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RESEARCH ARTICLE

Drug-related problems among hospitalized patients with COPD in mainland China

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Abstract

Background Data are lacking about the extent of drug-related problems in hospitalized patients with COPD in China. *Objective* Identify types and causes of drug-related problems and assess interventions performed by pharmacists. *Setting* Study was conducted in an academic teaching hospital in Shanghai, China. *Method* Between June 2017 and July 2018, 393 patients admitted to hospital for acute exacerbation of COPD hospitalized were enrolled. Patient demographics and clinical characteristics were collected. The drug-related problems and interventions were recorded and analyzed based on the Pharmaceutical Care Network Europe (PCNE)-DRP V 8.02 classification. *Main outcome measures* The number, types, causes, interventions, and outcomes of the problems were analyzed. *Results* A total of 640 DRPs, with 763 corresponding causes, were identified for 393 patients. "Treatment safety P2" was the most common type of problem (54.2%; 347/640), and the most common causes were "drug selection C1" (24.2%; 185/763), "dose selection C3" (21.5%; 164/763) and "treatment duration C4" (17.7%; 135/763). Antibiotics, corticosteroids, and proton pump inhibitors were the three primary medication classes associated with DRPs. Patients, hospitalized for more than eight days, taking ten or more drugs or having renal dysfunctions were more likely to have drug-related problems. Pharmacists totally proposed 1557 interventions to address the problems. Most interventions (91.0%; 1418/1557) were accepted, and 91.6% of the problems were solved. *Conclusion* The prevalence of drug-related problems among the studied COPD patients was high. Pharmacists can have an important role in addressing the problems and optimizing the safety and effectiveness of therapies for hospitalized COPD patients.

Keywords China · Chronic obstructive pulmonary disease · Clinical pharmacy services · COPD · DRP · Drug-related problem

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Impacts on practice

- Drug-related problems (DRPs) are common in hospitalized patients with chronic obstructive pulmonary disease (COPD) in China.
- Pharmacists may play an important role in identifying and solving DRPs in hospitalized COPD patients.
- COPD patients, with renal impairment, hospitalized for more than eight days and taking ten or more drugs are likely to have an increased number of DRPs, requiring prioritized pharmaceutical care.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1], acute exacerbations of COPD are common events that often lead to hospitalization with worsened quality of life, increased health-care costs, and increased mortality [2]. In China, COPD accounts for 1.6% of all hospital admissions [3]. The hospital represents a unique setting. Most hospitalized COPD patients are elderly patients (≥ 70 years) [4] and burdened with co-morbidities such as cardiovascular diseases, diabetes, and hypertension [5, 6]. Because of these compounding patient factors, patients hospitalized for COPD are at a higher risk of experiencing drug-related problems (DRPs). Various classification systems have been used to categorize DRPs, and the Pharmaceutical Care Network Europe (PCNE) Classification is a validated system in hospital settings [7, 8].

Most studies about DRPs among COPD patients are conducted in community patients with stable COPD [9–12], while the extent and characteristics of DRPs in hospitalized acute exacerbation COPD patients are unknown. Treatment regimens for stable and acute exacerbation COPD patients are different [13]. Hospitalized patients may possess a higher risk of DRPs [14], therefore a better knowledge of DRPs among hospitalized acute exacerbation COPD patients is needed.

Aim of the study

The primary objective was to categorize DRPs identified in hospitalized COPD patients and to assess interventions provided by pharmacists. The secondary objective was to identify factors associated with DRPs.

Ethics approval

The study was approved by the Ethical Committee of Tongren Hospital, Shanghai Jiao Tong University School of Medicine (Shanghai Tongren Hospital Ethics Committee 2016-021-01). Both the objectives and methodology of the study were explained to patients, and written consent forms were obtained from study participants.

Methods

Study design, setting, and participants

Data on DRPs in hospitalized COPD patients were prospectively collected from June 2017 to July 2018. Study subjects were COPD patients admitted at the Department of Respiratory Medicine or Respiratory Intensive Care Unit at the Tongren Hospital, Shanghai Jiao Tong University, a 1500-bed teaching hospital in Shanghai, the largest city in China.

