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Potential clinical and economic impact of optimised maintenance therapy on discharged patients with COPD after hospitalisation for an exacerbation in China

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ABSTRACT

Objectives Chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalisation are a considerable burden, both clinically and economically. Although long-acting maintenance therapy is recommended in both the GOLD (Global Initiative for Chronic Obstructive Lung Disease) and Chinese COPD guidelines, proper implementation is lacking. The objective of this study was to assess the clinical and economic impact of prescribing long-acting maintenance therapy to discharged patients with COPD after hospitalisation for an exacerbation in China by using an outcomes model.

Design This health economic analysis was conducted using a Markov cohort model from the Chinese healthcare payer perspective. Two health states (alive and dead) were modelled, and exacerbations were included as possible events.

Setting The target population was Chinese patients with COPD, >40 years of age, who were hospitalised for an exacerbation, with 1 year of follow-up. A recent COPD national prevalence study was referenced for population calculations.

Intervention A hypothetical future scenario, where 100% of patients would receive long-acting maintenance therapy after hospitalisation for an exacerbation, was compared with the current scenario, in which only 38.5% of patients are receiving long-acting maintenance therapy after hospitalisation.

Outcome measures Number of exacerbations, deaths and medical costs were measured.

Results We estimated that there were approximately 4 million Chinese patients with COPD who were hospitalised annually due to an exacerbation. By prescribing long-acting maintenance therapy, our model predicted that 917 360 exacerbations and 4034 deaths could be avoided, translating into cost savings of ¥3.5 billion (US$0.5 billion). Scenario analysis also showed that if the rate of exacerbations requiring hospitalisation was higher than our base case analysis, cost savings could reach up to ¥10.7 billion (US$1.5 billion).

Conclusion Administering long-acting maintenance therapy to more patients with COPD at hospital discharge could considerably reduce exacerbations and healthcare spending in China.

Strengths and limitations of this study

► This is the first and pragmatic health economic model for evaluating the clinical and economic impact of optimised long-acting maintenance therapy on discharged patients with chronic obstructive pulmonary disease (COPD) in China, which could be used to shape COPD reimbursement policy by local payer authorities.

► All outcome measures were based on up-to-date global/China COPD guidelines and the latest clinical data on prevalence and efficacy published in top peer-reviewed journals.

► The major limitation is that not all data indexes are specific to China, while all available published data involving Chinese populations have been referenced in this model.

► The time horizon of the model is only 1 year, given that extrapolating further would bring too much uncertainty.

► Cost of maintenance therapies was not included in this model and savings obtained through reducing exacerbations will be partly offset by increased spending on drugs. Future studies have to monitor the impact of the pharmaceutical budget to compare the investment in maintenance therapy with the savings obtained.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised and defined by limitation of expiratory airflow and associated symptoms, including dyspnoea, cough and sputum production.[1] These result from several pathological processes including loss of lung elastic recoil, fibrosis and narrowing of small airways.[1] Smoking and biomass fuel exposure are a leading cause of COPD due to the inflammatory response induced by smoke inhalation.[1] Genetic predisposition also plays a role in COPD, as

heterogeneity is observed with regard to susceptibility to smoke and other factors.[2]

COPD poses a considerable clinical and economic burden on healthcare systems worldwide.[3] It has been reported that even patients with mild COPD experience a substantially compromised quality of life.[4] Hospitalisation due to COPD represents more than 70% of all COPD-related medical costs, making it the second most costly respiratory disease.[5] COPD is considered twice as costly if productivity losses are taken into account because it may force both the patient and their caregiver to leave the workplace.[6]

A meta-analysis conducted in 2016 reported COPD prevalence in China as 9.9% for individuals who are ≥40 years of age.[7] However, a more recent study (2018) has reported a higher COPD prevalence (13.6%) for the same age group.[8] COPD is the fourth leading cause of death in China.[9] Various publications have reported that the total expenditure per patient with COPD accounts for 40% of an average family's income, whereas 32.5% of the direct economic burden of COPD in China was driven by hospitalisation.[10 11]

