Azithromycin use prior to ICU admission is associated with a lower short-term mortality for critically ill acute exacerbations of chronic obstructive pulmonary disease patients: A retrospective cohort study

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Abstract

Azithromycin was thought to prevent acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) by anti-microbial and anti-inflammatory effects. However, it's value in the treatment of critically ill patients with AECOPD before ICU admission remains unclear. Our study aimed to find whether azithromycin use prior to ICU admission leads to better clinical outcomes for those individuals. 533 critically ill patients with AECOPD from the MIMIC-IV database were included. Univariate followed multivariate logistic regression was used to select risk factors for short-term mortality. The multivariable logistic regression models were implemented to investigate the association between azithromycin use before ICU admission and short-term mortality. Lower short-term mortality was observed in the azithromycin group (p = .021), independent of differences in demographic data and other clinical outcomes (p>.05). Azithromycin use before ICU admission was proved to have a decreased short-term mortality by multivariable logistic regression (p<.05). The results remained consistent after being stratified by age, SOFA scores, pH, and cancer diagnosis. Azithromycin use prior to ICU admission was associated with lower short-term mortality for critically ill AECOPD patients.

Keywords

acute exacerbations of chronic obstructive pulmonary disease, azithromycin, critical care, intensive care unit, short-term mortality

Background

Chronic obstructive pulmonary disease (COPD) is still the third leading cause of death and disability worldwide, with an estimated medical cost of $36 billion annually in the United States.[1-4] Up to 60% of these costs are attributed to acute exacerbations of COPD (AECOPD), which could bring negative effects on health status, quality of life, and hospitalization rates.[1,4-6] When AECOPD is evaluated as life-threatening based on clinical presentations, further treatment in the intensive care unit (ICU) will be necessary.[1,7] However, despite advances in medical care,

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the mortality of these patients remains high.[8,9] Therefore, establishing an appropriate treatment regimen for critically ill patients with AECOPD is a high priority.

As a kind of macrolide antibiotic, azithromycin, with potent antimicrobial and immunomodulatory effects, was proved to bring large clinical benefits to COPD patients.[10–12] After repeated validation, long-term use of azithromycin has been established to prevent AECOPD for patients with COPD and was included in authoritative guidelines.[1,13,14] However, it remains controversial whether azithromycin should be routinely used at the beginning of AECOPD, especially for the severe ones requiring critical care in ICU, where azithromycin is often considered to be of limited benefit.[1,11,12] To address this question, we conducted this study to evaluate whether azithromycin use prior to ICU admission could provide better clinical benefits for critically ill patients with AECOPD.

Methods

Data source

All data were obtained from the Medical Information Mart for Intensive Care IV (MIMIC IV) open-source clinical database (version 1.0), which contains information for more than 50,000 patients who were admitted to the intensive care unit (ICU) of the Beth Israel Deaconess Medical Center during 2008 to 2019.[15,16] One author was obliged to complete the online course and pass the online exams to gain access to the database (Xuequn, Certification number: 35,875,386) after signing a data use agreement (https://physionet.org/content/mimiciv/view-dua/1.0/). Owing to all the data in the database being anonymous, the informed consent for the individual was not required.