Inclusion criteria were (1) patients with a confirmed diagnosis of COPD per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [13]; and (2) patients admitted to hospital for acute exacerbation of COPD. Exclusion criteria were (1) patients in terminal or palliative care [15], or (2) patients unable to understand the consent form written in Chinese.

Data collection

Two qualified doctors from the respiratory units were trained to assist in data collection. Five clinical pharmacists, had at least five-year hospital pharmacy experiences and have completed the PCNE-DRP classification training, attended COPD medication management sessions. Patient demographics and clinical information (COPD condition, co-morbidities, and treatment regimens) were obtained from medical records and patient interviews. Treatment regimens were assessed for indication, effectiveness, dosage, directions, practicability, drug–drug interactions, contraindications, duplication, duration, side effects, compliance, untreated indication, and monitoring information. The duration of individual patient data ranged from hospital admission to discharge.

PCNE-DRP classification

Clinical guidelines [1] and drug databases were consulted to identify DRPs and propose interventions. The Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert doctors to Right Treatment (START) tool kits were used to identify potentially inappropriate medicines [16]. DRPs were classified according to the PCNE-DRP V8.02 classification system. One Problem (P) may have multiple Causes (C), and lead to more than one Interventions (I), but it leads to only one Outcome (O). Data were independently verified by three pharmacists as shown in Fig. 1. One clinical pharmacist investigated and categorized DRPs based on the patient's clinical information, and

a second pharmacist re-investigated and re-classified those DRPs to ensure consistency. When inconsistency existed, a third pharmacist would re-investigate and re-classify. If results remained to be inconsistent, a consensus was reached through discussion [17].

Statistical analysis

Individual and problem-level analyses were performed separately because one patient may have multiple DRPs. All statistical analyses were carried out using SPSS (Version 23.0). Both univariate and multivariate analyses were conducted. Based on the univariate analysis, variables that were significant ($P < 0.05$) were included in the multivariate analysis to control for confounders and to identify factors independently associated with the number of DRPs. The results of univariate andmultivariate analysis were reported as crude odds ratio (COR) and adjusted odds ratio (AOR) at 95% confidence intervals (95% CI), respectively. A P value of < 0.05 was considered significant.

Results

Patient characteristics

As shown in Fig. 1, a total of 428 hospitalized patients with COPD were initially recruited into the study. A total of 35 patients withdrew during the assessment period. Data was ultimately collected and analyzed from 393 patients. The mean age was 76.4 ± 12.3 years, 77.6% were males, and 93.9% were past or current smokers (52 never smoke). The average FEV1 was 42.4%, rated as severe COPD based on the 2017 GOLD guideline. Based on stratification according to symptoms and prior history of exacerbations, 66.9% (263/393) of patients were categorized as Group D and 24.7% (97/393) were categorized as Group C COPD patients. Together these two groups accounted for 91.6% of total study patients. Participants had an average 4.2 co-morbidities, with 89.6% (352/393) of patients having hypertension, 53.2% (209/393) with coronary artery disease, and 49.4% with diabetes (194/393). The details of the patients' demographics and clinical characteristics are listed in Table 1. Polypharmacy (taking five or more medications) [18] was common, accounting for 96.9% (381/393) of patients, with an average of 11.2 medications per patient. The five most frequent medication classes were antibiotics, anti-hypertensives, bronchodilators,corticosteroids, and expectorants.

