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Piperacillin/tazobactam plus erythromycin improves clinical outcomes in AECOPD with bacterial lower respiratory tract infections: a retrospective cohort study

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Abstract

It remains uncertain whether patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and bacterial lower respiratory tract infections (LRTIs) could similarly benefit from β-lactam and macrolide antibiotics therapy as community-acquired pneumonia (CAP) does. In this study, we compared the clinical success rates of piperacillin/tazobactam (TZP) monotherapy versus its combination with erythromycin lactobionate injection (Ery) in patients with AECOPD and bacterial LRTIs and developed a machine learning (ML) model to predict treatment outcomes. The patients with AECOPD and bacterial LRTIs received antimicrobial therapy with either piperacillin-tazobactam (TZP) alone or TZP in combination with Ery. Inverse probability of treatment weighting (IPTW) was performed between the two groups. Subsequently, a stacking ensemble learning (SEL) model was developed and deployed as a web application to simultaneously predict clinical outcomes for both treatment options. The result demonstrated that TZP combined with Ery significantly reduced the incidence of clinical treatment failure compared to TZP monotherapy (14.00% vs. 19.75%; OR, 0.66; 95% CI, 0.49–0.89; *P*=0.006). In an independent test set, the SEL model demonstrated strong performance across multiple metrics, including ROC-AUC (0.71), recall (sensitivity) (0.72), and accuracy (0.69). Finally, a web application based on the SEL was developed (http://106.12.146.54/). This study demonstrated that the addition of Ery to TZP significantly reduced clinical treatment failure

in patients with AECOPD and bacterial LRTIs. This finding suggests that combination therapy may offer a clinical benefit in this patient population. Furthermore, an SEL model was developed to predict treatment outcomes for both regimens, providing a potential tool for future clinical decision-making and personalized treatment.

Keywords AECOPD, Lower respiratory tract infections (LRTIs), Piperacillin-tazobactam, Erythromycin, Machine learning, Web application

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of global morbidity and mortality, imposing a substantial and growing economic and social burden on individuals and healthcare systems[1]. With continued exposure to risk factors and an aging population, the disease burden of COPD is projected to increase further[2,3]. Acute exacerbations of COPD (AECOPD) are associated with significant mortality[4]. A 2020 systemic review showed that bacterial infections are responsible for approximately 50% of AECOPD cases, particularly in patients with moderate to severe AECOPD[5]. The most frequently identified bacterial pathogens include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, as well as atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*[6]. Consequently, the timely implementation of effective and appropriate antimicrobial therapy is critical in the

clinical management strategy for AECOPD with bacterial lower respiratory tract infections (LRTIs)[7].

So far, major clinical practice guidelines recommend antibiotics such as amoxicillin-clavulanate, cephalosporins, and respiratory fluoroquinolones for most patients with AECOPD with LRTIs. For patients with severe exacerbations and risk factors for *Pseudomonas aeruginosa* infection, broader-spectrum agents like piperacillin/tazobactam (TZP) are indicated[6,8]. Despite being informed by various factors, such as microbiological data, epidemiological surveillance, patient-specific factors, and disease severity assessments, antibiotic selection for LRTIs remains largely empirical due to the lack of robust clinical trial data and limitations in traditional pathogen detection methods[9,10].

For hospitalized patients with community-acquired pneumonia (CAP), a condition sharing similarities with AECOPD, guidelines consistently recommend a combination of a β-lactam and a macrolide antibiotic [11, 12]. The rationale for this is two-fold: ensuring empirical coverage against atypical pathogens, and leveraging the potent anti-inflammatory and immunomodulatory properties of macrolides. This latter mechanism has been strongly supported by recent evidence. For instance, a prospective randomised controlled trial demonstrated that adding oral clarithromycin to β-lactam antibiotics provided substantial and wide-ranging clinical benefits for the management of CAP, largely attributed to its effects on the host immune response[13]. However, this combination therapy has not

received clear recommendations for treating AECOPD with bacterial LRTIs, and it remains unclear whether patients with AECOPD could benefit from similar combination therapy as CAP patients do.

Given that CAP and AECOPD with bacterial LRTIs share some similarities in infection sites and common pathogens, we hypothesize that patients with AECOPD with bacterial LRTIs could also benefit from the combination therapy of β-lactam antibiotics and macrolides.

At our institution, TZP is a frequently used β-lactam antibiotic for the treatment of moderate to severe acute exacerbations of COPD, sometimes irrespective of specific risk factors for *Pseudomonas aeruginosa*. This observed local prescribing pattern provided the rationale to retrospectively evaluate the efficacy of this practice and the potential benefit of adding erythromycin lactobionate injection (Ery). This study used inverse probability of treatment weighting (IPTW) to compare the clinical efficacy of TZP alone and in combination with Ery in patients with AECOPD and bacterial LRTIs, leveraging historical data from varying physician prescribing practices[14]. Furthermore, to avoid unnecessary combination therapy and improve clinical outcomes, we developed a machine learning (ML) model for personalized treatment. This model could simultaneously predict treatment outcomes for both regimens. Finally, based on the flask web framework, we developed a web-based prediction system to assist physicians in clinical decision-making and provide support for future clinical research.

Methods

Study design

Our retrospective study aimed to determine if patients with moderate to severe AECOPD and bacterial LRTIs benefited from a combined regimen of TZP and Ery. We subsequently developed and deployed an online ML model to predict the outcome of either regimen, aiding physicians in informed decision-making. The entire study procedure is shown in **Fig. 1**.

Study objects

The inclusion criteria for the study were as follows: patients were admitted to the department of pulmonary and critical care medicine (PCCM) at Shanghai Pudong Hospital between January 1, 2021, and July 31, 2023. Patients were eligible for inclusion if they had a confirmed diagnosis of moderate to severe AECOPD with clinical evidence of bacterial LRTIs. All participants had to be 45 or older, regardless of gender. Their initial treatment regimen needed to consist of either TZP alone (4:1 formulation, administered as 3.125 g or 2.5 g every 8 hours) or combined with Ery (0.5 g every 12 hours). These dosing regimens reflect the standard protocol at our institution based on available drug formulations and local prescribing guidelines, which include dose adjustments for renal function.

