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Prevalence and treatment outcomes of latent tuberculosis infection among older patients with chronic obstructive pulmonary disease in an area with intermediate tuberculosis burden

Hung-Ling Huang[a,b,c,d], Meng-Hsuan Cheng[a,b,c,e], Meng-Rui Lee[f,g,h], Jung-Yien Chien[g,h], Po-Liang Lu[b,d], Chau-Chyun Sheu[a,b,c], Jann-Yuan Wang[g,h*], Inn-Wen Chong[a,c], Jinn-Moon Yang[i] and Wei-Chang Huang[j,k,l,m*]

[a]Division of Pulmonary and Critical Care Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [b]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [c]School of Medicine, Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [d]Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [e]Department of Respiratory Therapy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [f]Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, Hsin-Chu, Taiwan; [g]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [h]College of Medicine, National Taiwan University, Taipei, Taiwan; [i]Institute of Bioinformatics and Systems Biology, National Yang Ming Chiao Tung University, Hsinchu, Taiwan; [j]Department of Chest Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [k]Mycobacterial Center, Taichung Veterans General Hospital, Taichung, Taiwan; [l]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan; [m]School of Medicine, Chung Shan Medical University, Taichung, Taiwan

ABSTRACT

Chronic obstructive pulmonary disease (COPD) and aging both increase the risk of tuberculosis (TB), an important infectious disease in human. Exploring the burden and predictors of latent tuberculosis infection (LTBI) and treatment outcomes for older individuals with COPD is essential to guide LTBI intervention policy. We enrolled patients aged over 60 years with COPD between January 2021 and June 2023 for LTBI screening using interferon-gamma release assay (IGRA). LTBI treatment options included all World Health Organization (WHO)-recommended regimens. The final regimen was selected through shared decision-making between patients and their COPD physicians, leveraging the long-standing rapport being established. We investigated the prevalence of LTBI in this population, identified risk factors using logistic regression analysis, and evaluated treatment outcomes. A total of 810 COPD patients (mean: 72.8-years) underwent LTBI screening, with an IGRA-positive rate of 23.8%. IGRA positivity was correlated with smoking pack-years (adjusted odds ratio [aOR]: 1.02, $p < 0.001$), current smoking status (aOR 1.40, $p = 0.030$), COPD duration (aOR 1.10, $p = 0.03$), inhaled corticosteroid use (aOR 3.06, $p < 0.001$), and a cumulative equivalent dose of prednisolone exceeding 210 mg over 2 years (aOR 3.13, $p < 0.001$). Treatment was initiated in 150 patients (77.7%), predominantly with weekly rifapentine plus isoniazid (3HP) (60.7%). The overall completion rate was 82.0%, with adverse reactions being the primary reason for discontinuation. Our findings support that the LTBI intervention is recommended for older patients with COPD, especially those at higher risk, as nearly 25% of them have tuberculosis infection. The high treatment completion rate highlights the safety and feasibility of the WHO-recommended regimens.

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KEYWORDS Latent tuberculosis infection; chronic obstructive pulmonary disease; prevalence; preventive therapy; safety

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a major global health challenge and causes substantial morbidity and mortality worldwide [1]. COPD, encompassing emphysema and chronic bronchitis, attenuates the immune system and increased susceptibility to lower respiratory tract infections [2]. In patients with tuberculosis (TB), COPD is a common comorbidity second only to diabetes [3]. A systematic review involving 711,389 participants revealed that COPD patients experience a 1.44- to 3.14-fold higher risk of developing pulmonary TB compared with those without COPD [4]. Moreover, COPD is also an important consequence of TB, which accelerates COPD progression, shortening life expectancy by approximately five years per patient, even under promptly TB treatment [5]. Additionally, COPD patients with active TB experience double the all-cause mortality rate within the first year compared to those without COPD [6].

CONTACT Jann-Yuan Wang @ntu.edu.tw Department of Internal Medicine, National Taiwan University Hospital, #7, Chung-Shan South Rd., Zhongzheng Dist., Taipei, 100225, Taiwan
*These authors contributed equally.

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Therefore, targeted TB prevention strategies in the COPD population could significantly reduce morbidity, mortality, and enhance the cost-effectiveness of TB interventions.

Latent TB infection (LTBI) affects nearly one-quarter of the global population, serving as a major reservoir for TB reactivation. To eradicate TB, both active TB and LTBI must be addressed simultaneously [7]. Cost-effectiveness analyses should guide LTBI interventions, considering risk profiles, healthcare systems, and economic conditions [8]. Due to the lack of logistical screening policies and the uncertain risk–benefit assessment of TB preventive therapy (TPT), the World Health Organization (WHO) does not prioritize COPD patients for LTBI intervention. However, LTBI screening and treatment are supported when prevalence exceeds 20%, as the incremental cost-effectiveness ratio would likely remain below $100,000 per QALY, a widely accepted willingness-to-pay threshold for public health interventions [9].