The China National Strategy for COPD Management encourages physicians in China to adopt the recommendations of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). However, proper implementation of these guidelines is lacking.[1 12] In this context, we expect that Chinese patients who are hospitalised for a COPD exacerbation are not receiving optimal COPD treatment as per the GOLD recommendations when leaving the hospital.[12–14] For pharmacological treatment, the GOLD 2019 recommendations state that long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are more convenient and effective in maintaining symptom relief than short-acting therapies.[1] However, short-acting treatments are frequently prescribed rather than long-acting maintenance therapy.[12] Currently, only a small proportion of patients with COPD in China receive long-acting maintenance therapy. For Chinese patients with COPD, there is no evidence regarding the impact of prescribing long-acting maintenance therapy after a hospitalisation for an exacerbation on reducing future exacerbations and rehospitalisations, which hinders the promotion and implementation of the national strategy for COPD. Thus, this study aimed to present the findings of a model which evaluates an alternative health policy for COPD in China that could reduce the clinical and economic burden on both patients and payers. We hypothesise that if all patients with COPD who are hospitalised due to a severe exacerbation were treated with long-acting maintenance therapy after hospital discharge, this would result in improvements in clinical and economic outcomes, compared with current clinical practice. It is expected that the findings from this study will improve clinical and policy decisions regarding COPD in China, and provide data for other countries that are also facing the rising challenges of this disease.
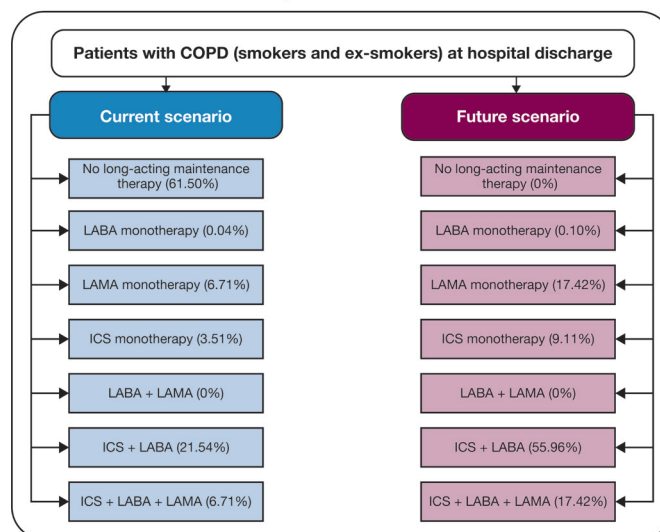

Figure 1 Compared scenarios. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

METHODS

Study design

The current study examined the difference in health outcomes and costs for two treatment scenarios for patients with COPD in China: (1) a future (hypothetical) scenario in which all patients with COPD are treated with long-acting maintenance therapy after hospitalisation due to a severe exacerbation; and (2) a scenario representative of the current treatment paradigm, in which only some (ie, 38.50%) of the patients with COPD are treated with long-acting maintenance therapy after hospital discharge.[15]

The possible long-acting maintenance treatments included in this analysis were LABA, LAMA, inhaled corticosteroids (ICS), LABA+LAMA combination, ICS+LABA combination, ICS+LABA+LAMA combination and the option of receiving no long-acting inhaled maintenance treatment (some of this population may receive theophylline and short-acting treatments). The study was a cost–outcome description study in which the outcomes and costs of the respective scenarios were assessed separately, as shown in the schematic diagram (figure 1). In this analysis, we presented outcome results as the number of deaths and avoided deaths, the number of exacerbations and avoided exacerbations, and finally the number of avoided hospitalisations. Cost results are shown as event costs and avoided healthcare costs between the two scenarios.

Model structure

Several methodologies can be used to develop a model in COPD. We opted to use the Markov technique. This has been the most applied modelling technique in COPD.[16] Thus, the model was a simple Markov model with two health states (alive and dead) developed in Microsoft Excel (figure 2). The starting cohort consisted of patients
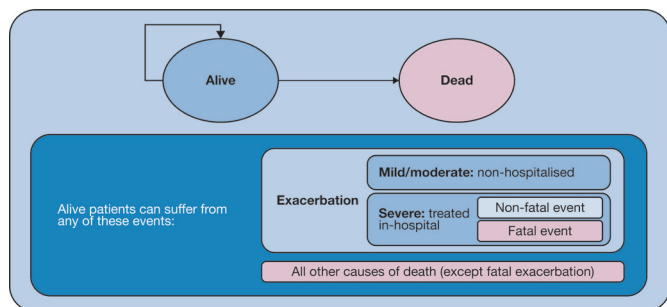
Figure 2 Health states.

with COPD who were discharged from hospital after a severe exacerbation. The model had a time horizon of 1 year and a cycle length of 1 month. Each month the patient had a risk of experiencing a moderate or severe exacerbation, where severe exacerbation is defined as one that required hospitalisation and could be fatal. Also, each month there was a possibility of dying due to other causes.

