


Management of acute exacerbation of chronic obstructive pulmonary disease under a tiered medical system in China

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Abstract

Background: The Chinese government has promoted the ‘tiered medical services’ policy in which diseases are classified by severity, mode of onset and difficulty of treatment since 2015 to optimize medical resources. We evaluated the diagnosis and treatment of acute exacerbation (AE) of chronic obstructive pulmonary disease (AECOPD) under the tiered system.

Methods: We conducted a cross-sectional study. COPD characteristics and treatments were compared among hospitals in different tiers. Associations were examined by univariate and multivariable logistic regression analysis. In addition, multivariate logistic regression was performed to identify the possible influencing factors of antibiotics, glucocorticoids and anticoagulant usages.

Results: Eligible COPD patients ($n=432$) were consecutively recruited from eight hospitals in different tiers in China. Patients in the countryside preferred the community hospitals, whereas patients in cities preferred second-tier and teaching hospitals when they suffer from AECOPD. It indicates most COPD patients are likely to treat their disease locally. The severity of COPD AE increased with tiers of hospitals ($p < 0.001$). However, our results clearly show that most community hospitals can only deal with mild exacerbation of COPD. Approximately 90% of AE patients received antibiotics. We speculated that antibiotics abuse might exist in the three tiers of hospitals. Multivariate analysis demonstrated that long-term antibiotics usage (≥ 14 days) was associated with moderate exacerbation [odds ratio (OR): 5.295, 95% confidence intervals (CI) 2.248–12.473, $p < 0.001$], radiographic progression (OR: 2.176, 95% CI: 1.047–4.522, $p = 0.037$), positive sputum etiology (OR: 3.073, 95% CI: 1.477–6.394, $p = 0.003$) and increased white blood cells (OR: 2.470, 95% CI: 1.190–5.126, $p = 0.015$). The proportion of glucocorticoids increased with the hospital hierarchy (18.6% versus 45.6% versus 69.2%, $p < 0.001$). The proportions of severe cases in the second-tier hospitals were 26.9%; however, non-invasive positive pressure ventilation (NPPV) rate was only 14.7%. Anticoagulant is not commonly used in AECOPD, and the community hospitals had the lowest proportion of anticoagulation regimen (1.7% versus 14.3% versus 20.5%, $p = 0.002$).

Conclusions: The ‘tiered medical services’ policy in AECOPD management has been unsatisfactory in the past years. Irrational treatment strategies in different hospitals were still found when comparing with international guideline. Further reform of the policy is still needed to optimize the management of AECOPD in China.

Keywords: AECOPD, acute exacerbation, tiered medical system

Received: 24 October 2021; revised manuscript accepted: 7 January 2022.

Ther Adv Respir Dis

2022, Vol. 16: 1–14

DOI: 10.1177/
17534666211075499

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the three causes of death worldwide,¹ and it is also a major cause of chronic morbidity. It is estimated that the global prevalence of COPD at about 174 million cases² and COPD caused approximately 3,000,000 deaths worldwide every year.³ Even worth, the mortality is increasing rapidly.⁴ Wang *et al.* conducted a national cross-sectional survey study in China in 2018. They reported that the prevalence of COPD in people aged 40 years or older was 13.7%. Considering the large Chinese population, it was estimated that there might be approximately 99.9 million COPD patients in China.⁵ COPD represents an important public health challenge that is both preventable and treatable. In China, people in large cities mostly trust high-tier hospitals. They prefer teaching hospitals much more than other hospitals, which causes a waste of high-quality medical resources. To optimize medical resources, in 2015, the Chinese government began to carry out a new policy, 'tiered medical services', in which diseases are classified by severity, mode of onset and difficulty of treatment. Hospitals in different tiers are encouraged to play their strengths in different diseases. For instance, community hospitals should focus on managing chronic disease and primary prevention and health care. The teaching hospitals should play their strength in the difficult, complicated, severe or rare diseases, and in the meantime, accomplish the teaching of the medical students and the scientific research related to clinical medicine. Until now, this concept has not been ideally implemented for COPD management in China.

The characteristics of COPD patients in hospitals in different tiers need to be identified. Our study was designed to detect the differences among the three levels of hospitals. We evaluated the diagnosis and treatment of acute exacerbation (AE) of COPD (AECOPD) under the tiered system. By clarifying those features, we may have a better idea on how to optimize the 'tiered medical services' to manage the widespread of COPD more efficiently and economically. In this survey, we focused on AECOPD in hospitals from the three tiers to discuss the 'tiered medical services' application.

Methods

The tiered medical system of China

The tiered medical system is an important component of China's medical reform, aiming to allocate

medical resources rationally. Public hospitals are integral components of China's health care system. All public hospitals were graded into three tiers according to the scale of the hospitals, scientific research direction, talent of the medical staff, technical strength, medical hardware and equipment, among other aspects. Community hospitals are primary hospitals that directly provide comprehensive medical treatment, prevention, rehabilitation and health care to the community. Second-tier hospitals are regional hospitals that provide health services across several communities and are regional medical technology centers. Finally, teaching hospitals are medical centers that provide comprehensive medical treatment and have teaching and research capabilities. Patients can select hospitals according to their condition, and referrals can also be made between hospitals of different tiers. In general, higher-tier hospitals are associated with the treatment of more severe diseases.

Study design and subjects

This was a cross-sectional study. Adult subjects (≥ 18 years old) diagnosed with COPD were consecutively recruited from the clinics of eight hospitals in Shanghai and Suzhou from July 2017 to December 2018. These eight hospitals included one teaching hospital (Zhongshan Hospital, Fudan University), three second-tier hospitals (Qingpu branch of Zhongshan Hospital, Punan Hospital and Taicang First Peoples Hospital) and four community hospitals (Nanmatou Community Hospital, Jinze Community Hospital, Zhaoxiang Community Hospital and Waitan Community Hospital).