Cohort selection

Our inclusion criteria were as follows: (1) Patients were older than 18 years and stayed in the ICU for more than 24 hours; (2) Patients were diagnosed as AECOPD by ICD-10 code[17–19] on admission; (3) To ensure that patients were admitted to ICU because of AECOPD, combined type II respiratory failure was set as an inclusion criterion. Type II respiratory failure is defined by the max partial pressure of carbon dioxide (PaCO2) > 45 mmHg (6 kPa) and the min pH < 7.35 within 12 hours before ICU admission.[20] Exclusion criteria are surgically related complications like severe trauma, burns and vital organ surgery. The primary outcome was short-term (30 days) mortality. Only the data from the first hospital and the first ICU admission was retained (Figure 1).
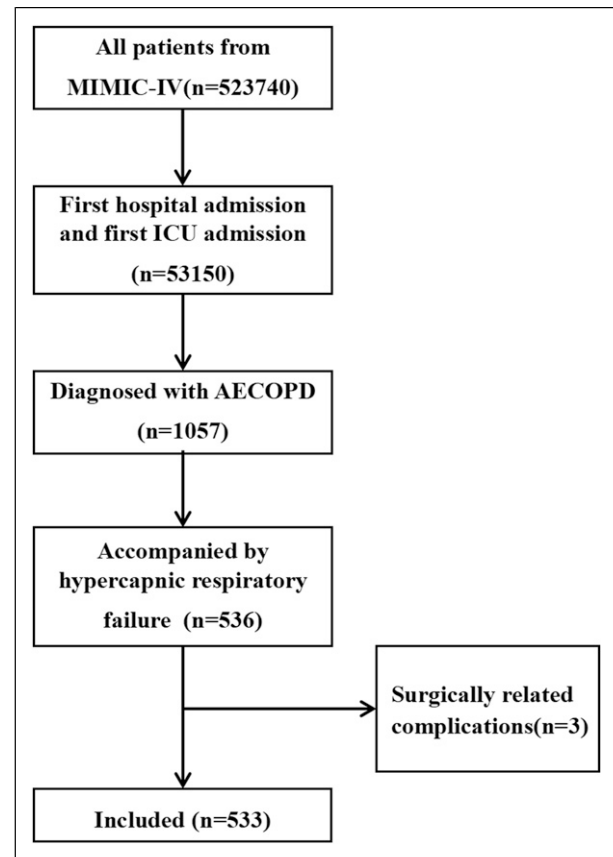

Figure 1. The flowchart of patient enrollment.

Data collection and outcomes

In the present study, we extracted data of baseline parameters including age, gender, ethnicity, body mass index (BMI), sequential organ failure assessment score (SOFA), blood gas results, comorbidities, some treatments like antibiotic use, non-invasive ventilator use and invasive ventilator use, and some clinical outcomes like short-term mortality, long-term mortality, hospital duration and ICU duration. Comorbidities were erected by the Elixhauser, a table created from past retrieval codes summarized in the ICD-10 codes.[17,18] Data elicitation was performed by PostgreSQL (version 10, www.postgresql.org).

Statistical analysis

SKTEST order was run in STATA (Skewness and kurtosis tests for normality), which presents a test for normality based on skewness and another based on kurtosis and then combines the two tests into an overall test statistic, to validate the variables to assess whether they fit normal distribution. Then, continuous data were presented in the tables as the mean with standard deviation (normal distribution) or median with interquartile

ranges (non-normal distribution) and compared by Student t-test (normal distribution) or Wilcoxon rank-sum test (non-normal distribution). Categorical data were presented as percentages, while the significance of the differences was determined through Chi-squared test. Univariate followed stepwise back multivariate logistic regression was used to identify the risk factors for short-term death. Multivariate logistic analysis with complex models adjusted for risk factors selected above was employed to investigate the independent effects of azithromycin use before ICU admission on short-term mortality. The complex models were as follows: no adjustment (Model1), adjusted for age (Model 2), adjusted for age and SOFA scores (Model 3); adjusted for age, SOFA scores and pH (Model 4); adjusted for age, SOFA scores, pH and diagnosis of cancer (Model 5). Variance inflation factor (VIF) was taken to test collinearity between continuous variables, and VIF ≤5 was seen as non-collinearity.[21] Stata 15.1 software (StataCorp, Texas, USA) and R software (version 4.0.0, www.r-project.org) was implemented for the statistical analysis, and $p < .05$ was considered statistically significant.