Target population

As mentioned above, the target population consisted of patients with COPD discharged from hospital after a severe exacerbation. To estimate the size of this population, a stepwise approach was followed. First, we calculated the number of patients in the population, based on the prevalence of COPD in China in people >40 years of age (13.6%).[8 17] Among these, we applied an estimated proportion of patients who had a history of admission to hospital for COPD (50.84%) over the previous year.[8] Based on this, we estimated that 4 078 838 patients in China are hospitalised annually for COPD exacerbations.

Regarding the exacerbation rates, international published literature was sought to provide an estimate as, to the best of our knowledge, there are no data specific to China on COPD exacerbation risks. We conducted a pragmatic literature search to identify the best available evidence on the impact of long-acting maintenance therapies on COPD exacerbation rates. Our search criteria targeted publications in which outcomes included exacerbation rates for patients who had a history of ≥1 exacerbation, in addition to publications that included all the drug classes accounted for in the current analysis. A total of 14 publications were identified, but only 2 were considered to fit our model concept.[18–31] The two publications were by Mills et al[28] and Pavord et al.[22] The publication by Mills et al[28] reported the annual number of exacerbations per year without long-acting maintenance treatment (1.21) and the associated relative risks of all maintenance treatments compared with placebo. The exacerbation rate without long-acting maintenance treatment was converted into a monthly exacerbation rate (0.1019) to fit the 1-month cycle length.

We also looked at recent publications which reported the relative risk of LABA+LAMA and ICS+LABA+LAMA compared with ICS+LABA.[32 33] For the LABA+LAMA combination, the reported HR (0.86; 95% CI 0.76 to 0.99) was used to calculate the relative risk of exacerbation compared with ICS+LABA.[32] For ICS+LABA+LAMA triple therapy, Calzetta et al[33] reported the relative risk of (fixed) ICS+LABA+LAMA versus fixed ICS+LABA, which was 0.78 (95% CI 0.71 to 0.85).[33] We applied these relative risks to compute the relative risk of exacerbation with the combination of LABA+LAMA and triple therapy with ICS+LABA+LAMA, respectively. The proportion of exacerbations requiring hospitalisation (ie, severe exacerbation) for non-treated and treated patients was also derived from the literature (non-treated=16.8%; treated=17.8%).[22]

The defined target population for this analysis included both smokers and former/non-smokers with COPD in China. Because smokers have a higher risk of exacerbations compared with former/non-smokers, a distinct incidence rate of exacerbation was applied to each subpopulation. The proportion of smokers was informed by the results from a published cross-sectional survey of a nationally representative sample of individuals from mainland China ≥40 years of age.[8] In this sample, 31.4% of individuals were reported to be current smokers. An HR for former/non-smokers (0.84) compared with current smokers was computed, which allowed for a different incident rate of exacerbations for the two subpopulations.[34] The exacerbation rate for patients not receiving long-acting maintenance treatment (0.1019) could then be deconstructed into a distinct exacerbation rate for former/non-smokers and smokers (formula 1) where the exacerbation rate for former/non-smokers was calculated separately (formula 2):

► Formula 1: exacerbation rate for smokers × proportion of smokers + exacerbation rate for non-smokers × proportion of non-smokers=0.1019.
► Formula 2: exacerbation rate for smokers × HR for non-smokers (0.84).

Thus, the imputed exacerbation rate was 0.1145 for smokers and 0.0962 for non-smokers.

All model inputs are listed in table 1.

Treatment paradigm

The distribution of patients per treatment option in both scenarios reflected the current and future (potential) scenarios. For the current scenario, we used the Chinese Health Insurance Database to extract the percentage of patients receiving each treatment option in 2015.[15] In 2015, only 38.5% of all patients with COPD in China were treated with long-term maintenance therapy. The proportion of patients receiving each long-acting maintenance treatment in the current scenario is shown in table 1.

In the future scenario, it was assumed that 100% of patients would receive long-acting maintenance treatment after discharge from the hospital due to a COPD exacerbation. As we had no information on what the preferred treatments would be, we redistributed patients to the different long-acting maintenance treatments. Note that theophylline, often used in China, was considered as background therapy in both scenarios.