Patients were excluded if they had incomplete clinical data or if treatment efficacy could not be determined. Patients with severe complications or other serious uncontrolled underlying conditions were also excluded. These included, but were not limited to, acutely

decompensated or NYHA Class IV heart failure, uncontrolled diabetes (e.g., ketoacidosis), severe hepatic dysfunction (Child-Pugh class B or higher), and severe renal dysfunction (estimated glomerular filtration rate (EGFR) below 20 ml/min). In contrast, a history of stable, chronic comorbidities (such as chronic heart failure or controlled diabetes) was recorded as a covariate for the analysis. Additionally, patients who died within 72 hours of treatment initiation were excluded, as treatment efficacy at the 72-hour endpoint could not be assessed. Pregnant women were also not included.

The diagnosis of COPD was made in accordance with the Chinese COPD guidelines. A diagnosis requires pulmonary function testing, with a post-bronchodilator FEV_1/FVC ratio of <70% confirming persistent airflow limitation. After excluding other diseases, COPD can be definitively diagnosed[15]. The severity of AECOPD was assessed based on the criteria outlined in the GOLD guidelines[16].

A diagnosis of bacterial infection was made based on the following criteria: presence of all three symptoms (worsening dyspnea, increased sputum volume, purulent sputum) or two symptoms (one being purulent sputum), elevated levels of at least one bacterial pneumonia-associated laboratory marker (white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), neutrophil-to-lymphocyte ratio (NLR), or heparin-binding protein (HBP)), and negative results for common viral pathogens (coronavirus disease 2019 (COVID-19), influenza), atypical bacteria

such as *Mycoplasma pneumoniae*, and pulmonary fungal infections[8,17,18]. These specific pathogens were excluded because the baseline therapy for both groups, TZP, is an inappropriate treatment for them (e.g., atypical bacteria like *Mycoplasma pneumoniae* lack a conventional cell wall). Their inclusion would have introduced significant confounding, making a fair comparison of the additive effect of Ery impossible.

Definition of covariates or features

This study initially considered 23 factors as covariates for IPTW. These features encompassed patient demographics (e.g., sex, age, and weight), infection-related factors (e.g., temperature, WBC, and NLR), comorbidities (e.g., diabetes mellitus (DM), active malignancy, and bronchiectasis), and antimicrobial therapy details (e.g., TZP dosage). All aforementioned laboratory measurements were obtained within 24 hours prior to or on the day of hospital admission. Subsequently, a 24th feature, concomitant Ery administration, was added to the initial 23 factors for the development of ML models. Detailed descriptions of all variables are presented in **Table 1**.

Endpoint assessment and data collecting

To objectively assess treatment efficacy, evaluations will occur 72 hours post-treatment initiation, focusing on the following: 1) temperature consistently below 37.3°C (tympanic temperature) for 24 hours without antipyretics; 2) respiratory improvements including a ≥20% decrease in respiratory rate from baseline or return to normal, no need for supplemental oxygen or a ≥20%

decrease in FiO2, and significant reduction or absence of abnormal lung sounds; 3) laboratory improvements including normalized WBC count or a ≥20% decrease from baseline, a ≥50% decrease in CRP, and (optionally) a ≥80% decrease in PCT or return to normal; and 4) imaging improvements via chest X-ray or CT scan assessed by semi-quantitative scoring or radiologist description. Clinical cure is defined by meeting all criteria; clinical improvement by meeting at least two but not all. Treatment failure was defined as any worsening of clinical criteria after 72 hours, the occurrence of new infectious complications (e.g., sepsis, bacteremia, empyema, lung abscess, or extrapulmonary infection confirmed by clinical, microbiological, or radiological evidence), the need for escalation or change of antibiotic therapy due to inadequate clinical response or new infection, or death from any cause during the treatment period. Clinical cure and clinical improvement are both considered treatment success. 'Treatment failure' was intentionally chosen as the positive class for the ML models. This approach aligns with the clinical priority of proactively identifying patients at high risk of a negative outcome, thereby making performance metrics such as recall (sensitivity) directly interpretable as the model's ability to detect these at-risk individuals.

Based on the above inclusion and exclusion criteria as well as diagnostic standards, cases were retrospectively collected from the hospital information system (HIS). Data collected included the aforementioned 23 variables, the use of TZP (either as monotherapy

or in combination with Ery), and clinical treatment outcomes. Combination therapy had to be initiated within 48 hours[19]. For a patient to be included in the analysis, the assigned treatment regimen had to be administered for a minimum of 72 hours. This required at least 72 hours of piperacillin/tazobactam for the monotherapy group, and at least 72 hours of both piperacillin/tazobactam and erythromycin for the combination therapy group. For patients with multiple admissions during this period, only the first episode was included[20].

Development of machine learning models

The dataset was initially randomly split into training and test sets using a 4:1 ratio. The rates of missing data for each variable were calculated and are presented in **Supplementary Table S1**. For the training set, missing values in continuous variables were imputed using the K-Nearest Neighbors (KNN) method, while categorical binary variables were imputed using mode imputation (SimpleImputer). Subsequently, continuous variables were standardized (StandardScaler) after imputation. The imputers and standardizers derived from the training set were then applied to process the test set data. Prior to model fitting, the processed training data underwent random under-sampling to ensure balanced classes in the outcome variable.

In this study, feature selection was performed using the SHapley Additive exPlanations (SHAP) method and the Boruta algorithm to identify the top 15 most important features[21,22]. The optimal number

of features was then determined by assessing the overall performance of base and ensemble models trained with different feature subsets. Moreover, due to the research aims, co-administration of Ery was a required input feature for the final ML model.

In this study, four common ML algorithms were chosen as the base models: Random Forest (RF), Support Vector Machine(SVM), Logistic Regression(LR), and Gradient Boosting Decision Tree (GBDT). Subsequent to an initial feature selection step, feature subsets were selected from the training set and then subjected to undersampling. A preliminary hyperparameter search was conducted using grid search, followed by bootstrap validation using these hyperparameters. The models were then retrained using the refined parameters. The final hyperparameter configurations for each model are detailed in **Supplementary Table S2**. Finally, model performance was evaluated on the independent test set. This iterative process, spanning from feature selection to final evaluation on the test set, was performed to identify the optimal model. Subsequently, a stacking ensemble learning (SEL) model was performed using the three best-performing models.

Model performance was evaluated using the following metrics: Receiver Operating Characteristic Area Under the Curve (ROC-AUC), accuracy, precision, recall (sensitivity), specificity, F1-score, and log loss.