Results

After execution of inclusion and exclusion criteria, data of 533 critically ill AECOPD patients with hypercapnic respiratory failure were included in the final cohort, including 445 survivors and 88 non-survivors, spelling overall short-term mortality of 16.5% (Table 1). Among these patients, 94 had received azithromycin before ICU admission, 197 had received azithromycin after ICU admission, and 47 had both. As the ATS guidelines recommending the use of macrolides for the prevention of AECOPD were published in 2017,[22] we analyzed the proportion of patients using azithromycin pre- and post- 2017. However, no significant difference was observed ($p = .55$). Compared to the survival group, The non-survival group held older age ($p = .002$) and higher SOFA scores ($p < .001$). Differences in pH ($p < .001$) were observed at admission. When it came to pre-ICU treatment, only azithromycin was found to be statistically different between the survival and non-survival groups ($p = .021$). Notably, when we retained only patients who used azithromycin before ICU admission, the total times of azithromycin use ($p = .577$) and the total dose of azithromycin use ($p = 0.231$) did not differ between the survival and non-survival groups. In addition, azithromycin use after ICU admission had no effect on short-term death. Then, Samples were divided into two groups based on whether azithromycin was used prior to ICU admission as shown in Table2, including 94 samples who received azithromycin before admission to ICU and 439 who did not. No significant differences in age, gender, BMI, ethnicity or SOFA scores were observed between the azithromycin and non-azithromycin groups, the same to blood gas results ($p > .05$). Regarding treatments, the ratio of non-invasive ventilator use and invasive ventilator use did not differ between the two groups ($p>0.05$). As for clinical outcomes, a lower short-term mortality (non-A vs A = 18.2 vs 8.2%) was observed in the azithromycin group, without difference in long-term mortality (non-A vs A = 18.9 vs 11.7%), length of hospital stay (non-A vs A = 9 vs 10days), and length of ICU stay (non-A vs A = 4 vs 3days).

Univariate followed multivariate analysis indicated that age ($p < .001$), SOFA score ($p < .001$), pH ($p = .022$) and cancer ($p = 0.001$) were independent predictors for short-term mortality, with no association existing in dosage and frequency of azithromycin before admission to ICU, other antibiotics use before ICU admission and some other comorbidities ($p > .05$), as shown in Table 3. After adjusting for predictors above individually or together (Model1 = No adjust; Model2 = Adjust for Age; Model3 = Model2 + SOFA; Model4 = Model3 + pH; Model5 = Model4 + cancer), multivariate logical analyses demonstrated that non-azithromycin use before ICU admission was an independent risk factor for short-term mortality (Model1 OR = 0.42, 95% CI 0.19–0.90; Model2 OR = 0.41, 95% CI 0.19–0.88; Model3 OR = 0.44, 95% CI 0.20–0.95; Model4 OR = 0.41, 95% CI 0.19–0.91; Model4 OR = 0.41, 95% CI 0.18–0.92, Table 4).

Discussion

Our study showed that critically ill ACOPD patients who received azithromycin prior to ICU admission had a lower short-term mortality rate. This association was independent of the dose or times of azithromycin use and other antibiotic use before ICU admission. To our knowledge, the present study is the first time for this view to be suggested.

Despite progress in treatment, poor prognosis, including declining lung function, poorer quality of life and increased risk of mortality, is commonly seen in AECOPD patients when they are identified as life-threatening exacerbations.[1,5,6] Thus, the critical care in ICU is required for these patients. A meta-analysis focusing on AECOPD patients admitted to ICU showed mortality for the collective was extremely high, reaching 17.6%–48.8% during hospitalization.[9] Another study with a similar subject gave a mortality rate as high as 27%.[23] All suggested that treatment for AECOPD patients requiring ICU admission is particularly important.

AECOPD, arousing by various infectious and noninfectious stimuli, was usually accompanied by higher inflammation status from the very beginning, making early identification and management of AECOPD meaningful in clinical practice.[24,25] Research has shown that this series of inflammatory responses are not limited to lungs, but occurs throughout the body.[26] Despite the exact mechanism remains unclear, some inflammatory factors, like CRP,

Table 1. Comparisons of demographics between survivors and non-survivors.