Drug-related problems identified for inpatients with COPD

A total of 640 DRPs were identified, averaging 1.6 per patient, with more than half (56.7%; 223/393) of the patients having at least one DRPs. The distribution and causes of DRPs are shown in Fig. 2 and Table 2. Among the 640 DRPs, "treatment safety P2" was the major type of DRP (54.2%; 347/640) identified, followed by "treatment effectiveness P1" (24.1%; 154/640). A total of 763 causes were categorized, with the three most frequent causes being "drug selection C1" (24.2%; 185/763), "dose selection C3"

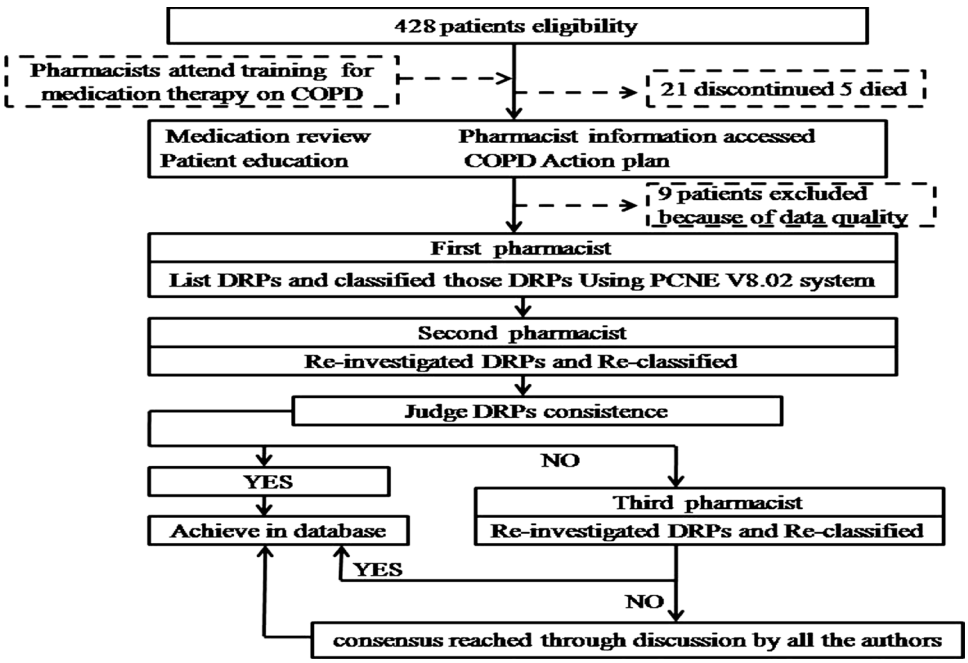

Fig. 1 Patient flow chart and drug-related problems identification in the study

Table 1 Demographics and clinical characteristics of participants (n = 393)

Characteristics	Value
Gender, male, n (%)	305 (77.6%)
Age, mean ± SD, years	76. 4 ± 12. 3
FEV_1 %, mean ± SD	42.4 ± 14.7
FEV_1/FVC, mean ± SD	41.7 ± 17.3
CAT score, mean ± SD	27.9 ± 8.4
Severity as per GOLD, n (%)	
C group	97 (24.7%)
D group	263 (66.9%)
Smoking status, n (%)	
EX-smoker	287 (73.0%)
Current smoker	82 (20.9%)
During of COPD (mean ± SD), years	11.8 ± 4.7
Past medical history, n (%)	
Hypertension	352 (89.6%)
Coronary artery disease	209 (53.2%)
Diabetes mellitus	194 (49.4%)
Renal impairment	117 (29.8%)
Congestive heart failure	101 (25.7%)
Stroke (past)	99 (25.2%)
Chronic prostate disease	86 (21.9%)
Liver impairment	43 (10.9%)
Others	19 (4.8%)

N, number; SD, standard deviation; GOLD, global initiative for chronic obstructive lung disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; CAT, COPD assessment test, range from 0 to 40, a higher score indicates a worse health status; both C group and D group patients had ≥ 2 moderate (severe) exacerbation history or > 1 leading to hospital admission in the past year, CAT score of C group < 10 and CAT score of D group ≥ 10

(21.5%; 164/763) and "treatment duration C4" (17.7%; 135/763). Pharmacists proposed 1557 interventions to solve the DRPs, averaging 2.4 interventions per DRP identified. As shown in Fig. 3, about half of the interventions were made at the "drug level I3" (45.5%; 708/1557) followed by at the "prescriber level I1" (32.6%; 507/1557) and at the "patient level I2" (16.2%; 252/1557). As shown in Table 3, the top three major drug classes causing DRPs were antibiotics (36.7%; 235/640), corticosteroids (19.8%; 127/640), and proton pump inhibitors (PPIs; 10.2%; 65/640).