Given the high global burden of COPD patients at risk for active TB, identifying LTBI prevalence and predictors is crucial. Additionally, assessing treatment efficacy and safety is essential to refining LTBI strategies and advancing TB elimination efforts.

Materials and methods

Patient selection and study setting

This prospective multicenter study was conducted at Taichung Veterans General Hospital, Kaohsiung Medical University Hospital, National Taiwan University Hospital, and their affiliated hospitals between January 2021 and February 2024. Following Taiwan's national policy of LTBI intervention for TB high risk population [10], we enrolled COPD patients aged >60 years, diagnosed per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 strategy [1], based on pulmonary function tests with a forced expiratory volume in 1 (FEV1) s to forced vital capacity (FVC) ratio <70%. Exclusion criteria included (1) prior TB history, (2) suspected or active TB, (3) history of close contact with TB, (4) prior LTBI treatment, or (5) Human Immunodeficiency Virus (HIV) infection. The study was approved by the institutional ethics committees of each site (KMUHIRB-E(I)-20200434, CE21118A, NTUH-202202025RINB), and written informed consent was obtained from each participant before enrollment.

LTBI screening and treatment

Eligible participants underwent LTBI screening using an interferon-gamma release assay (IGRA) with the QuantiFERON-Gold or QuantiFERON-Gold-Plus tests (QFT/QFT-Plus, Cellestis/Qiagen, Carnegie, Australia). For IGRA-positive patients, their primary care physicians, who had managed their COPD evaluated and discussed the benefits and risks of LTBI treatment with them. The physicians then introduced the WHO-recommended LTBI treatment regimens [11] for consideration. The regimens included 3HP, once-weekly isoniazid (INH, 15 mg/kg, maximum 900 mg) and rifapentine (RPT, 900 mg for body weight >50.0 kg; 750 mg for 32.1–50.0 kg; 600 mg for 25.1–32.0 kg; and 450 mg for 14.1–25.0 kg) for 12 weeks; 1HP, with daily INH (300 mg) and RPT (600 mg for body weight ≥45.0 kg; 450 mg for <45.0 kg) for 28 days; 3HR, with daily rifampin (10 mg/kg, maximum 600 mg) and isoniazid (5 mg/kg, maximum 300 mg) for 3 months; 4R, with daily rifampin (10 mg/kg, maximum 600 mg) for 4 months; or 9H, with daily INH (5 mg/kg, maximum 300 mg) for 9 months.

Following a comprehensive discussion on each regimen's efficacy and potential adverse drug reactions (ADRs), the final regimen was selected through shared decision-making between the patients and their COPD physicians. All LTBI treatment regimens were administered under directly observed preventive therapy (DOPT), either in-person or electronically (eDOPT), according to Taiwan's National TB Program. Observation frequency varied: ≥5 doses/week for 1HP, 3HR, 4R, and 9H, while every dose was observed for 3HP.

ADR monitoring

Before treatment, participants underwent baseline tests, including hepatitis B and C, HIV, complete blood count, renal and liver function. During treatment, adherence and ADRs were programmatically monitored by government-paid DOPT supporters and research nurses through phone interviews or messaging apps [12,13]. Specifically, ADRs were assessed daily for participants on 1HP, 3HR, 4R and 9H, and within two days after each dose for those on 3HP, continuing until seven days post-treatment. In addition, hemogram and biochemical tests, including renal and liver function assessments, were conducted monthly during the first two months of treatment for 3HR, 4R and 9H, biweekly throughout the treatment period for 1HP, and whenever deemed necessary by the primary care physician. The causal relationships of ADRs with the study medications were determined using the Naranjo score [14], and the severity of ADR, hepatotoxicity [15], and systemic drug reactions (SDRs) [16] were defined as previous reports. Phenotypes of SDRs were categorized into flu-like syndrome, hypotension, urticaria, conjunctivitis, general edema, and bronchospasm. ADR management was based on severity and patient preference: grade 3 ADRs led to treatment discontinuation, grade 2 were treated symptomatically, and grade 1 were observed. Participants could discontinue treatment

after a thorough discussion of consequences with their primary physician.

The completion of 3HP, 1HP, 3HR, 4R, and 9H regimen was defined by the completion of 12 doses within 16 weeks, 28 doses within 60 days, 90 doses within 4 months, 120 doses within 20 weeks, and 270 doses within 12 months, respectively.

Outcome assessment

This study is aimed to investigate the prevalence and predictors of LTBI, defined as IGRA-positivity, among older patients with COPD. Additionally, the study unraveled the completion rate and safety profiles of each LTBI treatment regimen in the study population.