	Survivors (n = 445)	Non-survivors (n = 88)	p value
Demographics			
Age (years,±SD.)	71.4±10.3	75.2±10.3	0.002
Male (n%)	219 (48.1)	43 (57.9)	0.952
BMI(kg/m2,±SD.)	29.4±8.6	27.5±8.0	0.053
Ethnicity (n%)			
white	297 (65.3)	51 (57.9)	0.255
black	31 (6.8)	2 (2.3)	
asian	11 (2.4)	2 (2.3)	
others	106 (23.3)	33 (37.5)	
SOFA (IQR)	6 (4–8)	8 (5–11)	<0.001
Blood gas at ICU admission			
pH(IQR)	7.28 (7.22–7.34)	7.24 (7.16–7.32)	<0.001
PaO2(mmHg,IQR)	50 (37–71)	44 (34–69)	0.341
PaCO2(mmHg,IQR)	62 (52–79)	66 (57–83)	0.071
FiO2 (%,IQR)	50 (40–80)	55 (40–100)	0.095
PaO2/FiO2 (mmHg, IQR)	109 (72–162)	94 (59–151)	0.097
Comorbidities (n%)			
Congestive heart failure	213 (46.8)	44 (50.0)	0.714
Myocardial infarction	101 (22.2)	19 (21.6)	0.820
Hypertension	86 (18.9)	19 (21.6)	0.625
Cerebrovascular disease	37 (8.1)	7 (7.9)	0.911
Diabetes	134 (29.5)	22 (25.0)	0.229
Renal disease	97 (21.3)	16 (18.2)	0.448
Treatments			
Azithromycin before ICU admission (n%)	86 (19.3)	8 (9.1)	0.021
Total times of azithromycin before ICU admission (only for the azithromycin group; times, IQR)	1 (1–2)	1 (1–2)	0.577
Total dose of azithromycin before ICU admission (only for the azithromycin group; mg, IQR)	500 (250–500)	500 (375–875)	0.231
Azithromycin after ICU admission (n%)	164 (36.9)	33 (37.5)	0.909
Azithromycin before and after ICU admission (n%)	39 (8.8)	8 (9.1)	0.921
Penicillins before ICU admission (n%)	52 (11.7)	7 (7.9)	0.308
Cephalosporin before ICU admission (n%)	129 (28.9)	19 (21.6)	0.157
Quinolone before ICU admission (n%)	67 (15.1)	14 (15.6)	0.839
Vancomycin before ICU admission (n%)	16 (3.6)	2 (2.3)	0.746
Carbapenems before ICU admission (n%)	114 (25.6)	23 (26.1)	0.826
Non-invasive ventilator use (n%)	196 (44.0)	31 (35.2)	0.126
Invasive ventilator use (n%)	240 (53.9)	55 (62.5)	0.140

Continuous data are presented as mean ± standard deviation (SD) or median (interquartile ranges), and categorical data are presented as frequency (percentage).

Abbreviations: BMI, body mass index; SOFA, Sequential organ failure assessment; pH, potential of Hydrogen; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide; FiO2, fraction of inspiration oxygen; IQR, interquartile ranges.

interleukin-6 (IL-6), interleukin-8 (IL-8), leukotriene B4 (LTB4), and tumor necrosis factor-α (TNF-α), were discovered be associated with occurrence and prognosis of AECOPD.[27,28] This may be the root cause of the positive effect of corticosteroids and other anti-inflammatory drugs on the short-term recovery of symptoms and long-term clinical outcomes of AECOPD patients.[1,29–31]

Azithromycin, as a kind of macrolide, with both antimicrobial and anti-inflammatory effects, has repeatedly been proved to have significant effects on chronic inflammation.[11–13] In the anti-microbial aspect, azithromycin has a wide spectrum, which has a strong antibacterial effect on not only Gram-positive bacteria, but also some Gram-negative bacteria, *mycoplasma*, *chlamydia* and

Table 2. Comparisons of population information and clinical outcomes between Azithromycin and Non-Azithromycin groups.