Analysis of factors associated with the number of drug-related problems

Univariate binary logistic regression analysis showed that patients who had three or more disease conditions, took ten or more drugs, stayed in hospital eight or more days and renal dysfunction were more likely to have DRPs. Multivariate logistic regression analysis indicated that only ten or more drugs taken, eight or more days stayed in hospital and renal dysfunction had a significant association with DRPs. The details are summarized in Table 4.

Acceptance of interventions and the status of drug-related problems

Total 91.0% interventions (1418/1557) were accepted. Among these, 80.0% were fully implemented. Most identified DRPs (91.6%; 586/640) were solved (Table 5).

Discussion

To the best of our knowledge, this is the first prospective study conducted in China to categorically evaluate DRPs in hospitalized COPD patients, and to analyze the utility of pharmacist intervention. Remarkably, more than half (56.7%) of the study participants had at least one DRP, with an average of 1.6 DRPs per patient. But this finding is consistent with a recent study in community-dwelling COPD adults using the PCNE classification [19], further suggesting

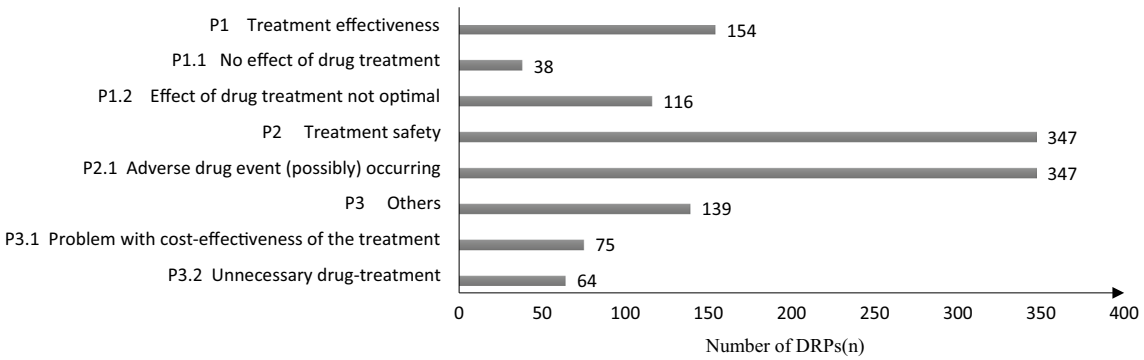

Fig. 2 Distribution of DRPs according to the PCNE DRP classification V8.02

Table 2 Cause of DRPs according to the PCNE DRP classification V8.02

Primary domain	Code	Detailed classification	n	%
Cause of problem				
Drug selection	C1	Total	185	24.2
	C1.1	Inappropriate drug according to guidelines/formulary	2	0.3
	C1.2	Inappropriate drug (within guidelines but otherwise contra-indicated)	47	6.2
	C1.3	No indication for drug	38	5.0
	C1.4	Inappropriate combination of drugs or drugs and herbal medication	66	8.7
	C1.5	Inappropriate duplication of therapeutic group or active ingredient	32	4.2
Drug form	C2	Total	23	3.0
	C2.1	Inappropriate drug form (for this patient)	23	3.0
Dose selection	C3	Total	164	21.5
	C3.2	Drug dose too high	152	19.9
	C 3.4	Dosage regimen too frequent	12	1.6
Treatment duration	C4	Total	135	17.7
	C4.2	Duration of treatment too long	135	17.7
Dispensing	C5	Total	15	2.0
	C5.3	Wrong drug, strength or dosage advised (OTC)	15	2.0
Drug use process	C6	Total	34	4.5
	C6.1	Inappropriate timing of administration and/or dosing intervals	34	4.5
Patient related	C7	Total	115	15.1
	C7.7	Inappropriate timing or dosing intervals	12	1.6
	C7.8	Patient administers/uses the drug in a wrong way	103	13.5
Other	C8	Total	92	12.1
	C8.1	No or inappropriate outcome monitoring (incl. TDM)	92	12.1
	I 3.5	Drug stopped	74	4.8
	I 3.6	New drug started	42	2.7
Treatment duration	I 4	Total	90	5.8
	I 4.2	Side effect reported to authorities	90	5.8