Data collection

We recorded data on the eligible patients' baseline demographic characteristics, comorbidities, baseline laboratory data (hemogram, renal/liver function, hepatitis B/C profile, and HIV), COPD severity (assessed according to the GOLD stage [1]), COPD medication (inhaled bronchodilators, inhaled corticosteroids [ICS], and oral corticosteroids [OCS]), frequency of acute exacerbations of COPD (AECOPD) in the preceding 2 years of enrollment, and the completion rate and safety profiles of the LTBI treatment.

The variable for ICS use was as a binary variable (use or nonuse), with defined as cumulative ICS use exceeding 6 months in the 2 years prior to enrollment. The cumulative OCS dose over the 2-year period before enrollment was calculated and converted into the cumulative equivalent dose of prednisolone (in grams).

Statistical analysis

Individuals who did not receive any TPT doses were excluded from the treatment outcome analysis. Categorical variables are presented in terms of frequency (percentage), and continuous variables are presented in terms of mean ± standard deviation or median (interquartile range). Intergroup differences between continuous variables were assessed using either Student's *t*-test or the Mann–Whitney U test, depending on normality. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Multivariate logistic regression was used to calculate adjusted odds ratios (aORs), 95% confidence intervals (CIs), and *p* values to identify potential risk factors for IGRA positivity. Statistical significance was set at a two-sided *p*-value of <.05. All statistical analyses were conducted using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Results

Enrolled population

As illustrated in Figure 1, a total of 920 patients aged over 60 years with COPD were eligible for recruitment during the study period. Of these, 819 (89.0%) agreed to receive LTBI screening, with 193 (23.6%) testing IGRA-positive and 9 (1.1%) testing IGRA-indeterminate. Among those with IGRA positivity, 26 (13.5%) refused to receive TPT, 3 (1.6%) were diagnosed with culture-confirmed pulmonary TB, and 14 (7.3%) had abnormal imaging findings requiring follow-up evaluation. The remaining 150 (77.7%) IGRA-positive cases received TPT, with 12 (8.0%), 91 (60.7%), 24 (16.0%), 11 (7.3%), and 2 (1.3%) receiving the 1HP, 3HP, 3HR, 4R, and 9H regimens, respectively.

Characteristics of COPD patients receiving LTBI screening

Among the IGRA-positive and IGRA-negative individuals (Table 1), the mean age was 72.7±7.5 years, and most (84.9%) were men. A total of 197 participants (24.3%) were current smokers. Hypertension (53.8%) was the most common comorbidity, followed by hyperlipidemia (33.7%) and asthma (33.1%). The mean duration of COPD diagnosis was 4.4 ± 3.6 years, and 55 participants (6.8%) experienced more than one episode of AECOPD within 2 years prior to enrolment. Nearly half (47.7%) of participants had GOLD 2 severity (50% ≤ FEV1 < 80%), and 30.2% had GOLD 1 severity (FEV1 ≥ 80%). A total of 386 participants (47.7%) had a COPD assessment test (CAT) score ≥10, 430 (53.1%) used dual bronchodilators, and 300 (37.0%) concomitantly used long-acting bronchodilators with ICS. The cumulative prednisolone dose was ≥210 mg in 112 participants (13.8%).

Compared with the IGRA-negative COPD patients, the IGRA-positive patients had a higher BMI (24.5 ± 4.4 vs. 23.7 ± 3.7 kg/m², $p = 0.032$), greater cumulative exposure to cigarette smoke in pack-years (46.0 ± 30.2 vs. 28.9 ± 28.1, $p<0.001$), longer COPD duration (5.4 ± 3.4 vs. 4.1 ± 3.6 years, $p < 0.001$), and higher CAT scores (11.9 ± 7.5 vs. 10.6 ± 7.7, $p = 0.041$). The IGRA-positive patients had a higher cumulative equivalent prednisolone dose within 2 years (349.5 ± 725.5 vs. 94.1 ± 359.3 mg, $p<0.001$). They were also more likely to be current smokers (36.3% vs. 20.6%, $p< 0.001$), more likely to have hypertension (62.7% vs. 51.1%, $p = 0.005$), have coronary artery disease (23.3% vs. 16.4%, $p = 0.028$), have more than one AECOPD episode within 2 years before enrollment (13.0% vs. 4.9%, $p<0.001$), and have concomitant ICS use (60.6% vs. 29.7%, $p<0.001$). The IGRA-positivity rate is similar between COPD patients with