All the subjects had been diagnosed with COPD before, and clinicians confirmed the diagnosis according to the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2021 Report. The patients had symptoms such as dyspnea, chronic cough or sputum production, and a history of exposure to risk factors for COPD. A pulmonary function test (PFT) is required to make the diagnosis in this clinical context, and a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) lower than 0.70 confirms the presence of persistent airflow limitation and indicates the presence of COPD in patients with the expected symptoms and predisposing risk factors.¹

All patients were recruited in exacerbation condition, defined as an acute worsening of respiratory

symptoms that resulted in additional therapy. These events were classified as mild, moderate, or severe.¹ Mild exacerbation was defined as no respiratory failure, which meant normal respiratory rate, no assistant breathing muscles working, no mental or consciousness change, no hypercapnia and hypoxemia that can be improved by nasal catheterization or Venturi mask oxygen therapy (28–35% oxygen concentration). Moderate exacerbation was defined as non-life-threatening acute respiratory failure characterized by a respiratory rate above 30 rpm, assistant breathing muscles working, no mental or consciousness change, hypercapnia and hypoxemia that can be improved by nasal catheterization or Venturi mask oxygen therapy (25–30% oxygen concentration). Usually, moderate exacerbation patients were admitted into general wards. Severe exacerbation was defined as life-threatening acute respiratory failure. Except for the symptoms mentioned above, severe exacerbation patients suffered an abrupt change of mind or consciousness and severe hypoxemia that cannot be improved by Venturi mask oxygen therapy (>40% oxygen concentration). The hypercapnia was severe, and sometimes the patients developed acidosis. Due to the life-threatening respiratory failure, the patients need to be admitted into intensive care unit (ICU) for strict treatment and observation. We excluded subjects who were pregnant, breastfeeding, or had chronic unstable diseases of other systems or malignancies.

The institutional review board at Zhongshan Hospital, Fudan University, reviewed and approved this study (2017BJYYEC-080-02). All included patients and physicians gave written informed consent before participation.

Data collection and clinical assessments

Multidimensional assessments that included demographic characteristics, COPD duration, comorbidities, medication use, other treatment conditions and expenses, among other data, were performed in all included patients. In addition, the latest PFT results, including FVC%pred, FEV1%pred and FEV1/FVC, were also recorded.

Data analysis

Analyses were performed using SPSS (version 22.0; SPSS). Frequencies were calculated for classified data, and differences among groups

were explored using χ^2 , Fisher exact and Mann–Whitney *U* tests, where appropriate. Mean \pm SD described continuous data and the differences were analyzed using one-way analysis of variance. Associations were examined by univariate and multivariable logistic regression analysis, using odds ratios (ORs) and 95% confidence intervals (CIs). Variables were included in multivariable models if the *p* value was ≤ 0.05 . Models were built forward stepwise, using the likelihood ratio test statistic to determine the significance of the contribution of each variable to the outcome before fitting the variable to the final model. Thus, the multivariable analyses were adjusted if a clinical variable was potentially confounding for the model (e.g. age, sex). Furthermore, we assessed the relationship between the severity of acute exacerbation (AE) and the treatment measures using scatter plots, and we added a Spearman correlation coefficient *R*.

Results

Demographic and clinical characteristics of COPD patients in three tiers of hospitals in China

Among the 432 participants included in our study, 156 were from teaching hospitals, 217 were from second-tier hospitals and 59 were from community hospitals. The sociodemographic and clinical characteristics of the patients from teaching to community hospitals are shown in Table 1. Compared with the teaching group, a higher proportion of the patients from second-tier and community groups lived in villages. In addition, patients from community groups had a high proportion of smoking history. Patients in the community hospitals had the highest comorbidity numbers, and those in the second-tier hospitals had the lowest (1.71 ± 1.02 versus 0.98 ± 0.84 versus 1.66 ± 0.97 , $p < 0.001$, community versus second-tiered versus teaching hospitals).

When the COPD patients were evaluated, the proportion of patients who used inhaled drugs in the last year increased in the hospital tier (13.6% versus 50.7% versus 56.4%, $p < 0.001$, community versus second-tiered versus teaching hospitals) (Table 1). In addition, the proportions of patients in the community group using theophylline, expectorant and Chinese patent medicine were significantly higher than those in the teaching and second-tier groups ($p < 0.001$).

Table 1. Demographic and clinical characteristics of COPD patients in three tiers of hospitals in China.

<i>N</i>		Community hospital (%)	Second-tier hospital (%)	Teaching hospital (%)	χ^2/F	<i>p</i>	Comparison between groups (<i>p</i>)
		59	217	156			
Gender	Male	30 (51.7)	182 (83.9)	125 (80.1)	24.462	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.350
	Female	28 (48.3)	35 (16.1)	31 (19.9)			
Age		80.16 ± 12.53	77.45 ± 9.83	77.12 ± 9.71	2.243	0.107	1 versus 2: 0.048 1 versus 3: 0.047 2 versus 3: 0.902
Education	Uneducated or primary	35 (59.3)	129 (59.4)	16 (10.3)	14.884	0.061	1 versus 2: 0.507 1 versus 3: <0.001 2 versus 3: <0.001
	Middle school	15 (25.4)	41 (18.9)	14 (9.0)			
	High school	4 (6.8)	21 (9.7)	4 (2.6)			
	College or above	0 (0.0)	7 (3.2)	1 (0.6)			
	Unknown	5 (8.5)	19 (8.8)	121 (77.6)			
Living condition	City	25 (42.4)	96 (44.2)	117 (75.0)	52.249	<0.001	1 versus 2: 0.918 1 versus 3: <0.001 2 versus 3: <0.001
	Village	28 (47.5)	111 (51.2)	25 (16.0)			
	Unknown	6 (10.2)	10 (4.6)	14 (9.0)			
Smoking status	Never	37 (62.7)	51 (23.5)	31 (19.9)	29.270	<0.001	1 versus 2: <0.001 1 versus 3: 0.003 2 versus 3: 0.071
	Ever	20 (33.9)	111 (51.2)	46 (29.5)			
	Current	2 (3.4)	20 (9.2)	17 (10.9)			
	Unknown	0 (0.0)	35 (16.1)	62 (39.7)			
COPD duration	≤3 years	11 (18.6)	12 (5.5)	14 (9.0)	22.423	<0.001	1 versus 2: 0.004 1 versus 3: 0.074 2 versus 3: 0.006
	3–5 years	7 (11.9)	28 (12.9)	9 (5.8)			
	5–10 years	7 (11.9)	55 (25.3)	25 (16.0)			
	>10 years	34 (57.6)	122 (56.2)	108 (69.2)			
Number of comorbidities		1.71 ± 1.02	0.98 ± 0.84	1.66 ± 0.97	26.515	<0.001	1 versus 2: <0.001 1 versus 3: 0.713 2 versus 3: <0.001
<i>N</i>		59	190	126			
Number of AE in the last year	0	0 (0.0)	19 (8.8)	0 (0.0)	26.770	<0.001	1 versus 2: 0.004 1 versus 3: 0.078 2 versus 3: <0.001
	1	9 (15.3)	61 (28.1)	30 (19.2)			
	2	4 (6.8)	24 (11.1)	21 (13.5)			
	≥3	2 (3.4)	23 (10.6)	20 (12.8)			
	Unknown	44 (74.6)	90 (41.5)	85 (54.5)			