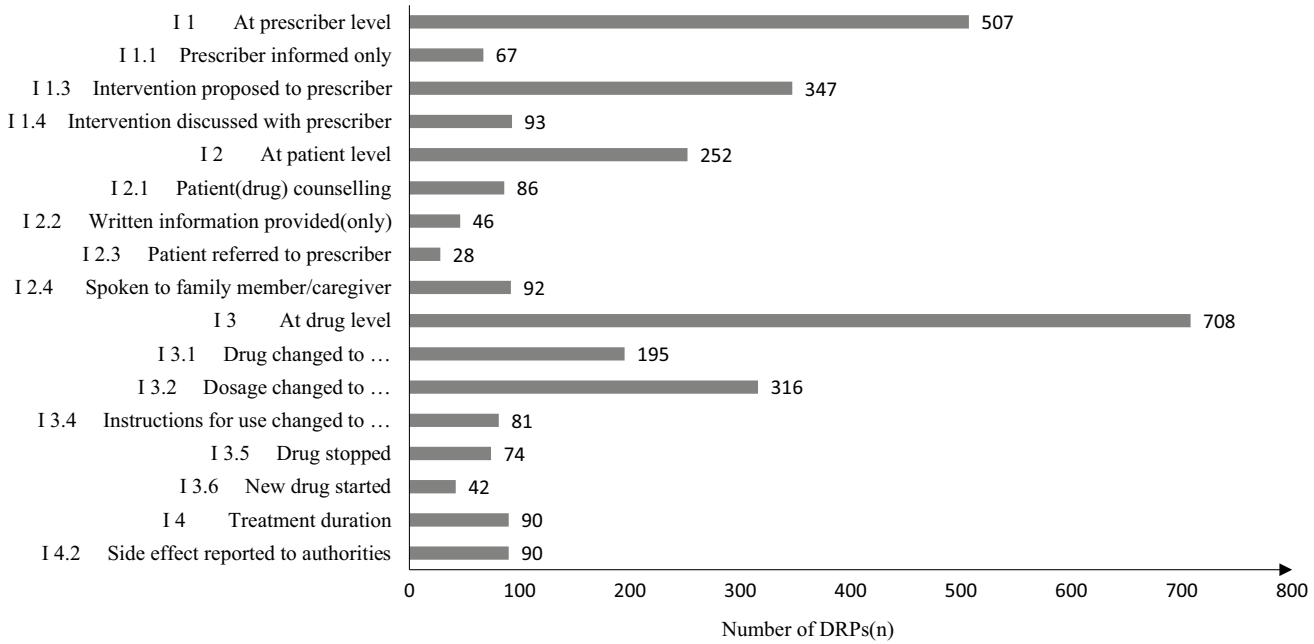

Fig. 3 Distribution of interventions according to the PCNE DRP classification V8.02

Table 3 The top three drug categories causing drug-related problems

Drug group	Type of problem	Causes of problem	n
Antibiotics	P1.2—Effect of drug treatment not optimal	C6.1—Inappropriate timing of administration and/or dosing intervals	28
	P2.1—Adverse drug event (possibly)occurring	C1.4—Inappropriate combination of drugs or drugs and herbal medication	12
		C3.2—Drug dose too high	86
		C8.1—No or inappropriate outcome monitoring (incl. TDM)	36
	P3.1—Problem with cost-effectiveness of the treatment	C4.2—Duration of treatment too long	73
Corticosteroid	P2.1—Adverse drug event (possibly)occurring	C7.8—Patient administers/uses the drug in a wrong way	101
		C8.1—No or inappropriate outcome monitoring (incl. TDM)	26
PPI	P1.2—Effect of drug treatment not optimal	C1.4—Inappropriate combination of drugs or drugs and herbal medication	38
	P2.1—Adverse drug event (possibly) occurring	C1.5—Inappropriate duplication of therapeutic group or active ingredient	15
		C4.2—Duration of treatment too long	12