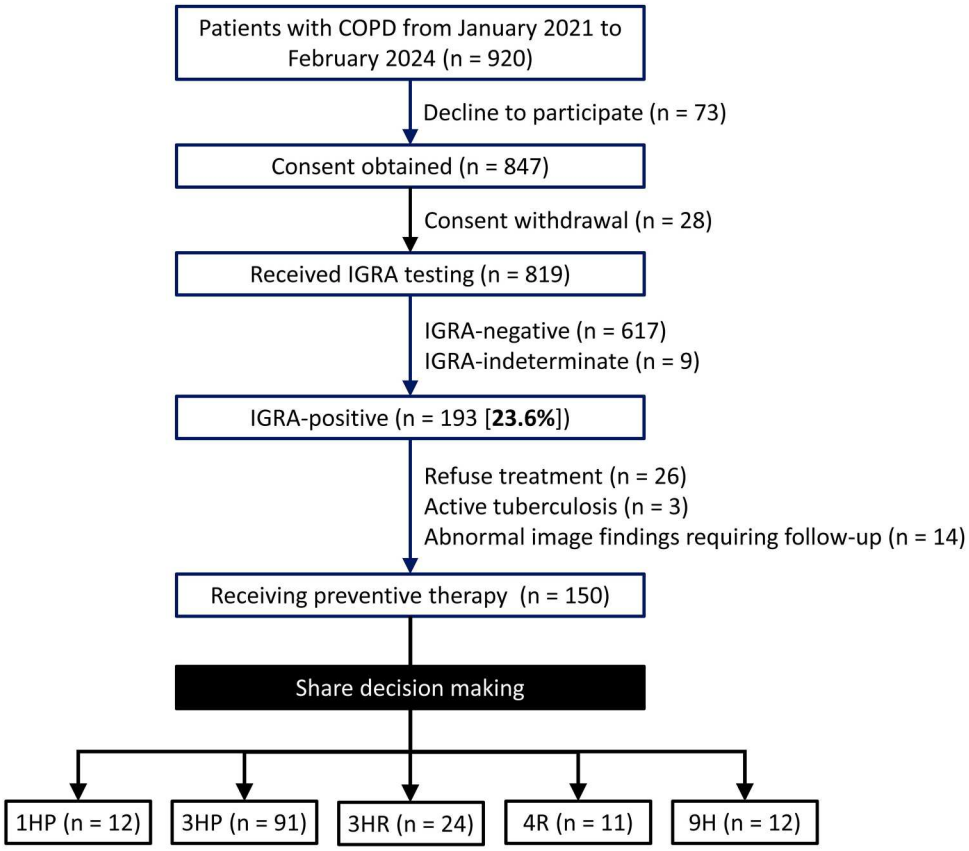

Figure 1. Patient Enrollment. COPD, chronic obstructive pulmonary disease. IGRA, interferon-gamma releasing assay. TB, tuberculosis. 1HP, daily isoniazid and rifapentine for 28 days. 3HP, weekly isoniazid and rifapentine for 12 weeks. 3HR, daily isoniazid and rifampin for 3 months. 4R daily rifampin for 4 months. 9H, daily INH for 9 months.

and without asthma-features (23.5% vs. 24.0%, $p = 0.950$). Additionally, 51 (45.5%) of the 112 participants with a cumulative equivalent dose of prednisolone over 210 mg were IGRA -positive, and 117 (39.0%) of the 300 participants using long-acting bronchodilators with ICS were IGRA-positive.

Predictors of IGRA positivity in patients with COPD

The multivariate logistic regression results (Table 2) revealed that IGRA positivity was associated with cumulative exposure to cigarette smoke in pack-years (aOR [95% CI] per pack-year increment: 1.02 [1.01–1.02], $p<0.001$), COPD duration (per year increment: 1.10 [1.05–1.16], $p<0.001$), current smoking status (1.40 [1.03–1.90], $p = 0.030$), history of cerebrovascular accident (2.11 [1.05–4.24], $p = 0.036$), ICS use (3.06 [1.05–4.24], $p = 0.036$), and a cumulative equivalent dose of prednisolone over 210 mg within 2 years (3.13 [1.68–5.86], $p<0.001$).

Characteristics and outcomes of patients with COPD receiving TPT

The baseline characteristics of 150 COPD patients receiving TPT are presented in Table 3. The mean age of these patients was 72.1 years, with 82.0% being men. In total, 50% had GOLD 2 severity, 52.0% had a CAT score ≥10, and 14.7% had experienced more than one episode of AECOPD within the previous 2 years. Patients receiving 9H treatment tended to be older, with a mean age of 76.8 years, and a higher proportion had a CAT score ≥10 (75%) than those in other groups.

A summary of the treatment outcomes is presented in Table 4. The overall completion rate of TPT among COPD patients was 82.0%, with the highest rate observed in the 3HP group (91.2%) and the lowest in the 9H group (50.0%). ADRs were the primary reason for TPT discontinuation. In the 3HP group, 9 patients (9.8%) developed SDRs, manifesting as flu-like syndrome in six cases (66.7%) and urticaria in three cases (33.3%); three patients with flu-like syndrome discontinued treatment. One case in the 1HP group developed SDR with urticaria but completed TPT. Under the 3HR regimen, two cases developed flu-like syndrome and one developed urticaria; all three discontinued TPT. Three patients discontinued TPT due to hepatitis, one in the 3HR group and two in the 9H group. During TPT, 10 patients (6.7%) experienced AECOPD, three of whom died from pneumonia or respiratory failure. Another patient died of a cardiac event that was deemed unrelated to LTBI treatment.