Variable	Non-azithromycin before ICU admission (n = 439)	Azithromycin before ICU admission (n = 94)	p value
Demographics			
Age (years,±SD.)	72±10	72±11	0.971
Male (n%)	217 (49.4)	45 (47.9)	0.784
BMI(kg/m2,±SD.)	28.9±8.6	29.5±8.3	0.545
Ethnicity (n%)			
White	287 (65.4)	61 (64.9)	0.489
Black	20 (4.6)	13 (13.8)	
Asian	10 (2.3)	3 (3.2)	
Others	122 (27.8)	17 (18.1)	
SOFA (IQR)	6 (4–9)	6 (4–8)	0.482
Clinical outcomes			
Short-term death (n%)	80 (18.2)	8 (8.5)	0.021
Long-term death (n%)	83 (18.9)	11 (11.7)	0.096
Hospital duration (days,IQR)	9 (6–17)	10 (6–16)	0.975
ICU duration (days,IQR)	4 (2–7)	3 (2–6)	0.358
Non-invasive ventilator use (n%)	183 (41.7)	44 (46.8)	0.362
Invasive ventilator use (n%)	248 (56.5)	47 (50.0)	0.251

Continuous data are presented as mean ± standard deviation (SD) or median (interquartile ranges), and categorical data are presented as frequency (percentage).
Abbreviations: BMI, body mass index; SOFA, Sequential organ failure assessment; IQR, interquartile ranges.

legionella.[13,32,33] In the meantime, there is a post anti-microbial effect of azithromycin. After drug withdrawal, the concentration of the drug released in the cell still exceeds the minimum inhibitory concentration of common sensitive bacteria within 5–7 days[32–34] Azithromycin is often recommended for ACOPD patients with infective evidence but milder illness state and fewer comorbidities during acute exacerbation periods. For AECOPD patients evaluated as life-threatening, labeled older age, more severe state and more comorbidities, azithromycin is not the first choice and early combination with other antibiotics is not recommended.[1,35,36]

In addition to the coverage for common pathogenic bacteria of lung infection in AECOPD patients, azithromycin, like other macrolides, are involved in multiple ant-inflammatory activities, including suppression of some pro-inflammatory cytokines, attenuated chemotaxis and adhesion of neutrophils, hypoactive proliferation of monocytes, enhanced phagocytosis of apoptotic cells, alleviation of oxidant burst, reduction of mucous secretion, inhibition of angiogenesis, and decrease of virulence factors.[10,11,37–42] Besides, azithromycin may join the response to corticosteroids by enhancing the recruitment of histone deacetylase 2, which is seen as a major contributor to the inflammatory gene repression produced by corticosteroids in patients with COPD, thus resulting in less corticosteroid use.[30,31,43] Based on this anti-inflammatory effect, several studies suggested chronic azithromycin in

COPD patients to prevent AECOPD.[1,13,44] Numerous controlled trials implied inclusion of azithromycin in the treatment regimen may bring clinical benefits for critically ill patients with AECOPD, including reductions in hospital readmissions, improvements in time to next readmission and decrease of ICU costs.[11,45,46] In a study involving more than 25,000 patients with AECOPD admitted to the ICU, macrolides initiated within 2 days of admission reduced hospital costs and 30-days ICU readmission rates.[11] Azithromycin is also used in other ICU conditions due to its antibacterial and anti-inflammatory effects. Afshar et al.[47] found that azithromycin was associated with less ICU stay days in severe sepsis patients received mechanical ventilation. Another study showed macrolide antibiotics could decreased death risk from septic shock and multiple organ dysfunctions for severe sepsis patients with ventilator-associated pneumonia.[48]

There were several limitations to our study. For one thing, as a retrospective study, all our data is based on the MIMIC-IV databases. Although the sample size of our study was not small, future larger multicenter prospective studies are warranted to further validate our points. For another, in order to ensure that the extracted data were admitted to ICU because of AECOPD, we only selected patients with type II respiratory failure, which would inevitably lead to selection bias. Additionally, the use of azithromycin may simply be a surrogate marker for an unknown confounder, such as access to a primary care

Table 3. Univariate and multivariate logistic analysis of variables and short-term mortality.