(Continued)

Table 1. (Continued)

<i>N</i>		Community hospital (%)	Second-tier hospital (%)	Teaching hospital (%)	χ^2/F	<i>p</i>	Comparison between groups (<i>p</i>)
		59	217	156			
PFT in the last year	0	0 (0.0)	3 (1.4)	0 (0.0)	21.833	0.001	1 versus 2: 0.008 1 versus 3: 0.059 2 versus 3: 0.007
	1	0 (0.0)	31 (14.4)	9 (5.8)			
	2	0 (0.0)	3 (1.4)	0 (0.0)			
	Unknown	59 (100.0)	178 (82.8)	147 (94.2)			
Inhaled drugs	Yes	6 (13.6)	110 (50.7)	88 (56.4)	111.450	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.514
	No	46 (78.0)	36 (16.6)	21 (13.5)			
	Unknown	5 (8.5)	71 (32.7)	47 (30.1)			
Theophylline	Yes	42 (71.2)	33 (15.2)	36 (23.1)	77.278	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.154
	No	12 (20.3)	113 (52.1)	73 (46.8)			
	Unknown	5 (8.5)	71 (32.7)	47 (30.1)			
Antibiotics	Yes	26 (44.1)	42 (19.4)	62 (39.7)	34.320	<0.001	1 versus 2: <0.001 1 versus 3: 0.002 2 versus 3: <0.001
	No	28 (47.5)	104 (47.9)	47 (30.1)			
	Unknown	5 (8.5)	71 (32.7)	47 (30.1)			
Chinese patent medicine	Yes	33 (55.9)	1 (0.5)	2 (1.3)	134.916	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: <0.001
	No	21 (35.6)	145 (55.9)	107 (68.6)			
	Unknown	5 (8.5)	71 (32.7)	47 (30.1)			
Expectorants	Yes	37 (62.7)	45 (20.7)	51 (32.7)	40.985	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.029
	No	17 (28.8)	101 (46.5)	58 (37.2)			
	Unknown	5 (8.5)	71 (32.7)	47 (30.1)			

¹versus 2, community hospital versus second-tier hospital; 1 versus 3, community hospital versus teaching hospital; 2 versus 3, second-tier hospital versus teaching hospital; AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test.

Severity assessment of acute exacerbation (AE) in three tiers of hospitals

The patients received an assessment of severity when they were admitted to hospitals. Unexpectedly, patients of second-tier hospitals seemed to have had more severe dyspnea with accessory muscle use compared with the patients

from teaching hospitals (0% versus 90% versus 70%, $p < 0.001$, community versus second-tiered versus teaching hospitals) (Table 2). However, the proportion of disturbance of consciousness was the lowest in the second-tier hospital patients ($p = 0.005$). The final assessment of the severity of COPD AE increased with tiers ($p < 0.001$). We

Table 2. Severity assessment of acute exacerbation in three tiers of hospitals.

		Community hospital (%)	Second-tier hospital (%)	Teaching hospital (%)	χ^2/F	<i>p</i>	Comparison between groups (<i>p</i>)
Severity of AE	Mild	59 (100.0)	50 (23.0)	56 (35.9)	144.599	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: <0.001
	Moderate	0 (0.0)	86 (39.6)	42 (26.9)			
	Severe	0 (0.0)	42 (26.9)	50 (32.1)			
	Unknown	0 (0.0)	25 (11.5)	8 (5.1)			
Cardiac insufficiency	Yes	8 (13.6)	16 (7.4)	32 (20.5)	17.340	0.002	1 versus 2: 0.098 1 versus 3: 0.266 2 versus 3: <0.001
	No	44 (74.6)	187 (86.2)	109 (69.9)			
	Unknown	7 (11.9)	14 (6.5)	15 (9.6)			
Consciousness disorder	Yes	8 (13.6)	7 (3.2)	15 (9.6)	10.457	0.005	1 versus 2: 0.002 1 versus 3: 0.404 2 versus 3: 0.010
	No	51 (86.4)	210 (96.8)	141 (90.4)			
Hemodynamic instability	Yes	0 (0.0)	11 (5.1)	8 (5.1)	5.717	0.057	1 versus 2: 0.078 1 versus 3: 0.076 2 versus 3: 0.207
	No	59 (100.0)	206 (94.9)	148 (94.9)			
Number of symptoms including dyspnea, Sputum increase or purulent sputum	≤ 1	9 (15.3)	28 (12.9)	19 (12.2)	122.078	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.676
	2	43 (72.9)	24 (11.1)	22 (14.1)			
	3	7 (11.9)	165 (76.0)	115 (73.7)			

1 versus 2, community hospital versus second-tier hospital; 1 versus 3, community hospital versus teaching hospital; 2 versus 3, second-tier hospital versus teaching hospital; AE, pulmonary function test; PCO₂, arterial partial pressure of carbon dioxide; PO₂, arterial partial pressure of oxygen. The specific details of severity assessment of AE severity including PO₂, PCO₂ and involved accessory respiratory muscle. Patients in the community hospitals had less respiratory failure than the others tiers of hospitals ($p < 0.001$), including type I and type II respiratory failure. Patients of second-tier hospitals had more severe dyspnea with accessory muscle use compared with teaching hospitals (0% versus 90% versus 70%, $p < 0.001$, community versus second-tiered versus teaching hospitals).

also collected the number of symptoms in each patient, including dyspnea, increased sputum and purulent sputum. We found that patients in the community hospitals had fewer symptoms than patients in the second-tier and teaching hospitals ($p < 0.001$), which illustrates that some patients with minor exacerbation will choose community hospitals first.