Table 1. Characteristics of patients with chronic obstructive pulmonary disease (COPD) receiving LTBI screening, stratified by the results of interferon-gamma release assay (IGRA) test.

	Total ($n = 810$)	IGRA-negative ($n = 617$)	IGRA-positive ($n = 193$)	p-value
Male sex	688 (84.9%)	526 (85.3%)	162 (83.9%)	0.656
Age (year-old)	72.7 ± 7.5	72.9 ± 7.6	72.5 ± 7.0	0.496
60–65	107 (13.2%)	82 (13.3%)	25 (13.0%)	>0.999
65–75	394 (48.7%)	295 (47.8%)	99 (51.3%)	0.446
75–85	248 (30.6%)	189 (30.6%)	59 (30.6%)	>0.999
≥ 85	61 (7.5%)	51 (8.3%)	10 (5.2%)	0.207
Body-mass index (kg/m^2)	23.9 ± 4.0	23.7 ± 3.7	24.5 ± 4.4	0.032
Smoking status				<0.001
Never smoker	171 (21.1%)	140 (22.7%)	31 (16.1%)	
Ex-smoker	442 (54.6%)	350 (56.7%)	92 (47.7%)	
Current smoker	197 (24.3%)	127 (20.6%)	70 (36.3%)	
Cumulative cigarettes (pack-year)	33.0 ± 29.5	28.9 ± 28.1	46.0 ± 30.2	<0.001
Comorbidities				
Hypertension	436 (53.8%)	315 (51.1%)	121 (62.7%)	0.005
Hyperlipidemia	273 (33.7%)	198 (32.1%)	75 (38.9%)	0.082
Pure COPD	542 (66.9%)	412 (66.7%)	130 (67.4%)	
COPD with asthma-features[a]	268 (33.1%)	205 (33.3%)	63 (32.6%)	0.859
Diabetic mellitus	210 (25.9%)	154 (25.0%)	56 (29.0%)	0.262
Coronary artery disease	146 (18.0%)	101 (16.4%)	45 (23.3%)	0.028
Congestive heart failure	98 (12.1%)	72 (11.7%)	26 (13.5%)	0.578
Old cerebral vascular disease	73 (9.0%)	59 (9.6%)	14 (7.3%)	0.328
Chronic kidney disease stage >3	39 (4.8%)	32 (5.2%)	7 (3.6%)	0.377
COPD severity				
COPD diagnosis duration (years)	4.4 ± 3.6	4.1 ± 3.6	5.4 ± 3.4	<0.001
Number of AE within 2 years	0.3 ± 0.8	0.2 ± 0.7	0.5 ± 1.3	<0.001
Acute exacerbation > 1 time	55 (6.8%)	30 (4.9%)	25 (13.0%)	<0.001
Severity of airflow limitation				
FEV1 ≥ 80%	245 (30.2%)	196 (31.8%)	49 (25.4%)	0.092
50% ≤ FEV1 < 80%	386 (47.7%)	282 (45.7%)	104 (53.9%)	0.047
% ≤ FEV1 < 50%	143 (17.7%)	108 (17.5%)	35 (18.1%)	0.841
< 30%	36 (4.4%)	31 (5.0%)	5 (2.6%)	0.152
CAT score	10.9 ± 7.7	10.6 ± 7.7	11.9 ± 7.5	0.041
CAT ≥ 10	386 (47.7%)	286 (46.4%)	100 (51.8%)	0.185
COPD Control medication in 2 years				
LAMA or LABA	81 (10.0%)	72 (11.7%)	9 (4.7%)	0.005
LABA + LAMA	429 (53.0%)	362 (58.7%)	67 (34.7%)	<0.001
Combination with ICS use	300 (37.0%)	183 (29.7%)	117 (60.6%)	<0.001
Cumulative prednisolone doses (mg)	154.2 ± 483.8	94.1 ± 359.3	349.5 ± 725.5	<0.001
Cumulative dose ≥ 210 mg	112 (13.8%)	61 (9.9%)	51 (26.4%)	<0.001

Data are presented as mean ± standard deviation or number (%, the denominator is the correspondence column of title).
p value was calculated using Student's t test, chi-square test, or Fisher's exact test.
FEV1, first second of forced expiration; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist
[a]Asthma features includes eosinophilic inflammation and reversible airflow obstruction with positive response to bronchodilator.