Online deployment of the model

A low-resource server platform utilizing Windows Server 2012 R2 served as the deployment environment for the web application leveraging ML models. Flask (version 2.2) was employed for the development of the web application's front-end.

To ensure the responsible use of the tool and prevent predictions for patient populations outside the scope of our training data, a disclaimer was added to the web application's interface. This disclaimer clearly outlines the study's main inclusion and exclusion criteria and specifies that the model's predictions are intended for patients who meet these criteria.

Sample size calculation

Based on findings from a previous study[23], we anticipated treatment failure rates of 19.6% and 32.3% in the combination and monotherapy groups, respectively. The sample size was calculated using a two-sided significance level of 0.05 and a power of 0.80. To account for the potential loss of statistical efficiency due to IPTW, a variance inflation factor of 1.2 was used. The initial sample size calculation suggested a minimum of 195 patients per group. Our final study included 169 patients in the combination therapy group and 489 patients in the monotherapy group (allocation ratio ≈ 1:2.89). Post-hoc power analysis confirmed that the final sample size provided adequate statistical power to detect the hypothesized difference in treatment failure rates between groups, despite the anticipated efficiency loss associated with inverse probability weighting.

Statistics

All data preprocessing, sample size estimation, IPTW, and ML model development were performed using Python (version 3.10.9). Key packages included scikit-learn (version 1.3.0) for model building and evaluation, SHAP (version 0.46.0) for model interpretation, and BorutaPy (version 0.3) for feature selection. The standardized mean difference (SMD) was employed to assess between-group differences in covariates. Balance was considered excellent when the absolute SMD value was ≤10%, acceptable when between 10% and 20%, and poor when >20%. For descriptive statistics, categorical variables were expressed as counts (percentages), normally distributed continuous variables as mean ± standard deviation, and non-normally distributed continuous variables as median (interquartile range, IQR).

Results

Data collecting

During the study period from January 1, 2021, to July 31, 2023, a total of 2498 inpatients admitted to the Department of PCCM of Shanghai Pudong Hospital with a primary diagnosis of AECOPD were assessed for eligibility. Of these, 1840 patients were excluded for reasons detailed in **Fig.1**. This resulted in a final cohort of 658 patients with AECOPD complicated by bacterial LRTIs who were included in the study. Within this cohort, 489 patients received TZP monotherapy and 169 patients received TZP combined with Ery (**Fig.1**).

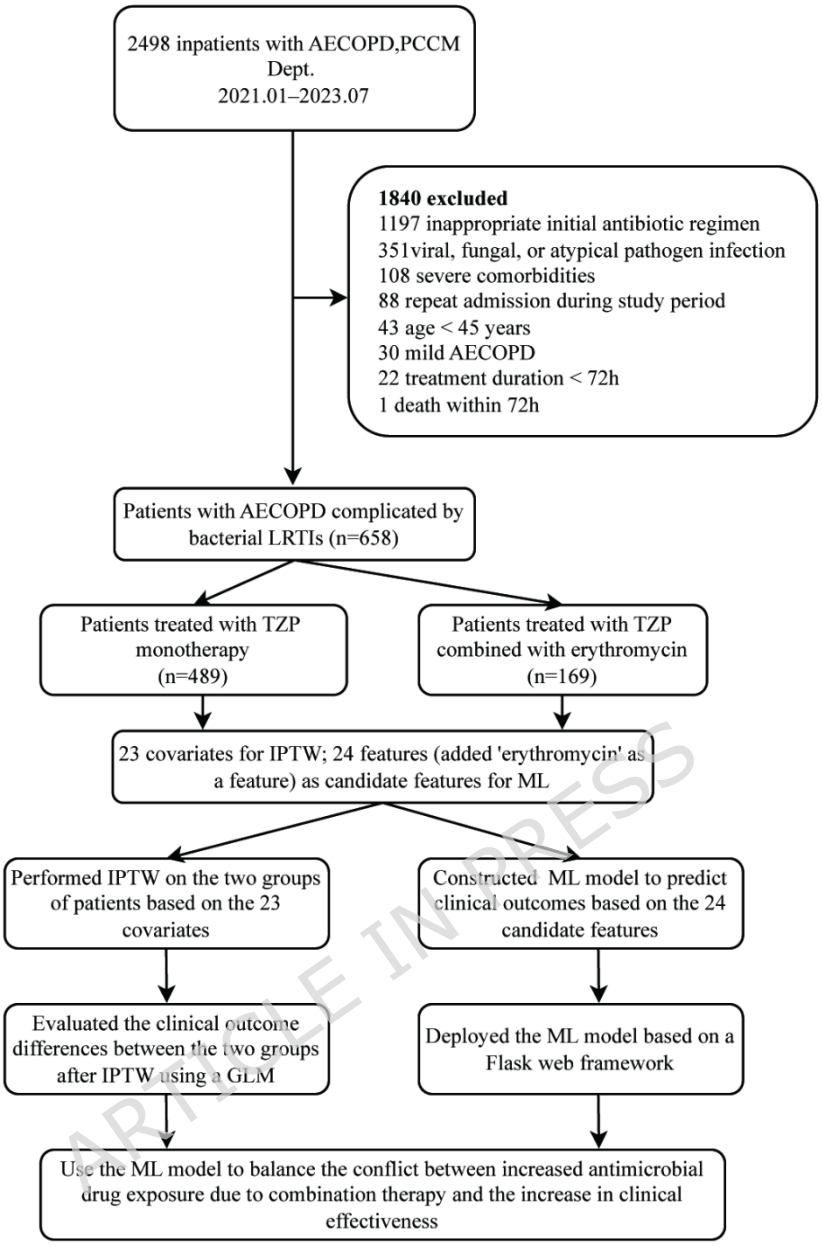

Fig.1. Flow diagram of patient selection and study design. The flowchart illustrates the screening and selection process for the study cohort. Of the 2498 patients with AECOPD initially assessed for eligibility, 1840 were excluded for the reasons listed, resulting in a final cohort of 658 patients for analysis. The diagram also outlines the dual methodological pathways used in the study: the IPTW analysis for comparing treatment outcomes and the development and deployment of the ML model for outcome prediction. AECOPD indicates acute exacerbations of chronic obstructive pulmonary

disease; PCCM, Department of Pulmonary and Critical Care Medicine; LRTIs, lower respiratory tract infections; TZP, piperacillin-tazobactam; IPTW, inverse probability of treatment weighting; ML, machine learning; and GLM, generalized linear model.