Differences in the therapy of AE in three tiers of hospitals

Different levels of hospitals reflect different medical levels. It is common to consider that teaching hospitals have the best treatment, and that perhaps the community hospitals need some kind of improvement. Therefore, we investigated the differences in treatment in different levels of hospitals. Together with the increase of hierarchy, the proportion of antibiotics, glucocorticoids and

hospitalization charges increased ($p < 0.001$) (Table 3). As the proportion of antibiotics in the teaching hospitals was the highest, we then investigated the kinds of antibiotics used in all the hospitals and the course of antibiotics treatment. The results showed that the teaching hospitals had the highest diversity of antibiotics (1.21 ± 0.42 versus 1.19 ± 0.43 versus 2.14 ± 0.73 , $p < 0.001$). The course of antibiotics treatment was the longest in the teaching hospitals (11.03 ± 11.27 versus 9.49 ± 3.52 versus 12.70 ± 7.73 , $p < 0.001$), which was in keeping with the hospitalization days (12.57 ± 4.80 versus 13.10 ± 10.49 versus 16.04 ± 10.02 , $p < 0.001$) and the hospitalization charge (2.27 ± 2.07 versus 14.79 ± 8.28 versus 18.41 ± 14.09 , $p < 0.001$) (*thousand RMB). We detected the use of glucocorticoids in the same way. The proportion of glucocorticoids increased with the hospital hierarchy (18.6% versus 45.6% versus 69.2%, $p < 0.001$). The number of days of

Table 3. Differences in therapy, hospital days and charges of acute exacerbation in three tiers of hospitals.

		Community hospital (%)	Second-tier hospital (%)	Teaching hospital (%)	χ^2/F	<i>p</i>	Comparison between groups (<i>p</i>)
Respiratory stimulant	Yes	0 (0.0)	14 (6.5)	19 (12.2)	13.747	0.001	1 versus 2: 0.044 1 versus 3: 0.050 2 versus 3: 0.058
	No	59 (100.0)	201 (93.5)	137 (87.8)			
Antibiotics	Yes	32 (54.2)	203 (93.5)	154 (98.7)	100.466	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.015
	No	27 (45.8)	14 (6.5)	2 (1.3)			
Different kinds of antibiotics		1.21 ± 0.42	1.19 ± 0.43	2.14 ± 0.73	156.149	<0.001	1 versus 2: 0.846 1 versus 3: <0.001 2 versus 3: <0.001
Antibiotics course (Day)		11.03 ± 11.27	9.49 ± 3.52	12.70 ± 7.73	25.090	<0.001	1 versus 2: 0.204 1 versus 3: 0.179 2 versus 3: <0.001
Antiviral therapy	Yes	0 (0.0)	3 (1.4)	0 (0.0)	4.152	0.125	1 versus 2: 0.239 1 versus 3: 0.283 2 versus 3: 0.802
	No	59 (100.0)	214 (98.6)	156 (100.0)			
Glucocorticoids	Yes	11 (18.6)	99 (45.6)	108 (69.2)	47.911	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: <0.001
	No	48 (81.4)	118 (54.4)	48 (30.8)			
Glucocorticoid course (Day)		1.75 ± 3.74	2.90 ± 3.88	6.70 ± 5.96	33.977	<0.001	1 versus 2: 0.144 1 versus 3: <0.001 2 versus 3: <0.001
Total dosage of glucocorticoids (mg)		107.05 ± 432.14	138.32 ± 190.05	299.32 ± 337.8	16.075	<0.001	1 versus 2: 0.468 1 versus 3: <0.001 2 versus 3: <0.001
Daily dosage of glucocorticoids (mg)		15.33 ± 52.93	20.88 ± 24.84	30.37 ± 29.70	6.344	<0.001	1 versus 2: 0.234 1 versus 3: 0.002 2 versus 3: 0.005
Cardiac stimulants	Yes	5 (8.5)	10 (4.6)	22 (14.1)	10.447	0.005	1 versus 2: 0.245 1 versus 3: 0.266 2 versus 3: 0.001
	No	54 (91.5)	207 (95.4)	134 (85.9)			
Diuretics	Yes	13 (22.0)	41 (19.0)	81 (51.9)	81 (51.9)	<0.001	1 versus 2: 0.601 1 versus 3: <0.001 2 versus 3: <0.001
	No	46 (78)	175 (81)	75 (48.1)			
Anticoagulants	Yes	1 (1.7)	31 (14.3)	32 (20.5)	12.109	0.002	1 versus 2: 0.007 1 versus 3: <0.001 2 versus 3: 0.113
	No	58 (98.3)	186 (85.7)	124 (79.5)			
Controlled oxygen therapy	Yes	25 (42.4)	210 (96.8)	145 (92.9)	135.391	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.089
	No	34 (57.6)	7 (3.2)	11 (7.1)			
Atomizing inhalation	Yes	2 (3.4)	183 (84.7)	6 (3.8)	340.278	<0.001	1 versus 2: <0.001 1 versus 3: 0.875 2 versus 3: <0.001
	No	57 (96.6)	33 (15.3)	150 (96.2)			
Mechanical ventilation	Yes	2 (3.4)	32 (14.7)	54 (34.6)	32.234	<0.001	1 versus 2: 0.019 1 versus 3: <0.001 2 versus 3: <0.001
	No	57 (96.6)	186 (85.3)	102 (65.4)			
Hospital days		12.57 ± 4.80	13.10 ± 10.49	16.04 ± 10.02	8.743	<0.001	1 versus 2: 0.728 1 versus 3: 0.212 2 versus 3: <0.001
<i>N</i>		59	216	156			
Hospitalization charge (thousand RMB)		2.27 ± 2.07	14.79 ± 8.28	18.41 ± 14.09	52.533	<0.001	1 versus 2: <0.001 1 versus 3: <0.001 2 versus 3: 0.001
<i>N</i>		59	217	156			

1 versus 2, community hospital versus second-tier hospital; 1 versus 3, community hospital versus teaching hospital; 2 versus 3, second-tier hospital versus teaching hospital; ICU, intensive care unit.