Discussion

Despite the well-documented increased risk of active TB in COPD patients, studies evaluating the implementation of LTBI intervention in this population remain scarce. This further underscores the unique value of our real-world data on the feasibility in this special population and the urgent need for research in this area. A cross-sectional study of Singapore residents aged 18–79 years found a positive association between increasing age and IGRA positivity [17]. Another study on patients with poorly controlled diabetes in Taiwan also reported a similar finding [13]. Unpublished data from the Taiwan Centers for Disease Control on household contacts – a recognized high-risk group – show IGRA-positive rates of 22.2% in those aged 50–64 years, 26.2% in 65–74 years, 25.7% in 75–84 years, and 23.0% in those ≥85 years, which are comparable to those observed in our COPD cohort (25.3%, 25.1%, 23.6%, and 16.4%, respectively). Given these findings, we speculate the prevalence of LTBI in the elderly general population is likely lower than that observed in COPD patients aged ≥60 years.

Post-TB sequelae impose a significant global burden, with nearly half of TB survivors experiencing pulmonary dysfunction [18]. Notably, COPD is a

Table 2. Predictors for interferon-gamma release assay (IGRA) positivity in patients with chronic obstructive pulmonary disease (COPD).

Variables	Adjusted Odds Ratio	95% Confidence Interval	P value
Smoking pack-years (per unit increment)	1.02	1.01–1.02	<0.001
Duration of COPD (per year increment)	1.10	1.05–1.16	<0.001
Current smoker	1.40	1.03–1.90	0.030
Old cerebral vascular accident	2.11	1.05 –4.24	0.036
Inhaled corticosteroid use (yes vs. no)	3.06	2.11–4.43	<0.001
Cumulative equivalent dose of prednisolone > 210mg	3.13	1.68–5.86	<0.001

Variables with significance in Table 1 except for laboratory data were entered into the multivariate regression model.

Table 3. Characteristics of patients with chronic obstructive pulmonary disease (COPD) receiving LTBI treatment, stratified by regimens.

	All ($n = 150$)	1HP ($n = 12$)	3HP ($n = 91$)	3HR ($n = 24$)	4R ($n = 11$)	9H ($n = 12$)
Male sex	123 (82.0%)	10 (83.3%)	73 (80.2%)	19 (79.2%)	10 (90.9%)	11 (91.7%)
Age (year)	72.1 ± 7.1	72.5 ± 6.4	70.3 ± 6.8	75.1 ± 6.7	74.6 ± 4.6	76.8 ± 8.3
Age ≥65 years	86 (57.3%)	10 (83.3%)	63 (69.2%)	4 (16.7%)	7 (63.6%)	2 (16.7%)
Body-mass index (kg/m^2)	24.8 ± 4.5	23.7 ± 3.6	24.8 ± 4.5	26.4 ± 5.5	23.6 ± 3.3	23.6 ± 4.3
Smoking status						
Never smoker	24 (16.0%)	0	15 (16.5%)	6 (25.0%)	2 (18.2%)	1 (8.3%)
Ex-smoker	70 (46.7%)	0	44 (48.2%)	12 (50.0%)	4 (36.4%)	9 (75.0%)
Current smoker	56 (37.3%)	12 (100%)	32 (35.2%)	6 (25.0%)	5 (45.5%)	2 (16.7%)
Cumulative cigarettes (pack-year)	45.8 ± 30.5	65.5 ± 33.5	41.2 ± 28.8	44.0 ± 36.2	55.4 ± 22.8	56.4 ± 26.2
COPD severity						
COPD diagnosis duration (years)	5.5 ± 3.3	5.5 ± 4.1	5.5 ± 3.0	5.0 ± 3.2	4.7 ± 3.5	6.8 ± 5.1
Number of AE within 2 years	0.5 ± 1.0	1.2 ± 1.3	0.6 ± 1.0	0.1 ± 0.4	0.4 ± 0.7	0.5 ± 0.9
AE > 1 time	22 (14.7%)	4 (33.3%)	15 (16.5%)	1 (4.2%)	1 (9.1%)	1 (8.3%)
Severity of airflow limitation						
FEV1 ≥ 80%	39 (26.0%)	3 (25.0%)	25 (27.5%)	5 (20.8%)	3 (27.3%)	3 (25.0%)
50% ≤ FEV1 < 80%	77 (51.3%)	6 (50.0%)	43 (47.3%)	16 (66.7%)	6 (54.5%)	6 (50.0%)
30% ≤ FEV1 < 50%	30 (20.0%)	3 (25.0%)	20 (22.2%)	3 (12.5%)	1 (9.1%)	3 (25.0%)
FEV1 < 30%	4 (2.7%)	0	3 (3.3%)	0	1 (9.1%)	0
CAT score	12.1 ± 7.8	13.2 ± 6.8	12.2 ± 7.7	9.5 ± 7.1	11.8 ± 7.7	16.1 ± 9.4
CAT ≥ 10	78 (52.0%)	7 (58.3%)	48 (52.7%)	8 (33.3%)	6 (54.5%)	9 (75.0%)
COPD Control medication in 2 years						
LABA or LAMA	7 (4.7%)	0	6 (6.6%)	1 (4.2%)	0	0
LABA + LAMA	50 (33.3%)	1 (8.3%)	35 (38.5%)	12 (50.0%)	1 (9.1%)	1 (8.3%)
Combination with ICS use	93 (62.0%)	11 (91.7%)	50 (54.9%)	11 (45.8%)	10 (90.9%)	11 (91.7%)
Cumulative prednisolone doses (mg)	372.8 ± 727.5	865.8 ± 855.6	398.1 ± 786.6	104.6 ± 402.8	263.2 ± 567.3	324.6 ± 548.7
Cumulative dose ≥ 210 mg	44 (29.3%)	7 (58.3%)	28 (30.8%)	2 (8.3%)	3 (27.3%)	4 (33.3%)
Acute exacerbation during TPT	10 (6.7%)	1 (8.3%)	5 (5.5%)	1 (4.2%)	1 (9.1%)	2 (16.7%)

