: *Long-term exposure of air pollutions and in hospital mortality in hospital mortality in hospitalized COPD patients.*

Associations between long-term air pollutions exposure and COPD hospitalizations and re-hospitalizations rates were greater magnitude among current smokers (p=.001) and were of greater magnitude among patients with lower airflow obstruction at baseline.

Discussion

Significant differences in hospitalized exacerbations, re-hospitalizations and in-hospital mortality rates accordingly residency area concentrations of O_3, BC, $PM_{2.5}$ and NO_x in Baku area compared to non-metropolitan and rural areas. It is fact that in Baku as capital city of republic have accumulated around 75% of cars of all cars in country (around 2mln cars) and high density of traffic and long-term traffic can is associated with an increased air pollutions level and outdoor air pollution may be one of sources for COPD exacerbations. Furthermore, in this city a lot of new buildings and it is also may load to an increased air pollutions concentrations particularly, the level of $PM_{2.5}$ concentrations which is associated with increased hospitalized COPD exacerbations.

In this retrospective cohort study of patients with COPD exacerbations at a university hospital, Baku residents but not rural and non-metropolitan areas living residents were significantly higher hospitalization and re-hospitalization and in-hospitalization mortality rates. Environmental factors have been implicated as potential causes of observed exposure being associated with COPD exacerbations [21,22]. In our study, we have shown the correlation between high level of outdoor air pollutions, related to high traffic density, and hospitalized COPD exacerbations; which were characterized with an increased incidences as acute hypercapnic respiratory failure, need to NIV and IMV and ICU admission. Severe hospitalized COPD exacerbations also is associated with an increased incidence of pneumonia and in-hospital mortality. Our other findings was high incidence of severe COPD exacerbations requiring hospitalization among Baku residents despite similar comorbidities rate and smoking status between urban and rural areas. As known, higher prevalence of comorbidities in rural patients may also be responsible for rural-urban disparities in COPD [23].

Our findings were most robust and of greatest importance for $PM_{2.5}$, O_3 and BC. Systematic analysis of these outdoor pollutants related to traffic density has shown percent emphysema is related to respiratory symptoms, hospitalizations [23] and mortality even among

individuals without airflow obstruction [24], these associations in a community-based population demonstrate novel evidence that air pollution contributes to worsening lung health.

In our study the multi-pollutant ($PM_{2.5}$ + O_3 + BC + NO_x) impact to the hospitalized COPD exacerbations frequency was evident, however, the prevalence emphysema distribution in lung tissue and low pulmonary function were suggested about significantly changes in lung structure and function related to long-term exposure of air pollutants in Baku area.

In animals, $PM_{2.5}$ exposure leads to neutrophilic pulmonary inflammation and oxidative stress [25], and in healthy adults, controlled exposure to $PM_{2.5}$ leads to increased systemic inflammation and endothelial micro-particles, including those of lung origin [25]. This may be relevant because endothelial apoptosis causes emphysema in animals and endothelial micro-particles have been linked to lower lung function and l, specifically, percent emphysema in individuals with mild COPD [25]. In current study we have found greatest number of neutrophils and other inflammatory markers (IL-8, MMP-9) in induced sputum among hospitalized patients with COPD from Baku area and this linkage was more demonstrative in current smokes.

In considering road traffic factors and high density new building coverage there was higher incidence of lung cancer in Baku area (OR 2.02, 95% CI; 1.01-3.49; $p < .001$). Some studies have found a positive correlation between population density and lung cancer incidence, the explanation behind which is that traffic-related air pollution presents more severe in density populated areas [26]. We have found a positive correlation between population density (more than two million cars accounted in this city) and lung cancer incidence in the context of the completely urbanized and high-density area.

A new finding of this study is road and traffic factors may play a role in influencing of hospitalized COPD exacerbations frequency and long-term exposure of air pollutions from high density traffic may be associated with high incidence of hypercapnic respiratory failure, need to NIV and IMV, more prolonged time of length of hospital stay, and frequent ICU admission in patients.

Our other new finding was the assessment of in-hospital mortality among hospitalized patients with COPD exacerbations. In-hospital mortality higher among hospitalized patients from Baku residence area that is suggested the importance of air pollutions together with tobacco smoke in patient outcomes. Higher incidence of pneumonia and lung cancer among these patients was associated with an increased in-hospital mortality.

In assessing the limitations of our study, of first note is the small sample size a from a single center. Second, outdoor air pollution concentrations may not fully reflect individual air pollution exposures and dose in all microenvironments [25], outdoor concentrations do not explain all variation in indoor concentrations, and most individuals spend majority time indoors [26]. In our study we have not consider the impact of indoor air pollution to the hospitalized COPD exacerbations rate.

Third, the current study is limited by the lack of data occupational exposure. As known occupational exposure may play greatest risk for COPD exacerbations. Future study may consider to conduct occupation, indoor air pollution, and tobacco to better control for smoking, indoor air pollution [26], and occupational exposure. Despite these limitations, data regarding hospitalized COPD exacerbations disparities have paying attention in this population. These findings may support efforts to design large, systematic studies to assess and address hospitalized COPD patients in term on, together with main risk factors for exacerbations of the disease, impact of long-term air pollutants exposure.

Conclusion

In conclusion, metropolitan urban residence is an independent risk factor for hospitalized COPD exacerbations and in-hospital mortality. The patients hospitalized with COPD exacerbations living in metropolitan urban residence had unique characteristics and worse

non-metropolitan and rural residence area patients. This study provides preliminary data for future larger multicenter studies to address hospitalized COPD exacerbations in population.

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