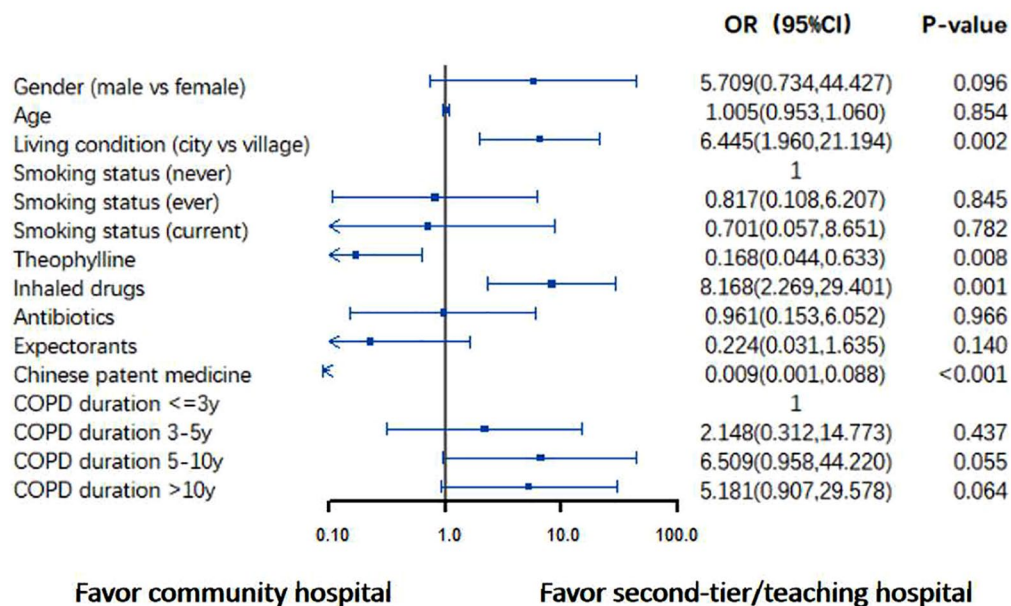


Figure 1. Factors associated with decision choices of different hospital tiers when COPD patients suffer an exacerbation.
COPD, chronic obstructive pulmonary disease.

glucocorticoids usage was the highest in the teaching hospitals (1.75 ± 3.74 versus 2.90 ± 3.88 versus 6.70 ± 5.96 , $p < 0.001$), which was in line with the total dosage of glucocorticoids (methylprednisolone, mg) (107.05 ± 432.14 versus 138.32 ± 190.05 versus 299.32 ± 337.8 , $p < 0.001$) and the daily dosage (15.33 ± 52.93 versus 20.88 ± 24.84 versus 30.37 ± 29.70 , $p < 0.001$). We also found that the teaching hospitals' diuretics and mechanical ventilation ratios were the highest ($p < 0.001$). The community hospitals had the lowest proportion of anticoagulation regimen (1.7% versus 14.3% versus 20.5%, $p = 0.002$) and controlled oxygen therapy (42.4% versus 96.8% versus 92.9%, $p < 0.001$). The second-tier hospitals had the highest proportion of atomizing inhalation therapy (3.4% versus 84.7% versus 3.8%, $p < 0.001$). However, there were no differences in antiviral treatment and ICU admission among the three levels of the hospital.

Factors associated with decision choices of different hospital tiers when COPD patients suffer an exacerbation

We then detected the possible factors that may influence the patients in choosing different levels of hospitals during AE of COPD. We found that patients in the countryside preferred the community hospitals more often than patients in the city ($p = 0.002$) (Figure 1). In addition, the patients

undergoing regular inhalant therapy were more frequent in second-tier hospitals and teaching hospitals ($p = 0.001$). Patients taking theophylline ($p = 0.008$) and Chinese patent medicine preferred community hospitals ($p < 0.001$). This phenomenon is common in China; rural patients with minor diseases tend to prefer nearby clinics or community hospitals. Some of these patients will move to cities or metropolitan for more advanced therapy if the disease develops.

Risk factors associated with the frequency of AE

We detected all the patients from the three levels of hospitals and analyzed the possible risk factors associated with AE frequency. Factors associated with the frequency of COPD AE are shown in Figure 2. Regular inhalant therapy (OR: 2.991, 95% CI: 1.234–7.246, $p = 0.015$) and expectorant (OR: 2.755, 95% CI: 1.018–7.454, $p = 0.046$) were positively correlated with COPD AE. Chinese patent medicine was negatively correlated (OR: 0.101, 95% CI: 0.011–0.934, $p = 0.043$).

Factors associated with long-term antibiotics usage in the treatment of AECOPD

We analyzed the usage of antibiotics in the treatment of AE in all the hospitals included in the study according to single logistic regression.

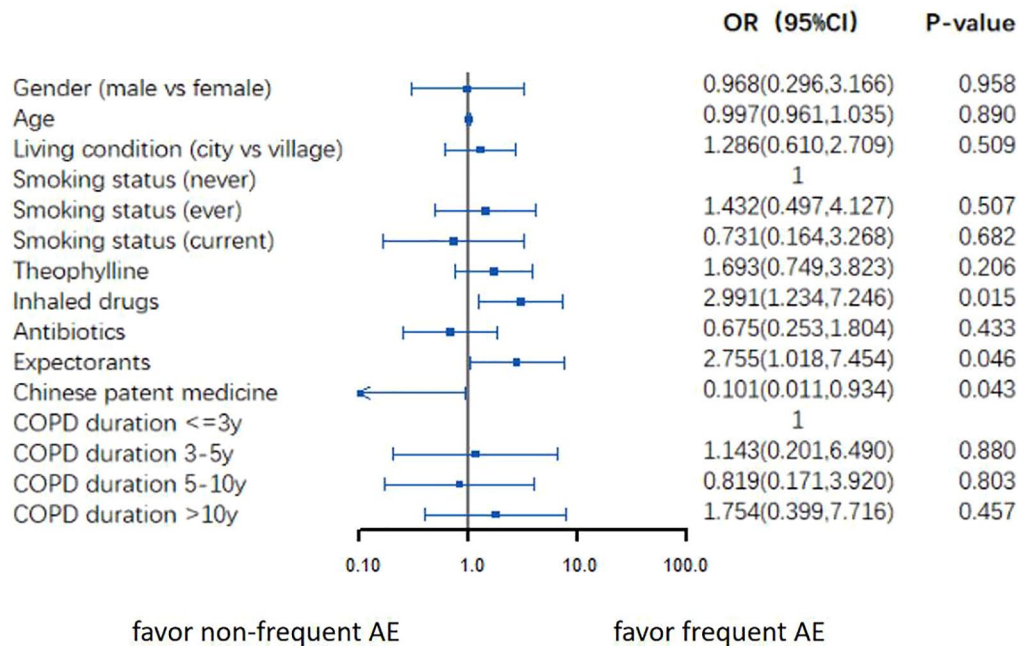


Figure 2. Risk factors associated with the frequency of acute exacerbation. COPD, chronic obstructive pulmonary disease.

Unfortunately, the results showed that antibiotics treatment has little relevance to the increased white blood cell (WBC) count and sputum etiology. As approximately 90% of AE patients received antibiotics, we believe that antibiotics abuse exists in China in the treatment of AECOPD. Furthermore, we investigated the possible risk factors of long course of antibiotics usage (which is defined as more than 14 days of antibiotics treatment). The results showed that moderate exacerbation (OR: 5.295, 95% CI: 2.248–12.473, $p < 0.001$), radiographic progression (OR: 2.176, 95% CI: 1.047–4.522, $p = 0.037$), positive sputum etiology (OR: 3.073, 95% CI: 1.477–6.394, $p = 0.003$) and increased WBC (OR: 2.470, 95% CI: 1.190–5.126, $p = 0.015$) were risk factors of long course of antibiotics (Figure 3).