Data are presented as mean ± standard deviation or number (%).
AE, acute exacerbation; FEV1, first second of forced expiration; CAT, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting β2 agonist; LAMA, long-acting muscarinic antagonist; TPT, TB preventive therapy.

major long-term complication of TB infection, with a 21% prevalence among TB survivors [19]. Furthermore, TB-related deaths from 2020 to 2050 are projected to cost $17.5 trillion [20]. A previous study in Taiwan illustrated a TB incidence of 895 per 100,000 person-years in COPD patients aged >60 years [21]. Since LTBI treatment reduces TB reactivation by up to 90% [22], its implementation could lower TB incidence to one-tenth of the original rate, significantly reducing the subsequent economic burden of post-TB sequelae. Additionally, integrating LTBI screening into routine COPD care is feasible, taking advantage

Table 4. Treatment outcome of patients with chronic obstructive pulmonary disease (COPD) receiving LTBI treatment, stratified by regimens.

	All ($n = 150$)	1HP ($n = 12$)	3HP ($n = 91$)	3HR ($n = 24$)	4R ($n = 11$)	9H ($n = 12$)
Completion[a]	123 (82.0%)	10 (83.3%)	83 (91.2%)	15 (62.5%)	9 (81.8%)	6 (50.0%)
Completion after regimen change[b]	2 (1.6%)	0	1 (1.2%)	0	1 (11.1%)	0
Systemic drug reactions[b]	7 (5.7%)	1 (10.0%)	6 (7.2%)	0	0	0
Flu-like syndrome[b]	3 (2.4%)	0	3 (3.6%)	0	0	0
Urticaria[b]	4 (3.3%)	1 (10.0%)	3 (3.6%)	0	0	0
Hepatitis[b]	3 (2.4%)	0	0	1 (6.7%)	0	2 (33.3%)
Hypertensive events[b]	4 (3.3%)	1 (10.0%)	2 (2.4%)	1 (6.7%)	0	0
Acute exacerbation during TPT	7 (5.7%)	1 (10.0%)	5 (5.5%)	0	0	1 (8.3%)
Permanent discontinuation[a]	25 (16.7%)	2 (16.7%)	7 (7.7%)	9 (37.5%)	1 (9.1%)	6 (50.0%)
Adverse drug reactions[c]	18 (72.0%)	2 (100.0%)	5 (71.4%)	7 (77.8%)	0	4 (66.7%)
Hepatitis[c]	3 (12.0%)	0	0	1 (11.1%)	0	2 (33.3%)
Systemic drug reactions[c]	6 (24.0%)	0	3 (42.9%)	3 (33.3%)	0	0
Doses received			3 [3, 4]	12 [11.5, 14]		
Flu-like syndrome[c]	5 (20.0%)	0	3 (42.9%)	2 (22.2%)	0	0
Urticaria[c]	1 (4.0%)	0	0	1 (11.1%)	0	0
Mortality[c]	4 (16.0%)	0	0	1 (11.1%)	1 (100.0%)	2 (33.3%)
AE of COPD with pneumonia[c]	3 (12.0%)	0	0	1 (11.1%)	1 (100.0%)	1 (16.7%)
Cardiac event[c]	1 (4.0%)	0	0	0	0	1 (16.7%)
Personal refused[c]	3 (12.0%)	0	2 (28.6%)[d]	1 (11.1%)[e]	0	0

Data are presented as number (%).
AE, acute exacerbation; TPT, tuberculosis preventive therapy.
[a]The denominator of each calculation of percentage in this row was the number of overall cases in each corresponding group.
[b]The denominator of each calculation of percentage in this row was the number of cases with treatment completion in each corresponding group.
[c]The denominator of each calculation of percentage in this row was the number of cases with permanent discontinuation of treatment in each corresponding group.
[d]One refused TPT due to night shifts at work and one refused to receive directly observed preventive therapy due to personal reasons.
[e]This patient refused TPT after contracting COVID-19.

of regular pulmonary visits and strong patient-physician rapport to enhance adherence, ensuring a cost-effective strategy for LTBI treatment. Overall, given the substantial financial burden of post-TB lung disease, targeted LTBI treatment in COPD patients could be a cost-saving intervention by preventing TB reactivation and subsequent respiratory complications.