Covariates/Features selection

A total of 23 covariates were collected for IPTW. 24 features (including treatment regimen) were used for ML model development (**Table 1**). These variables comprised both continuous and categorical measurements. Continuous variables included age, weight, EGFR, blood urea nitrogen (BUN), serum albumin (ALB), WBC, D-dimer (DD), CRP, PCT, NLR, lymphocyte count (LYM), and body temperature (Temp). Categorical variables were binary, coded as 0 or 1, including Sex, respiratory failure (RF), recent hospitalization history (within 3 months) (RH), DM, active tumor (CA), bronchiectasis (BE), interstitial lung disease (ILD), cerebrovascular disease (CVD), heart failure (HF), and outpatient treatment history within the 30 days prior to admission (OPTH). Piperacillin/tazobactam dosage (TZPD) was categorized as 3.125g Q8H=0 and 2.5g Q8H=1. Treatment regimen (Ery), which served as an additional feature for machine learning analysis, was coded as monotherapy=0 and combination therapy=1. The clinical outcome was defined as a binary variable (failure=1, success=0).

Table 1

Definitions and coding of variables used for IPTW and ML model development

Order number	Factors	Abbreviations	Assignments
1	Age	Age	As a continuous variable
2	Weight	Weight	As a continuous variable
3	Estimated glomerular filtration rate	EGFR	As a continuous variable
4	Blood urea nitrogen	BUN	As a continuous variable
5	Serum albumin	ALB	As a continuous variable
6	White blood cell count	WBC	As a continuous variable
7	D-dimer	DD	As a continuous variable
8	C-reactive protein	CRP	As a continuous variable
9	Procalcitonin	PCT	As a continuous variable
10	Neutrophil-to-lymphocyte ratio	NLR	As a continuous variable
11	Lymphocyte count	LYM	As a continuous variable
12	Body temperature	Temp	>=37.3°C=1; <37.3°C=0
13	Sex	Sex	Female=0; Male=1
14	Respiratory failure	RF	YES=1; NO=0
15	Recent hospitalization history (in 3 month)	RH	YES=1; NO=0
16	Diabetes mellitus	DM	YES=1; NO=0
17	Active tumor	CA	YES=1; NO=0
18	Bronchiectasis	BE	YES=1; NO=0
19	Interstitial lung disease	ILD	YES=1; NO=0
20	Cerebrovascular disease	CVD	YES=1; NO=0
21	Heart failure	HF	YES=1; NO=0
22	Outpatient treatment history within the 30 days prior to admission	OPTH	YES=1; NO=0
23	Dosage of piperacillin/tazobactam	TZPD	2.5g, Q8H=1; 3.125g, Q8H=0
24	Treatment regimen	Ery	Monotherapy=0;Combined therapy=1
	Clinical outcomes		Failure=1; Success=0

Demographic baseline and weighted effects

Table 2 presented the baseline characteristics of the study population and assessed the covariates balance before and after IPTW. Prior to IPTW, 13 variables exhibited substantial imbalances (|SMD| > 10%), including CRP, WBC, Age, and others. Following

IPTW adjustment, almost all variables achieved a good balance between the two groups (absolute SMD < 10%), with the exception of BUN, which had an absolute SMD of 10.6%. In the TZP group (*n*=489), the median age was 78.00 years (IQR: 12.00), and 366 (74.85%) were male. In the TZP+Ery group (*n*=169), the median age was 75.00 years (IQR: 12.00), and 130 (76.92%) were male. After weighting, laboratory parameters, comorbidities, and other clinical characteristics demonstrated comparable distributions between the two groups.

To provide further insight, the characteristics of patients stratified by both treatment received and clinical outcome are detailed in **Supplementary Table S3.**

Table 2

Baseline characteristics and covariate balance before and after IPTW

Factors	TZP (n=489)	TZP+Ery (n=169)	IPTW(SMD)	
	Median(IQR)/Count(Ratio)	Median(IQR)/Count(Ratio)	Before	After
CRP	6.50 (39.65)	14.04 (57.32)	19.31%	1.86%
ALB	37.90 (5.40)	38.22 (5.10)	10.89%	-1.34%
WBC	7.21 (4.19)	7.95 (4.33)	24.98%	-0.11%
DD	0.59 (0.85)	0.53 (0.70)	-5.93%	-0.37%
Age	78.00 (12.00)	75.00 (12.00)	-33.72%	-4.01%
PCT	0.11 (0.10)	0.09 (0.16)	9.09%	3.29%
BUN	6.76 (3.50)	6.40 (2.37)	-17.68%	-10.60%
NLR	0.77 (0.17)	0.80 (0.18)	14.23%	2.92%
LYM	1.01(0.71)	1.00 (0.78)	3.76%	0.37%
Weight	60.00 (18.00)	60.00 (16.00)	1.03%	-0.03%
EGFR	82.41 (26.63)	87.57 (23.90)	12.99%	0.54%
Sex	366 (74.85%)	130 (76.92%)	4.86%	-0.28%
Temp	70 (14.31%)	38 (22.49%)	21.20%	3.06%
RF	163 (33.33%)	50 (29.59%)	-8.08%	3.60%

RH	107 (21.88%)	28 (16.57%)	-13.51%	-3.24%
DM	77 (15.75%)	27 (15.98%)	0.63%	-1.07%
CA	85 (17.38%)	24 (14.20%)	-8.73%	-3.08%
BE	71 (14.52%)	36 (21.30%)	17.76%	1.31%
ILD	38 (7.77%)	11 (6.51%)	-4.90%	-0.12%
CVD	237 (48.47%)	79 (46.75%)	-3.45%	-1.05%
HF	308 (62.99%)	84 (49.70%)	-27.02%	-0.99%
OPTH	377 (77.10%)	102 (60.36%)	-36.71%	-1.29%
TZPD	338 (69.12%)	135 (79.88%)	24.88%	0.52%

SMD indicates standardized mean difference; IQR, interquartile range; IPTW, inverse probability of treatment weighting; TZP, piperacillin/tazobactam; Ery, erythromycin; CRP, C-reactive protein; ALB, serum albumin; WBC, white blood cell count; DD, D-dimer; PCT, procalcitonin; BUN, blood urea nitrogen; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocyte count; EGFR, estimated glomerular filtration rate; Temp, temperature; RF, respiratory failure; RH, recent hospitalization history; DM, diabetes mellitus; CA, active tumor; BE, bronchiectasis; ILD, interstitial lung disease; CVD, cerebrovascular disease; HF, heart failure; OPTH, outpatient treatment history within the 30 days prior to admission; and TZPD, Piperacillin/tazobactam dosage.