Table 1 Summary of inputs

Base case	Value used in model	Source
Population in China >40 years of age, n	999 715 200	7
Prevalence of COPD in the Chinese population >40 years of age, %	13.6	8
Proportion of patients with exacerbations, %	5.9	8
Patients experiencing COPD exacerbations, n	8 021 715	Calculated
Incidence of hospitalisation due to exacerbations per patient with COPD, %	50.8	8
Total number of hospitalised patients with COPD, n	4 078 838	Calculated
Smokers in China, %	31.4	8
HR of exacerbations (ex-smokers vs smokers)	0.84	33
Patients per treatment: current scenario, %		
LABA alone	0.04	15
LAMA alone	6.71	15
ICS alone	3.51	15
LABA+LAMA	0.00	15
ICS+LABA	21.54	15
ICS+LABA+LAMA	6.71	15
No long-acting inhaled treatment	61.50	15
Patients per treatment: future scenario, %		
LABA alone	0.10	Assumed
LAMA alone	17.42	Assumed
ICS alone	9.11	Assumed
LABA+LAMA	0.00	Assumed
ICS+LABA	55.96	Assumed
ICS+LABA+LAMA	17.42	Assumed
No inhaled treatment	0.00	Assumed
Rate of exacerbations per patient-month		
Placebo (reference), %	10.19	27
Risk reduction compared with placebo		
LABA alone	0.83	27
LAMA alone	0.74	27
ICS alone	0.79	27
LABA+LAMA	0.59	31
ICS+LABA	0.69	27
ICS+LABA+LAMA	0.54	32
Proportion of exacerbations requiring hospitalisations, %		
No inhaled controller treatment at discharge	16.8	21

Continued

Table 1 Continued

Base case	Value used in model	Source
Inhaled controller treatment at discharge	17.8	21
Mortality		
Monthly risk of death after a first hospitalisation	0.011	29
Risk of fatal rehospitalisation	0.034	35
Costs of events (¥)		
Moderate exacerbation (outpatient visit)	319	36
Severe exacerbation/rehospitalisation	24 373	37
Fatal severe exacerbation	24 373	Assumed

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Mortality

Patients with COPD may die due to a fatal severe exacerbation or other causes. Soler-Cataluña et al[30] showed that patients with more hospital readmissions due to a COPD exacerbation are at a higher risk of non-COPD-related death than patients who previously suffered fewer acute exacerbations. We computed the cumulative mortality at 12 months (0.1194) and converted this to a monthly risk of death (0.0105) using the formula by Miller and Homan[35]:

$$P_j = 1 - [1 - P^{1/t}]$$

where P_j is the monthly transition risk, t=12, and P represents the cumulative mortality of 12 months.

Also, a COPD exacerbation case fatality of 3.4% was applied to severe exacerbations.[36]

Costs

Events in the model were divided into moderate and severe. For moderate exacerbations, an outpatient visit cost was applied using results from published literature and adjusted for 2017 Chinese yuan (US dollar) values.[37] The literature reported that an outpatient visit in China costs ¥319 (US$46).[37] For severe exacerbations, we adopted the average cost of hospitalisation as ¥24 373 (US$3544), sourced from a recent retrospective analysis based on medical record data from the First Affiliated Hospital of Guangzhou Medical University.[38] We assumed that the cost of a fatal exacerbation was the same as that for a severe exacerbation. The basis of this assumption is that a patient with COPD who has a fatal exacerbation will first experience a severe exacerbation requiring hospitalisation, which in turn can be fatal.

Table 2 Results base case

	Current scenario	Future scenario	Estimated reductions
Proportion/risk of patients dying, %	12.45	12.35	−0.10
Number of deaths, n	507 705	503 672	−4034
Number of exacerbations, n	4 070 088	3 152 728	−917 360
Number of hospitalisations, n	696 538	561 759	−134 779
Healthcare costs (¥)	18 052 707 442	14 518 128 038	−3 534 579 404

Time horizon and discount rate

The model had a time horizon of 1 year, which was deemed appropriate because the purpose of this study was to show the immediate impact of changing treatment behaviour for the Chinese healthcare payer. Given this 1-year time horizon, discounting of 0% was applied in the model to both costs and effects.[39] This means that there is no need to adjust the costs or health outcomes for net present value because they fall within a 1-year time frame (ie, not future costs or health outcomes).

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Base case results

By applying the settings described above to the model and using an estimated number of approximately 4 million Chinese patients with COPD, we calculated that approximately 0.9 million exacerbations, 134 779 rehospitalisations for exacerbations and 4034 deaths due to an exacerbation could be avoided by administering long-acting maintenance therapy to patients with COPD after discharge from hospital after an exacerbation (table 2). The resulting savings in healthcare costs are expected to be ¥3.5 billion (US$0.51 billion).