Factors associated with glucocorticoids usage in the treatment of AE COPD

We analyzed the usage of glucocorticoids in the treatment of AE in all the hospitals included in the study. The results showed that moderate exacerbation (OR: 2.983, 95% CI: 1.522–5.847, $p = 0.001$) and right heart failure (OR: 2.343, 95% CI: 1.079–5.085, $p = 0.031$) were risk factors of glucocorticoids therapy (Figure 4).

Furthermore, old age was negatively correlated with glucocorticoid usage (OR: 0.944, 95% CI: 0.916–0.974, $p < 0.001$). The results imply that patients with moderate exacerbation and right heart failure had a higher probability of receiving glucocorticoids therapy. However, one should be cautious about giving older patients glucocorticoids when they suffer AE because of complicated comorbidity and weakness in this subgroup.

Factors associated with mechanical ventilation in the treatment of AECOPD

We investigated the possible risk factors of mechanical ventilation therapy in our study. The results showed that consciousness disorder (OR: 13.273, 95% CI: 3.436–51.28, $p < 0.001$) and hypercapnia (PCO₂ > 50 mmHg) (OR: 5.437, 95% CI: 2.579–11.462, $p < 0.001$) were risk factors of mechanical ventilation therapy (Figure 5). Moreover, compared with relatively younger patients, older patients were statistically less likely to receive mechanical ventilation. However, the OR was 0.962, meaning little clinical significance (OR: 0.962, 95% CI: 0.926–0.999, $p = 0.047$). The results indicated that patients with consciousness disorder (OR: 13.273, 95% CI: 3.436–51.28, $p < 0.001$) and hypercapnia had an increased chance to receive mechanical ventilation therapy.

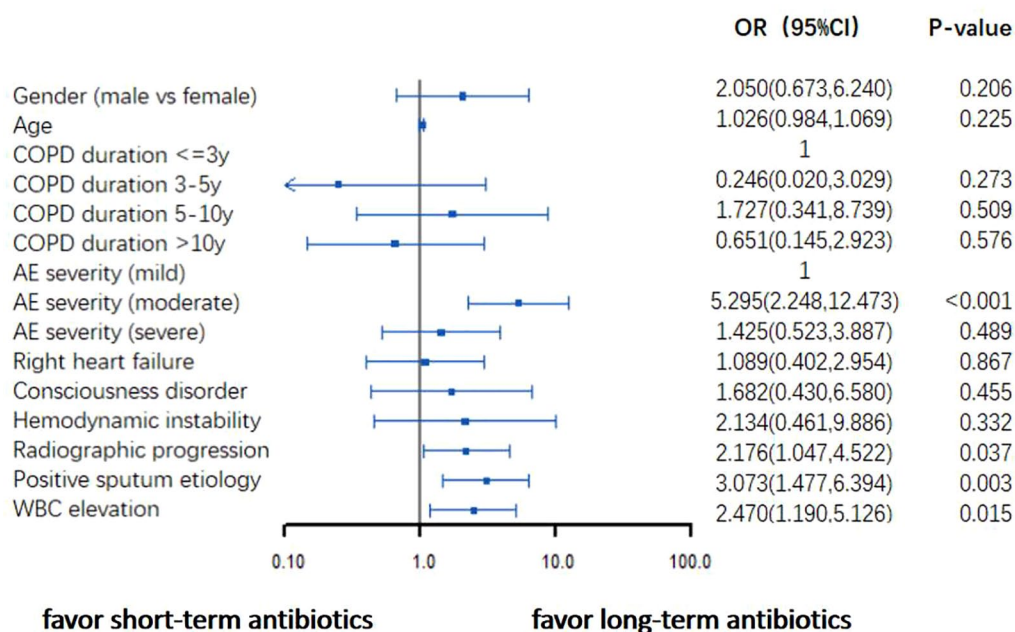


Figure 3. Factors associated with long-term antibiotics usage in the treatment of AECOPD. We define long-term antibiotics as more than 14 days of antibiotics. Short-term antibiotics was defined as less than 14 days. AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; WBC, white blood cells.

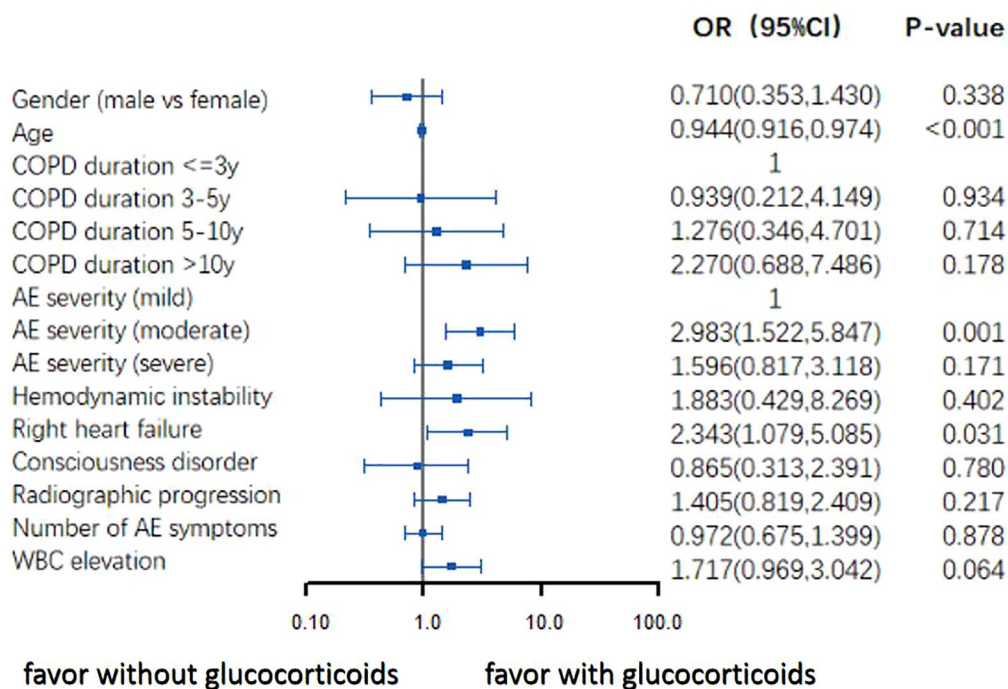


Figure 4. Factors associated with glucocorticoids usage in the treatment of AECOPD. AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; WBC, white blood cells.