Demographic baseline and weighted effects

After IPTW adjustment, a GLM with binomial distribution and logit link function was used to evaluate the difference in clinical outcomes between groups. The combination therapy group demonstrated significantly lower treatment failure rates compared to the monotherapy group (14.00% vs 19.75%, OR = 0.66, 95% CI 0.49-0.89, p = 0.006) (**Table 3**). Specifically, patients receiving TZP+Ery combination therapy had a 34% lower odds of treatment failure than those receiving TZP monotherapy, after adjusting for potential confounders through IPTW.

Table 3

GLM results for treatment outcomes after IPTW adjustment

Group	Coefficient (SE)	95% CI	Predicted Probability	*P* value	OR (95% CI)†
TZP	-1.40(0.10)	-1.59, -1.21	19.75%	<0.001	0.66 (0.49, 0.89)
TZP+Ery*	-0.41 (0.15)	-0.71, -0.12	14.00%	0.006	

SE indicates standard error; CI, confidence interval; OR, odds ratio; TZP, piperacillin/tazobactam; and Ery, erythromycin. * Reference group is the TZP group; † Calculated as exp (coefficient)

Feature importance and feature selection

To identify key factors influencing treatment outcomes, feature importance analysis was performed based on the training set. The SHAP summary plot ranked the top 15 features based on their importance to the model output (**Fig.2A**). Features closer to the top, such as ALB, WBC, and CRP, have a stronger impact on the model's predictions. The horizontal position of each point represented the SHAP value, indicating the magnitude and direction of each feature's impact. The Boruta algorithm feature importance ranking provides an alternative evaluation, where shorter bars indicate higher feature importance **(Fig.2B)**. Features like WBC, ALB, and CRP ranked as the most influential. The SHAP force plot provided an interpretative explanation for a single prediction, illustrating the contribution of individual features towards a treatment failure outcome (f(x) = 0.59) (**Fig.2C**). Positive contributions (e.g., CRP, WBC, and Weight) push

the prediction towards treatment failure, while negative contributions (e.g., Age and NLR) counteract this effect.

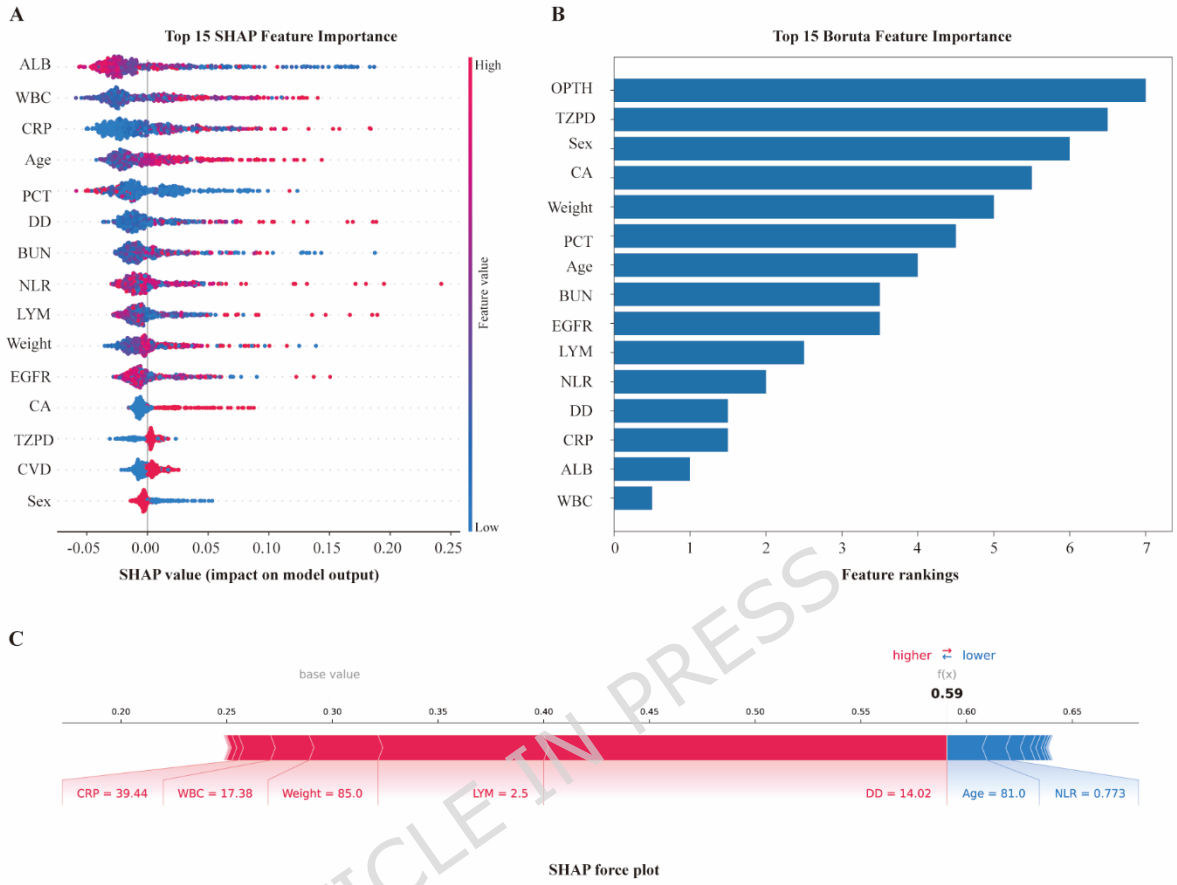

Fig.2. Feature importance and model interpretability results. (A) SHAP summary plot showing the top 15 most important features contributing to the model output. Each point represents a SHAP value for an individual sample, with the color scale indicating the feature value (high: red, low: blue). Features are ranked by importance, with ALB being the most impactful. (B) Boruta feature importance ranking, where the shorter the bar, the higher the feature importance. WBC, ALB, and CRP emerged as the top-ranked features in this analysis. (C) SHAP force plot for an individual prediction (treatment failure), illustrating the contributions of specific features (CRP, WBC, Weight, LYM) in pushing the prediction towards the positive class, while others (Age and NLR) counterbalance this effect. The predicted probability of treatment

failure is 0.59. CRP indicates C-reactive protein; ALB, serum albumin; WBC, white blood cell count; DD, D-dimer; PCT, procalcitonin; BUN, blood urea nitrogen; NLR, neutrophil-to-lymphocyte ratio; LYM, lymphocyte count; EGFR, estimated glomerular filtration rate; CA, active tumor; BE, bronchiectasis; ILD, interstitial lung disease; CVD, cerebrovascular disease; HF, heart failure; OPTH, outpatient treatment history before admission; and TZPD, Piperacillin/tazobactam dosage.