Scenario analysis

We modelled different scenarios to assess the robustness of the results after altering key assumptions (table 3). In the first scenario, we used a much lower prevalence of COPD in China (3.6%) as per an available publication, which hence reduced the starting target population from the base case of 4 million to 2.3 million.[40] Despite the smaller population size, the model still determined that many exacerbations and hospitalisations could be avoided and that savings in healthcare costs remained considerable (¥1.9 billion (US$0.28 billion); table 3).

We also tested a scenario in which the proportion of exacerbations requiring rehospitalisation was 48%, as per other publications, instead of the base case (16.8%).[41]

Results showed that approximately 0.5 million hospitalisations could be avoided, with a reduction in related healthcare costs of around ¥10 billion (US$1.45 billion).

Furthermore, we tested two scenarios where a proportion of patients on 'no treatment' in the current scenario did not shift to a treatment in the future scenario. The first scenario assessed the cost savings when only 20% of the patients currently on 'no treatment' received a treatment in the future scenario (table 3). The cost savings were ¥0.7 billion (US$0.1 billion) with 26 956 hospitalisations avoided. The second scenario tested the cost savings when 50% of patients currently on 'no treatment' received a maintenance treatment in the future scenario (table 3). The cost savings under this scenario were ¥1.7 billion (US$0.25 billion) with 67 390 avoided hospitalisations.

Finally, under the base case analysis, there were no patients treated with a LABA+LAMA combination, according to data from the China Health Insurance Database. So in our future scenarios, the use of LABA+LAMA continued to be non-existent.[15] However, there have been recent launches of LABA+LAMA combinations, but no data are yet available on the market shares of these medications.[42–44] Hence, we conducted a scenario where the percentage of patients receiving LABA+LAMA in the future scenario would be 5%, as a conservative approach. Under this scenario, ¥3.6 billion (US$0.52 billion) could be saved in healthcare costs, and 138 429 hospitalisations and 4143 deaths could be avoided (table 3).

DISCUSSION

In the current analysis, we observed that optimising the posthospitalisation treatment for patients with exacerbations of COPD to include a long-acting maintenance therapy can have a positive impact on both clinical and economic outcomes in China. Our model demonstrated that 134 779 hospitalisations could be avoided, translating into healthcare cost savings of ¥3.5 billion (US$0.51 billion). Avoiding hospitalisations is a priority for the Chinese healthcare system, in which hospital beds for patients with COPD are a scarce resource.[45] Our results indicate that adjusting the treatment strategy could help prevent rehospitalisations.

A major driver of this analysis was the relative proportion of all exacerbations that were hospitalised; this was expected since previous literature has reported that hospitalisations account for 32.5%–70% of all COPD-related medical costs.[5 11] Recent health economic studies reported a much higher proportion of hospitalised exacerbations than the percentage we used in the base case analysis.[41 46] Through our scenario analysis, adjusting for a higher percentage of hospitalisations, we observed that the number of avoided exacerbations and hospitalisations was maximised, leading to better net clinical outcomes and more considerable cost savings. Moreover, this study only took an average standard tariff for treatment of a COPD exacerbation in hospital. Because severe exacerbations/deteriorating patients may be transferred to

Table 3 Scenario analyses

	Current scenario	Future scenario	Estimated reductions
Adjusted target population			
Proportion/risk of patients dying, %	12.45	12.35	−0.10
Number of deaths, n	286 502	284 226	−2276
Number of exacerbations, n	2 296 784	1 779 111	−517 674
Number of hospitalisations, n	393 062	317 005	−76 057
Healthcare costs (¥)	10 187 292 121	8 192 699 729	−1 994 592 392
Adjusted hospitalisation rate			
Proportion/risk of patients dying, %	13.36	13.04	−0.32
Number of deaths, n	545 035	531 980	−13 055
Number of exacerbations, n	4 048 522	3 140 386	−908 136
Number of hospitalisations, n	1 943 291	1 507 385	−435 905
Healthcare costs (¥)	48 034 909 136	37 260 054 536	−10 774 854 600
'No treatment' proportion displaced in future scenario=20%			
Proportion/risk of patients dying, %	12.45	12.43	−0.02
Number of deaths, n	507 705	506 899	−807
Number of exacerbations, n	4 070 088	3 886 616	−183 472
Number of hospitalisations, n	696 538	669 582	−26 956
Healthcare costs (¥)	18 052 707 442	17 345 791 561	−706 915 881
'No treatment' proportion displaced in future scenario=50%			
Proportion/risk of patients dying, %	12.45	12.40	−0.05
Number of deaths, n	507 705	505 689	−2017
Number of exacerbations, n	4 070 088	3 611 408	−458 680
Number of hospitalisations, n	696 538	629 148	−67 390
Healthcare costs (¥)	18 052 707 442	16 285 417 740	−1 767 289 702
5% LABA+LAMA future scenario			
Proportion/risk of patients dying, %	12.45	12.35	−0.10
Number of deaths, n	507 705	503 562	−4143
Number of exacerbations, n	4 070 088	3 132 245	−937 843
Number of hospitalisations, n	696 538	558 109	−138 429
Healthcare costs (¥)	18 052 707 442	14 423 805 049	−3 628 902 393