Table 4 Univariable and multivariable binary logistic regression analysis of predicators of drug-related problems

Variables	Univariable analysis		Multivariable analysis	
	COR (95% CI)	*P* value	AOR (95% CI)	*P* value
Age ≥ 70	1.175 (0.278─2.987)	0.812		
Gender (male)	1.345 (0.456─3.125)	0.612		
Hospital stay days ≥ 8	2.234 (1.346–5.126)	0.015	2.147 (1.416–4.878)	0.041
Number of drugs ≥ 10	4.317 (2.127–8.328)	0.023	4.114 (2.223–7.997)	0.038
Number of Co morbidities ≥ 3	1.836 (0.576–3.536)	0.046	1.775 (0.657–3.406)	0.063
Renal function (eGFR) < 45 ml/(min 1.73 m^2)	3.742 (1.230–7.531)	0.021	3.268 (1.416–7.276)	0.034

eGFR estimated glomerular filtration rate

Table 5 Acceptance of interventions and the status of drug-related problems

Primary domain	Code	Detailed classification	n	%
Implementation				
Intervention accepted	A 1	Total	1418	91.0
	A1.1	Intervention accepted and fully implemented	1246	80.0
	A1.2	Intervention accepted, partially implemented	172	11.0
Intervention not accepted	A 2	Total	139	9.0
	A2.2	Intervention not accepted: no agreement	43	2.8
	A2.3	Intervention not accepted: other reason (specify)	96	6.2
Outcome of intervention				
Not known	O 0	Total	19	2.9
	O0.1	Problem status unknown	19	2.9
Solved	O 1	Total	492	76.9
	O1.1	Problem totally solved	492	76.9
Partially solved	O 2	Total	94	14.7
	O2.1	Problem partially solved	94	14.7
Not solved	O 3	Total	35	5.5
	O3.1	Problem not solved, lack of cooperation of patient	16	2.5
	O3.2	Problem not solved, lack of cooperation of prescriber	12	1.9
	O3.4	No need or possibility to solve problem	7	1.1

that hospitalized COPD patients were also at high risk for DRPs.

The most commonly identified DRP type was "treatment safety P2". However, this was inconsistent with the findings of the previous study on COPD in which the "treatment effectiveness P1" was the most common DRP category [19]. Discrepancy in the type of DRP may be explained by the following arguments: (1) the previous study was in the community setting, while the current study was in the hospital setting. Antibiotics and corticosteroids were more often used for the treatment of acute COPD exacerbations in hospitalized patients [20], thereby being associated with more drug-safety problems than community COPD patients [21]; (2) more drugs were administered to hospitalized patients, which required clinical pharmacists to pay more attention on drug regimens to improve drug safety [22], such as long-acting loop diuretic using as blood pressure-lowering agents in diabetic hypertension patients identified as potentially inappropriate medicines by the START tool; and (3) different PCNE-DRP classification versions were used. This study used the PCNE-DRP V8.2 classification system while the previous study used the V6.2 version. These two versions are not compatible as more sections were added or revised in V8.2. The three major sub-categories of DRP causes were "drug dose too high C3.2", "duration of treatment too long C4.2", and "patient administers/uses the drug in a wrong way C7.8". This indicates that the pharmacist should provide necessary patient education on the correct use of drugs when providing medication review.