Although the feature Ery (whether combined with Ery) did not rank highly in importance based on the SHAP and Boruta algorithms (**Fig.2A-B**), we deliberately included Ery as an input variable for the ML model due to clinical practice and research purposes. We then examined the ROC-AUC performance with and without Ery as a feature variable, based on RF, SVM, LR, and the ensemble model (EL) with preliminary optimized parameters. The results showed that the inclusion of Ery as a feature variable had a varying impact on model performance. A quantitative improvement in ROC-AUC was observed for the RF model (from 0.67 to 0.70) (**Fig. 3A-B**), the SVM model (from 0.66 to 0.67) (**Fig. 3C-D**), and the final stacking ensemble learning (SEL) model (from 0.69 to 0.71) (**Fig. 3G-H**), while the performance of the LR model remained unchanged (0.67) (**Fig. 3E-F**). For completeness, the corresponding performance data for the GBDT model, which was not selected for the final ensemble, is provided in **Supplementary Figure S1**.

Finally, based on the feature Ery and the top 15 features ranked by importance according to the SHAP and Boruta algorithms, and considering the ROC-AUC performance under different feature

combinations, we ultimately included 15 features as input features for the machine learning model: CRP, ALB, WBC, DD, Age, PCT, BUN, NLR, LYM, Weight, EGFR, TZPD, CA, OPTH, and Ery.

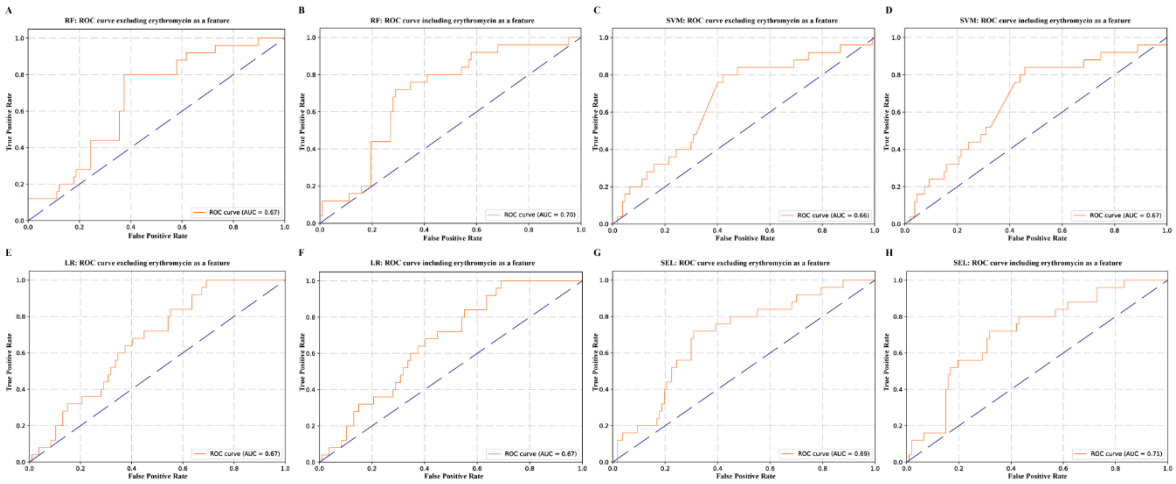

Fig.3. Improvement in model performance with and without Ery as a feature variable. This figure illustrated the effect of including Ery as a feature on the performance of different machine learning models, as assessed by ROC-AUC. (A-B) RF model; (C-D) SVM model; (E-F) LR model; (G-H) SEL model. The inclusion of Ery resulted in an increase in ROC-AUC for almost all models, as shown by comparing the left (without Ery) and right (with Ery) subplots for each model type. RF indicates Random Forest; SVM, Support Vector Machine; LR, Logistic Regression; SEL, Stacking Ensemble Learning; ROC-AUC, Receiver Operating Characteristic Area Under the Curve; Ery, Erythromycin.

Model selection and model evaluation

RF, SVM, LR, and GBDT were chosen as base models. Following data cleaning, feature selection, hyperparameter optimization, and cross-validation, the models were evaluated on an independent test set. ROC-AUC, recall, accuracy, precision, F1 score, and log loss

were used as evaluation metrics. The evaluation results demonstrated that RF, SVM, and LR achieved better overall performance (**Table 4**).

Table 4

Performance metrics of the base and SEL models

Model	Accuracy	Precision	Recall (sensitivity)	Specificity	F1 score	ROC-AUC	Log loss
RF	0.68	0.34	0.72	0.67	0.46	0.70	0.68
SVM	0.65	0.32	0.76	0.63	0.45	0.67	0.69
LR	0.61	0.28	0.64	0.61	0.39	0.67	0.69
GBDT	0.61	0.26	0.60	0.61	0.37	0.61	0.68
SEL	0.69	0.35	0.72	0.68	0.47	0.71	0.69

RF indicates Random Forest; SVM, Support Vector Machine; LR, Logistic Regression; GBDT, Gradient Boosting Decision Tree; ROC-AUC, Receiver Operating Characteristic Area Under the Curve; and SEL, stacking ensemble learning model.

Building upon the RF, SVM, and LR models, which demonstrated superior performance, model ensembling was performed using a StackingClassifier. To assess the SEL model's performance, a bootstrap cross-validation method with 1000 iterations was employed. The SEL model was subsequently evaluated on an independent test set using the previously mentioned metrics. The results revealed a cross-validated ROC-AUC of 0.72 (**Fig.4A**) and an ROC-AUC of 0.71 on the independent test set (**Fig.4B**). The recall (sensitivity) was 0.72 (**Fig.4C-D**). The accuracy, precision, F1 score, log loss, and specificity were 0.69, 0.35, 0.47, 0.69, and 0.68, respectively (**Fig.4D**).