The study demonstrated that the overall completion rate of LTBI treatment in older COPD patients reached 82% regardless of the treatment regimen, indicating that the WHO-recommended regimens for TPT, when guided by trusted COPD physicians, are safe and feasible.

Tobacco smoking, the predominant risk factor for COPD, is strongly linked to an increased risk of pulmonary TB development, recurrence, and mortality [23,24]. A retrospective study demonstrated that smoking in COPD patients was associated with a higher risk of LTBI (OR: 22, 95% CI: 2.7–179.2), although its small sample size limits generalizability [25]. Smoking impairs mucociliary clearance, facilitating *M. tuberculosis* persistence[26]. Nicotine weakens immunity, reducing key macrophages and T-cells, promoting intracellular *M. tuberculosis* survival and proliferation [26,27]. While smoking remains a major risk factor for COPD, the finding that 21.1% of COPD patients in this study were never-smokers aligns with a 2022 epidemiological study, which revealed that up to 30% of cases worldwide occur in never-smokers [28].

This study highlights the heterogeneity of COPD phenotypes, with 33% of patients exhibiting asthma-COPD overlap (ACO), characterized by eosinophilic inflammation, ICS responsiveness, and reversible airflow obstruction [1]. This prevalence aligns with previous reports [29,30], and we unravel that the IGRA-positivity rate was comparable between patients with and without ACO.

ICS is essential for managing frequent COPD exacerbators [31] and ACO [1]. However, long-term ICS use (≥1 year) increases the risk of respiratory infections by 41% compared with long-acting bronchodilator therapy alone [32]. A meta-analysis reported that ICS use raises the risk of TB infection by 46%, with an even higher risk (63%) in those concomitantly using OCS [33], suggesting ICS may contribute to TB reactivation. In this study, all COPD patients received bronchodilators. Among those using ICS, the IGRA-positive rate approached 40%, with ICS use identified as a predictor for LTBI. These findings suggest that long-term ICS therapy may not be advisable for patients with stable COPD, particularly those at risk for TB reactivation.

Although systemic corticosteroids can improve clinical outcomes in treating patients with AECOPD [34], caution is warranted due to the dose-dependent increase in TB risk, with a 2.8-fold increase at doses <15 mg/day and a 7.7-fold increase at doses ≥15 mg/day [35,36]. Therefore, prescreening for LTBI may be warranted, particularly in older patients with COPD using high-dose corticosteroids.

The optimal TPT regimen for patients with COPD remains unclear. In this study, most patients preferred the short-course regimens, especially 3HP. The WHO guidelines endorse the use of this regimen [11], which offers comparable protective efficacy, fewer prescription doses, higher completion rate, and greater feasibility than 4R [37] and 9H [38]. Additionally, the reduced frequency of DOPT minimizes disruption for patients, making 3HP became the preferred regimen for COPD patients. Although the incidence of adverse effects, particularly SDRs, is higher with 3HP than with other regimens, its safety has been demonstrated in older populations [12], those with poorly controlled diabetes [13], end-stage renal disease undergoing hemodialysis [39], rheumatoid arthritis [40], and individuals living with HIV [41].

This study has some limitations. First, the nonrandom assignment of treatment groups resulted in substantial variation in group sizes, hindering a comprehensive exploration of the effects of various regimens on treatment outcomes. Second, As WHO recommends case-by-case LTBI interventions, our findings from an intermediate TB incidence region may not be generalizable elsewhere.

Timely LTBI intervention in COPD patients is essential, given its prevalence exceeds 23%. High-risk subgroups – including current smokers, heavy smokers, those with longer COPD duration, cerebrovascular history, ICS users, and individuals receiving ≥210 mg prednisone-equivalent over two years – should be prioritized. Current LTBI regimens are both safe and feasible for COPD patients, with completion rates reaching 82%. These findings highlight the importance of targeted LTBI interventions to reduce TB risk in this vulnerable population.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability and sharing statement

Deidentified individual participant data that underlie the results reported in this article will be available immediately following publication upon request to the corresponding author.

Author contributions

Manuscript writing and figure preparation: HLH, JYW, WCH. Study design: HLH, JYW, WCH. Data collection: HLH, MHC, MRL, PLL, CCS, JYW, IWC, WCH. Data analysis and interpretation: HLH, MHC, JYW, JMY, IWC, WCH. Manuscript revision: JYW, IWC, WCH.

Key points

LTBI prevalence in older COPD patients exceeds 23% in an area with intermediate TB burden. Key risk factors include smoking, long COPD duration, and corticosteroid use. An 82% therapy completion rate shows LTBI intervention is both feasible and safe.

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