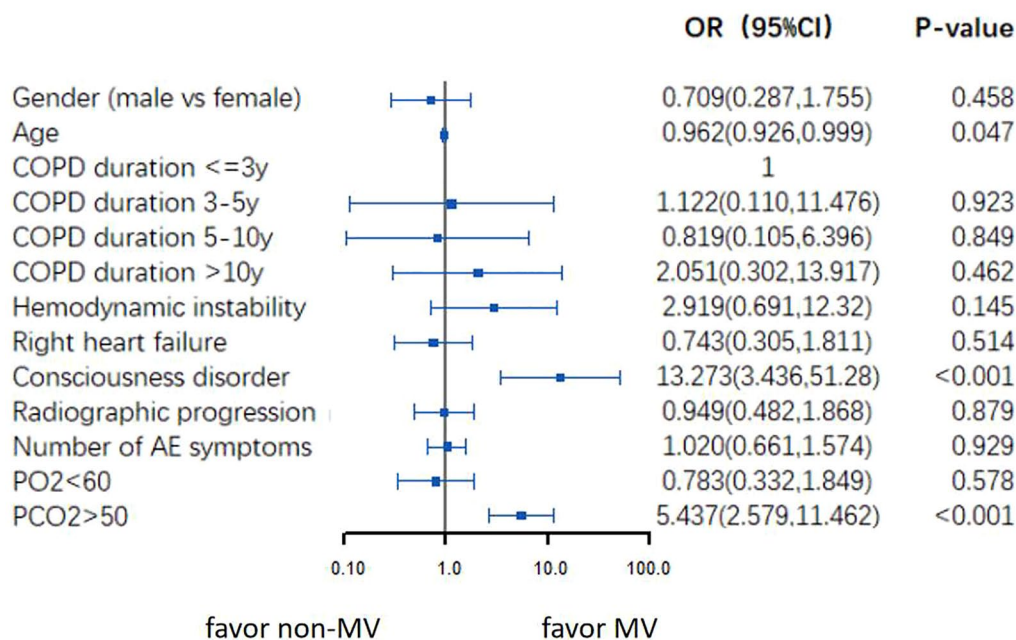


Figure 5. Factors associated with mechanical ventilation in the treatment of AECOPD.

AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; PCO₂, arterial partial pressure of carbon dioxide; PO₂, arterial partial pressure of oxygen.

Factors associated with anticoagulant usage in the treatment of AECOPD

We detected the possible factors associated with anticoagulation therapy in admission of the AE COPD patients included in the study. We found that patients with moderate exacerbation (OR: 3.833, 95% CI: 1.361–10.800, $p=0.011$) and high level of D-dimer (OR: 2.946, 95% CI: 1.203–7.211, $p=0.018$) were two risk factors of anticoagulation therapy (Figure 6). This means that moderate AECOPD with increased D-dimer had a higher probability to get anticoagulation therapy during this admission.

Discussion

In 2015, the Chinese government proposed a hierarchical medical system policy to allocate and promote health service resources rationally. The document suggested that the effective implementation of the mission should be done by the year 2017. COPD is the most important chronic disease worldwide. It has high morbidity and mortality not only in the world but also in China. For the sake of the effectiveness evaluation of the policy, we surveyed the different features of AECOPD management in the three tiers of hospitals.

In our survey, we found that patients who lived in a city underwent regular inhalant therapy and displayed longer course of disease preferred second-tiered hospitals or teaching hospitals mostly located in their cities. In contrast, the patients from villages treated with theophylline or Chinese herb medicine and displaying a shorter course of disease preferred community hospitals mostly located in their community. This means that most COPD patients are likely to treat their disease locally. However, our results clearly show that most community hospitals can only deal with mild exacerbation of COPD; for moderate and severe exacerbation, the rapid transfer mechanism should be build up. Residents in cities usually swarm to the top teaching hospital, even with mild disease, which causes medical resources. Our survey showed that the second-tiered hospitals (regional medical instruments in the city) could provide medical services for moderate and severe COPD exacerbation ideally, mostly equal to a teaching hospital. However, because of COPD exacerbation's pathophysiological complexity and treatment difficulty, the medical task could not be generalized to community hospitals in China. Strengthening medical instrument equipment and improving specialists' capacity in second-tiered hospitals might be an alternative

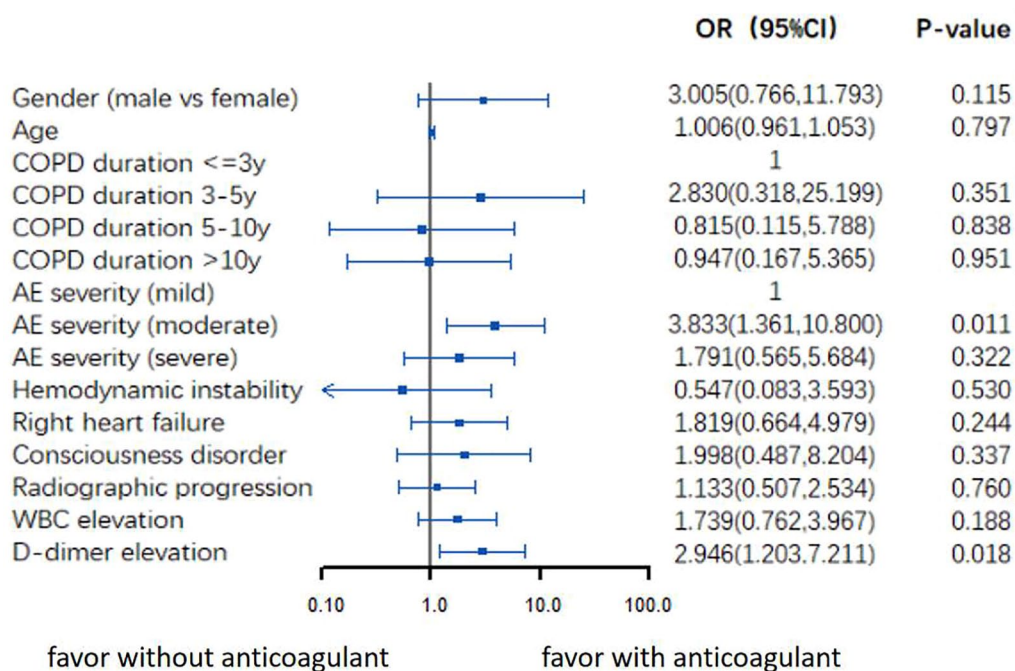


Figure 6. Factors associated with anticoagulant usage in the treatment of AECOPD. AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; WBC, white blood cells.

way to treat AECOPD regionally, thus relieving teaching hospitals from the current huge medical demands.