Variable	Univariate logistic analysis		Multivariate logistic analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.04 (1.01–1.06)	0.002	1.05 (1.02–1.07)	<0.001
Male	0.99 (0.62–1.56)	0.952		
BMI	0.97 (0.94–1.00)	0.054		
Ethnicity	0.93 (0.68–1.27)	0.660		
SOFA	1.15 (1.09–1.23)	<0.001	1.14 (1.07–1.22)	<0.001
pH	0.01 (0.00–0.08)	<0.001	0.04 (0.01–0.64)	0.022
PaO2	1.00 (0.99–1.01)	0.782		
PaCO2	1.01 (0.99–1.02)	0.125		
FiO2	1.01 (0.99–1.02)	0.107		
PaO2/FiO2	0.99 (0.99–1.00)	0.800		
Congestive heart failure	1.09 (0.69–1.72)	0.714		
Myocardial infarction	0.94 (0.54–1.63)	0.821		
Hypertension	0.94 (0.57–1.53)	0.793		
Cerebrovascular disease	0.95 (0.41–2.21)	0.911		
Diabetes	0.77 (0.46–1.31)	0.336		
Renal disease	0.80 (0.44–1.43)	0.449		
Cancer	2.08 (1.16–3.73)	0.014	2.83 (1.51–5.29)	0.001
Azithromycin before ICU admission	0.42 (0.19–0.90)	0.025	0.41 (0.18–0.92)	0.030
Total times of azithromycin before ICU admission (only for the azithromycin group)	0.63 (0.37–1.06)	0.081		
Total dose of azithromycin before ICU admission (only for the azithromycin group)	1.00 (0.99–1.00)	0.211		
Penicillins before ICU admission	0.65 (0.29–1.49)	0.311		
Cephalosporin before ICU admission	0.67 (0.39–1.17)	0.159		
Quinolone before ICU admission	1.07 (0.57–1.99)	0.839		
Vancomycin before ICU admission	0.62 (0.14–2.76)	0.534		
Carbapenems before ICU admission	1,03 (0.61–1.73)	0.919		
Non-invasive ventilator use	0.69 (0.43–1.11)	0.128		
Invasive ventilator use	1.42 (0.89–2.28)	0.141		

Abbreviations: OR, odd ratio; CI, confidence interval; BMI, body mass index; SOFA, Sequential organ failure assessment; pH, potential of Hydrogen; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide; FiO2, fraction of inspiration oxygen; IQR, interquartile ranges.

Table 4. ORs associated with azithromycin before ICU admission and short-term mortality by multiple regression models.

	Multiple regression models	
	OR (95% CI)	p value
Model1	0.42 (0.19–0.90)	0.025
Model2	0.41 (0.19–0.88)	0.023
Model3	0.44 (0.20–0.95)	0.037
Model4	0.41 (0.19–0.91)	0.028
Model5	0.41 (0.18–0.92)	0.030

Adjusted covariates: Model1 = No adjust; Model2 = Adjust for Age; Model3 = Model2 + SOFA; Model4 = Model3 + pH; Model5 = Model4 + cancer. Abbreviations: OR, odd ratio; CI, confidence interval; SOFA, Sequential organ failure assessment; pH, potential of Hydrogen.

physician, a respirology/pulmonology specialist, and or medicare, causing confounding bias. Furthermore, the absence of data on whether patients used azithromycin before admission will lead to a decrease in persuasiveness.

Conclusion

Azithromycin use prior to ICU admission was associated with lower short-term mortality for critically ill AECOPD patients, the correlation was independent of the dose and times of azithromycin use. Therefore, we recommend the routine use of azithromycin for AECOPD patients who are admitted to the emergency department in serious conditions or whose condition changes during hospitalization and may require further treatment in ICU.

Authors contributions

Declaration of conflicting interests

Funding

Ethics approval and consent to participate

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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