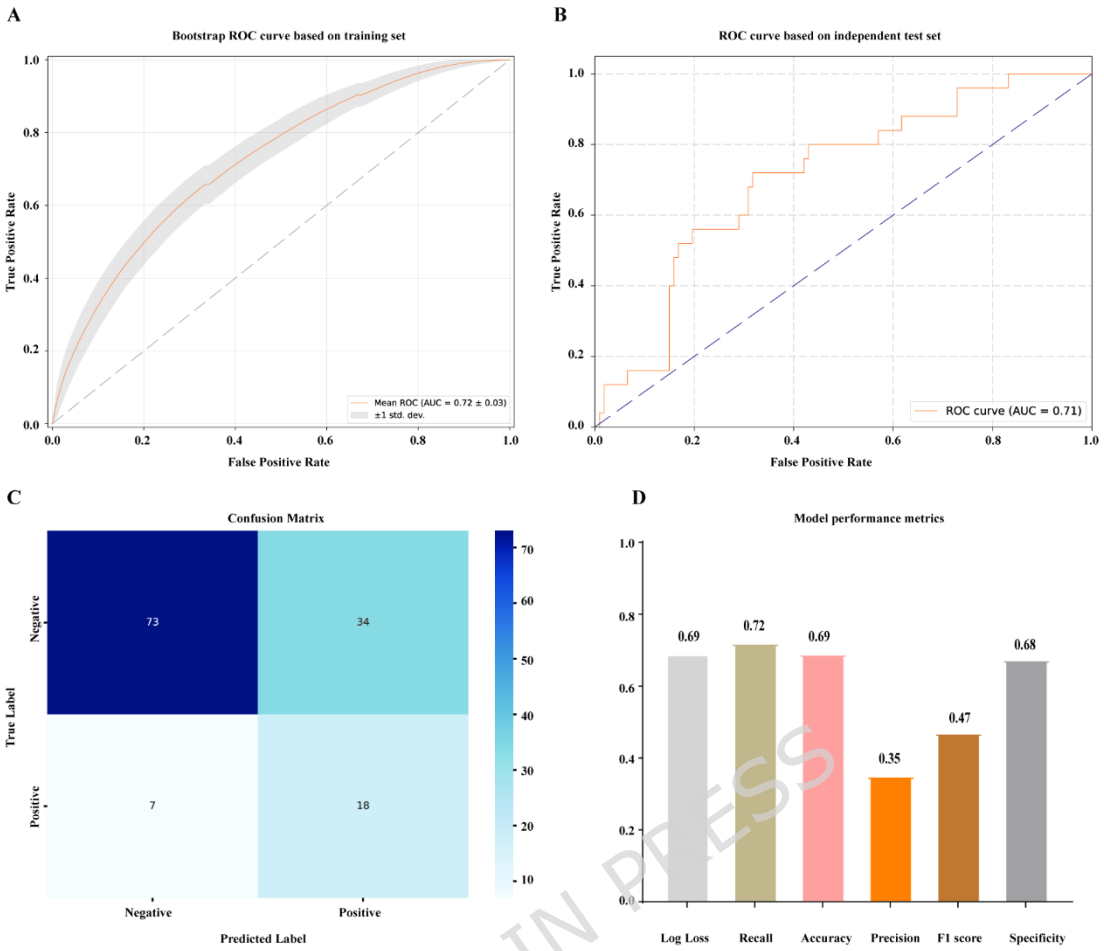

Fig.4. Performance evaluation of the SEL model. (A) Mean ROC curve obtained on the training set using a bootstrap method with 1000 iterations. The shaded area represents the standard deviation (AUC = 0.72 ± 0.03). (B) ROC curve obtained on an independent test set (AUC = 0.71). (C) The confusion matrix based on the test set, showing the number of true positives, false positives, true negatives, and false negatives. (D) Model performance metrics based on the independent test set: log Loss = 0.69, recall (sensitivity) = 0.72, specificity=0.68, accuracy = 0.69, precision = 0.35, and F1 score = 0.47. ROC indictes receiver operating characteristic and AUC, area under the curve.

Web app development

A web-based clinical decision support tool based on the EL model was developed and deployed at http://106.12.146.54. This tool, implemented using the Flask web framework, consists of a data input interface and a prediction result display (**Fig.5A**). Users input 14 variables, excluding Ery, for the backend separately calculates predictions for Ery=0 (TZP monotherapy) and Ery=1(TZP in combination with erythromycin), to predict clinical outcomes (Success or Failure). The tool provides a treatment recommendation (Recommended or Not Recommended) based on these predictions. Illustrative prediction scenarios include: (1) TZP monotherapy failure with combination therapy success (**Fig.5B**); (2) successful outcomes with both treatment strategies (**Fig.5C**); and (3) unsuccessful outcomes with both treatment strategies (**Fig.5D**).

Fig.5. User interface and illustrative prediction scenarios of the EL model-based web application for guiding antibiotic treatment. (A) The user interface consists of a data input section for 14 clinical variables (excluding Ery) and a result display section presenting predicted clinical outcomes (Success or Failure) and corresponding treatment recommendations (Recommended or Not Recommended) for TZP monotherapy (Ery = 0) and TZP combined with erythromycin (Ery = 1). (B) Example scenario 1: the tool predicted failure with TZP monotherapy but success with the addition of erythromycin. (C) Example scenario 2: the tool predicted successful outcomes

for both TZP monotherapy and TZP combined with Ery. (D) Example scenario 3: the tool predicted unsuccessful outcomes for both TZP monotherapy and TZP combined with Ery. TZP indicates piperacillin/tazobactam.

Discussion

This study explored the clinical efficacy of TZP combined with Ery in patients with AECOPD complicated by bacterial LRTIs. By employing IPTW methodology, we demonstrated that the addition of Ery to TZP significantly improved clinical outcomes compared to TZP monotherapy. Furthermore, we developed and deployed a ML-based web system for treatment outcome prediction, which has potential utility for real-time clinical decision-making.