Infection is the most common cause of AECOPD. Thus, the antimicrobial therapy based on etiology examination is the main treatment. As we investigated the therapeutic paths of the hospitals, we found that the sputum etiology and the WBC count had little influence on the practice of antibiotics. In other words, due to the high rate of antibiotics application in our study, we speculated that antibiotics abuse might exist in the three tiers of hospitals. Zheng Wang *et al.*⁶ reported that China is the most frequent user of antibiotics in the world. It has been reported that the rates of antibiotics in many developed countries were less than 30% during hospitalization, which is much lower than in China.⁷ World Health Organization reported that there would be 10 million deaths and approximately 100,000 billion dollars loss by 2050 due to antibiotics overuse.⁸ It has been reported that more than 150,000 patients died of antibiotics abuse annually in China from 2001 to 2005.⁶ It was also estimated that the fatality rate of antimicrobial resistance infection reached 11.7% in hospitalized patients in China in 2011.⁶ Antibiotics abuse and antimicrobial resistance

were so serious in China that the Chinese government has made great efforts to improve conditions since 2012. However, our study revealed that the irrational practice of antibiotics use is still ongoing. Thus, there is a need for controlling antibiotics abuse and reducing antimicrobial resistance. Vollenweider DJ *et al.* analyzed 16 trials of antibiotics in AECOPD. They discovered that there were no inconsistent differences between antibiotics groups and placebo groups.⁹ Fanning M *et al.* conducted a retrospect study. They found that clinical antibiotic therapies were often inconsistent with guidelines, and the differences were related to longer hospitalization days and higher cost.¹⁰ Clinical doctors still need to raise awareness for the rational management of antibiotics.

Glucocorticoids also play an important part in treating AECOPD to control the inflammation, especially in severe cases.¹¹ Long treatment periods and a high dose of glucocorticoids can provide a strong anti-inflammatory effect but with increased side effects at the same time. Leuppi JD *et al.*¹² reported that 5 days of systematic glucocorticoids had the same recurrence compared with 14 days of treatment. Kiser TH *et al.* suggested that patients in the ICU wards should receive a low dosage of glucocorticoids. They found that a low dosage of

methylprednisolone would not increase the mortality but could shorten the hospitalization days and cost, reduce the invasive mechanical ventilation and lower the fungal infection.¹³ Magnussen *H et al.*¹⁴ conducted the WISDOM (This is the name of the study) study in which they found that proper withdrawal of inhaled corticosteroids (ICS) would not increase the risk of exacerbation. Compared with the recommendation of GOLD (This is the name of the association) guidance,¹⁵ the use of glucocorticoids in our study was depressing. Our study showed longer periods and more dosages of glucocorticoids with various administrations. Previous studies showed that low dosage of oral administration had the same treating effect but fewer side effects than high dosage intravenous injection of glucocorticoids.^{11,12} Ceviker and Sayiner¹⁶ compared oral glucocorticoids with intravenous methylprednisolone. They found that the efficacy was almost the same, including the arterial blood gas analysis, symptom assessment, hospitalization days and readmission.

One of the most important breakthroughs in AECOPD was the practice of noninvasive mechanical ventilation in the treatment of respiratory failure with hypercapnia. It was reported that NIV could dramatically decrease endotracheal intubation, mortality caused by respiratory failure and complications by invasive mechanical ventilation.¹⁷ Currently, NIV is strongly recommended for the first-line treatment of type 2 respiratory failure.^{18,19} NIV therapy with proper drug treatment can get pulmonary rehabilitation and free of non-invasive ventilation (NIV) gradually in approximately 2–10 days.²⁰ Our study showed that the proportions of severe cases in the second-tier hospitals and teaching hospitals were 26.9% and 32.1%, respectively. The proportion of mechanical ventilation were 14.7% and 34.6% in the second-tier hospitals and teaching hospitals, respectively. It seemed that the NPPV in the second-tier hospitals maybe not be enough. Further investigation in the practice of NIV in the hospitals is needed to control AECOPD rationally.

Given the results of this survey, we conclude that the ‘tiered medical services’ in AECOPD management are unsatisfactory. The government needs to try to divert the AECOPD to the different tiers of hospitals according to the severity of the disease instead of relying on personal willingness. In community hospitals, medical insurance could be more favorable. In this way, the community hospitals could attract mild patients for the first visit of the

exacerbation. In addition, the teaching hospitals should put more effort into training specialists.

Furthermore, guideline or expert consensus for the diagnosis and therapy are essential. Doctors from different hospitals can follow it when practicing medicine. With increasing number of sufficient and capable specialists working in the second-tiered hospitals, more and more AE COPD patients will prefer the nearby regional hospitals (the second-tiered hospital) for more convenient and economical treatment instead of the crowded and distant top hospitals (the teaching hospital) for the same therapy.

Our study observed the AECOPD in the three tiers of hospitals, including the patient features and the treatment differences. The results indicated that the Chinese government policy of ‘tiered medical services’ does work somehow. However, there is still a lot of room for improvement. Meanwhile, irrational treatment strategies in different hospitals were still found, and some of the guidelines which instruct the diagnosis, examination and therapy are not always implemented. Thus, further reform of the policy is still needed to optimize the management of AE COPD in China.

Author contributions

Xiaoqing Liu: Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Chunling Du: Data curation; Investigation.

Fuying Hu: Data curation; Investigation.

Yunfeng Zhao: Data curation; Investigation.

Jintao Zhou: Data curation; Investigation.

Qian Wang: Data curation; Investigation.

Yutong Mu: Formal analysis.

Jinchang Lu: Conceptualization.

Lei Gao: Conceptualization.

Bo Cui: Conceptualization.

Yuan Ma: Conceptualization.

Tieying Sun: Methodology.

Feng Qian: Data curation; Methodology; Writing – original draft.

Zhihong Chen: Funding acquisition; Methodology; Project administration; Resources; Writing – original draft.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (81970023 by ZHC; 81770083 by SQL), the Shanghai Health Committee (201840288), the Shanghai Respiratory Research Institute and Young Scientists Training Program of Zhongshan Hospital, the Shanghai Top-Priority Clinical Key Disciplines Construction Project (2017ZZ02013) and the Shanghai Municipal Key Clinical Specialty (shslczdzk02201).

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