Antibiotics, corticosteroids, and PPIs were the top three DRP-causing drug classes identified in our study. Antibiotics and corticosteroids are first-line treatments for patients with COPD exacerbation [23]. As further confirmed through our study, the over-prescribing of antibiotics in China is particularly rampant. The imprudent prescribing of antibiotics has numerous unintended consequences. DRPs associated with antibiotics are commonly related to antibiotic selection, dose, and duration. Examples of common antibiotic DRPs include inappropriate renal dose adjustment [24] and lengthy durations of treatment. In our study, pharmacists provided interventions aimed at improving the use of antibiotics by suggesting "drug change I3.1" or "dosage change I 3.2" through participation in clinical rounds, consultations, and case discussions. When treating hospitalized COPD patients, providers and pharmacists should consider the effect of renal function on the pharmacodynamics and pharmacokinetics of drugs to avoid the occurrence of DRPs [25, 26], and pharmacists play an important role in the rational use of antibiotics given their specialized training in pharmacotherapy [27].

The two main causes of DRPs regarding corticosteroid use were "patient uses the drug in a wrong way C7.8" and "inappropriate outcome monitoring C8.1". In this study, pharmacists found that about 60% of patients were using their inhaler devices incorrectly although they were provided with instruction leaflets during prescription dispensing at their outpatient pharmacy. For many patients, proper use of inhalers is difficult. Studies have demonstrated that many patients fail to correctly use their inhalers even when written instructions are provided, therefore verbal instructions and device demonstration given by pharmacists are necessary during medication education [19]. In our study, once incorrect technique was discovered, patients were informed that the correct technique was essential for COPD control, and a "teach-back" technique was applied to demonstrate and teach the correct use of inhalers. In mainland China, the role of the clinical pharmacist is still in early development, and only major academic teaching hospitals have clinical pharmacy services available for hospitalized patients [28]. As demonstrated in this study inadequate patient education from healthcare professionals is common suggesting that pharmacists are urgently needed in COPD care management, given their medication-related expertise [19, 29]. Lack of or inappropriate safety monitoring, such as diabetic patients without monitoring for hyperglycemia upon commencement of systemic high-dose steroid therapy for acute COPD exacerbations [30], was another major corticosteroid-related problem. Over 90% of patients in this study had hypertension and/or diabetes, and constant monitoring of both blood pressure and blood glucose levels was crucial in order to prevent the occurrence of potential problems [30]. Pharmacists should play an important role in monitoring treatment efficacy and safety.

Inappropriate combinations of drugs with PPI were the major PPI-related DRPs, such as the combined use of clopidogrel and omeprazole. This interaction may increase the incidence of major adverse cardiovascular events especially in patients with coronary artery disease [31]. The high prevalence of PPI-related DRPs highlights the need for pharmacists to comprehensively collect and assess patients' medical histories and medication regimen through patients' interviews, in order to detect DRPs that may otherwise be missed with just relying on medical chart review.

In our study, age and gender were not factors predicting the occurrence of DRPs. However, in multivariate logistic regression, factors of hospitalized for more than eight days, taking ten or more drugs or renal dysfunctions were found to be independent predictors of DRPs. This is a natural consequence of using multiple medications (owing to longer hospitalizations) and therapeutic classes (owing to multi co morbidities) simultaneously.

The high acceptance rate of pharmacist-proposed interventions by prescribers and patients demonstrated a strong trust between pharmacists, physicians, and patients, and this highlights the role of clinical pharmacists in the team-based care in COPD patients. The following are potential impacts of our study: (1) clinical pharmacist participation in COPD

care is important in identifying, solving, and optimizing the pharmacotherapy of this vulnerable patient population; (2) face-to-face inhaler demonstration is needed to teach patients on the correct use of inhalers; and (3) our COPD pharmaceutical care model could be adopted by other hospitals in China to provide better COPD management in China. This study has the following limitations: (1) this is a single center study with a relatively small sample size, and the results may not generalizable to other hospitals; and (2) only DRP was used as a clinical outcome indicator, other clinical outcome indications were not assessed.

Conclusion

Our study demonstrates that within China, drug-related problems are remarkably high in hospitalized patients with COPD. More than half (56.7%) of the participants in this study had at least one DRP, with an average of 1.6 DRPs per patient. This study not only categorizes DRPs in COPD patients for the first time, but also demonstrates the value of clinical pharmacy service in the care of COPD patients.

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Conflicts of interest All authors declare that they have no conflict of interest.

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