LABA, long-acting β$_2$-agonist; LAMA, long-acting muscarinic antagonist.

respiratory high dependency units for non-invasive ventilation, the cost saving from this study may be underestimated. Therefore, if more patients with COPD received long-acting maintenance therapy after discharge from hospital, this could lead to better health outcomes and reduced medical costs over time.

Our hypothesis aligns with the GOLD recommendations for COPD (2019) and is further substantiated by the results of this analysis.[1] In addition, it is worth noting that our analysis considered only direct medical costs, and if indirect costs were taken into account the cost savings would likely increase. As described in previous literature, COPD is a disease that poses a challenge not only to the patient but also to their caregivers.[5]

To our knowledge, this is the first modelling study focusing on the clinical and economic impact of optimised posthospitalisation management for an exacerbation in patients with COPD in China. Our findings have several important implications. For clinicians in China, the findings imply that further efforts are needed to better adhere to the GOLD recommendations for posthospitalisation management of COPD exacerbations. For policymakers in China, it is suggested that a COPD prescription monitoring programme and reimbursement policy supporting long-acting maintenance after hospitalisation for exacerbation should be designed and implemented. For international management of COPD, our findings contribute by showing financial and health benefits from the use of long-acting maintenance therapies after hospital discharge, which is valuable for other countries that are facing the challenges of the rising prevalence of COPD and poor pharmacological management.

Finally, we would like to emphasise that besides the pharmacological management for COPD, the importance of other health interventions cannot be neglected, particularly smoking cessation among active smokers and post-discharge pulmonary rehabilitation. Positive effects of smoking cessation and postdischarge pulmonary rehabilitation on reducing COPD exacerbation have been well reported in literature.[47–49] Therefore, these health interventions need to be applied with pharmacological management to avoid further COPD exacerbation.

We note several limitations to this analysis, which should be addressed in future studies. First, some of the data used are not specific to China, including the key driver—the risk of hospitalisation for an exacerbation. However, during the conduct of the pragmatic literature search, which included both English and Chinese language publications, we found that available data on COPD in China were limited. Second, there was no consensus in the literature as to the proportion of COPD exacerbations that require rehospitalisation; therefore, we based our analysis on results from the TORCH study (16.8%–17.8%), whereas other publications have reported percentage ranges as high as 48%–62.5%.[22 41 46] This variable is a crucial element in computing the results, and we took a conservative approach by opting for the lower value. Third, this model did not include the cost of maintenance therapies; with new medicine launches, the current prices of inhaler therapies would be expected to change. Our study aimed to look only at public health impact; therefore, the savings obtained through reducing exacerbations will be partly offset by increased spending on drugs, which should be considered for further models. Also, a time horizon of only 1 year was considered. However, extrapolating assumptions would result in a greater amount of uncertainty. Fourth, as the purpose of this study was to develop a simple and easy-to-understand model, we ran analyses based on point estimates and did some scenarios changing some of the variables. A probabilistic sensitivity analysis based on the uncertainty around each parameter was not conducted, which could be considered in future studies.

Although the China National Strategy for COPD Management encourages physicians in China to adopt the GOLD recommendations, evidence of long-acting maintenance therapy use for patients with COPD after hospitalisation for an exacerbation is suboptimal. Through modelling, this study shows that by administering long-acting maintenance therapy after hospital discharge, the risk of experiencing more exacerbations, especially exacerbations requiring hospitalisation, could be decreased. The findings of this study provide strong evidence for clinical and policy actions to support the implementation of the national strategy for COPD.

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