The beneficial effect of combination therapy observed in our study aligns with previous findings in the treatment of CAP, where β-lactam plus macrolide combinations have shown superior outcomes[13]. This parallel suggests shared mechanisms of benefit between CAP and AECOPD with bacterial LRTIs, possibly due to similar pathogenic processes and causative organisms. The reduced failure rate with combination therapy may be attributed to both the antimicrobial and immunomodulatory properties of macrolides[24], although our study design cannot definitively determine the mechanism of benefit. Long-term use of Ery suppresses COPD exacerbations, and previous studies have supported the advantages of a 12-month macrolide prescription relative to placebo[25-27]. While Thotsaporn Morasert et al. reported a potential benefit of the short-term use of macrolides on mortality in hospitalized AECOPD patients,

several limitations warrant consideration[28]. The macrolide group received a combination of macrolides (clarithromycin, azithromycin, and roxithromycin) and heterogeneous concomitant medications (including carbapenems, penicillins, cephalosporins, and quinolones) with unequal group distribution. This heterogeneity limits the interpretability of their findings regarding specific macrolide/β-lactam combinations. Therefore, further research is needed to evaluate the clinical efficacy of specific single β-lactam and single macrolide combinations in AECOPD, which this study aims to provide.

An important aspect of our study design was the exclusion of patients with confirmed atypical bacterial infections. While this may limit the generalizability to that specific subpopulation, it provides a unique opportunity to evaluate the non-antimicrobial effects of Ery. The superior clinical outcomes observed in the combination therapy group, in a cohort where atypical pathogens were absent, lend strong support to the hypothesis that the primary benefit of macrolide co-therapy in these patients is derived from its immunomodulatory properties rather than a direct antimicrobial effect against atypical bacteria.

Our ML approach identified several key predictors of treatment outcomes. ALB, WBC, and CRP emerged as the most influential factors through both SHAP and Boruta analyses. These findings suggest that the combination of inflammatory markers and nutritional status may be crucial in determining treatment success.

Interestingly, while the addition of Ery showed clinical benefit, its importance as a predictive feature was relatively low in the ML models, indicating that baseline patient characteristics may be more deterministic of outcomes than treatment choice alone. Observational data indicated a marked increase in long-term macrolide use between 2004 and 2018, both in the general population and specifically among individuals with severe COPD. However, this increased utilization did not appear to translate into a measurable reduction in hospitalizations or emergency department presentations for COPD[29]. This observation raised the hypothesis that long-term macrolide therapy may not provide uniform clinical benefit across the COPD patient population. Accordingly, alongside consideration of findings from large-scale clinical investigations, the integration of personalized treatment approaches is warranted in the management of COPD. In the present study, we observed that the addition of Ery was associated with improved clinical outcomes in patients with moderate-to-severe AECOPD. Importantly, we further employed a ML model to integrate Ery administration with other significant variables known to influence clinical outcomes, thereby generating preliminary insights into personalized therapeutic strategies. This approach is of paramount importance in balancing the clinical benefits of pharmacotherapy with the need to minimize antimicrobial exposure and the potential for adverse drug reactions.

While the pharmacokinetics of TZP (4:1) and (8:1) are comparable across different renal function levels, the lower piperacillin dose in TZP (4:1), due to tazobactam limitations, requires careful clinical assessment of its effectiveness[30,31]. Our predictive model highlights scenarios where both TZP (4:1) alone and in combination with Ery may be insufficient (**Fig.5D**), prompting consideration of TZP (8:1) or escalation to broader-spectrum agents. If both treatment options are predicted to be effective, TZP (4:1) monotherapy is favored (**Fig.5C**). However, the decision to use combination therapy should be guided by individual patient characteristics and risk assessments (Figure 5B). The developed web-based ML tool represents a promising step toward personalized medicine, enabling clinicians to weigh the benefits of combination therapy against its potential risks, such as antibiotic resistance and adverse events. Future research should focus on integrating real-time data inputs, such as point-of-care inflammatory markers, into the predictive model. Additionally, exploring the cost-effectiveness of combination therapy in resource-constrained settings will be critical for broader implementation.

A key methodological choice in this study was the use of a stacking ensemble for the final prediction task. We acknowledge that its performance on the test set was only modestly better than a well-tuned standalone Random Forest model. The rationale for this decision was grounded in the principle of maximizing robustness through model diversity[32]. The ensemble combined three

heterogeneous base learners: a tree-based model (Random Forest), a linear model (Logistic Regression), and a maximal-margin classifier (SVM). Each of these models captures different types of patterns and relationships within the data. Our hypothesis is that a meta-learner, by integrating these diverse perspectives, can create a more generalizable model that is less susceptible to the specific weaknesses of any single modeling technique[33]. We recognize that this approach comes at the cost of increased computational complexity and reduced direct interpretability compared to a simpler model like logistic regression. However, in the context of developing a clinical support tool intended for broad application, we prioritized maximizing predictive robustness, accepting this trade-off.

It is plausible that the clinical benefits observed with the addition of erythromycin represent a class effect of macrolides. Other agents in this class, such as azithromycin and clarithromycin, also possess well-documented immunomodulatory and anti-inflammatory properties, which are thought to contribute significantly to their efficacy in respiratory infections[13,24]. Therefore, while direct comparative studies are needed, it is reasonable to hypothesize that similar benefits could be seen with other macrolides like azithromycin, which is more commonly used in many regions. Extrapolating these findings to different β-lactam antibiotics, however, requires more caution. The choice of β-lactam is highly dependent on disease severity and local resistance

patterns[8], and further research would be needed to determine if the additive benefit of a macrolide is consistent when paired with narrower-spectrum β-lactams.

Limitations

Our study has several limitations that warrant consideration. A primary limitation is its single-center, retrospective design. As such, our findings may be influenced by local prescribing habits, such as the specific choice of erythromycin, as well as regional patterns of bacterial pathogens and antimicrob leveraging historical data ial resistance. Another limitation is that our retrospective data did not include systematic recording of patient GOLD classifications, which prevented a sub-analysis based on disease severity staging. Future studies should aim to incorporate this data. Future prospective trials are warranted to validate these results in broader populations and different healthcare settings. Further refinement of the model, potentially through the inclusion of additional clinical and microbiological variables, could enhance its predictive capability. Our predictive model, while showing promising internal validation, lacks external validation, which is a critical step before any clinical implementation. Consequently, the findings presented in this paper should be considered exploratory and hypothesis-generating.

Additionally, while we excluded patients with confirmed atypical pathogen infections, we acknowledge a limitation regarding diagnostic sensitivity and coverage. Not all patients may have been

screened for every atypical pathogen (e.g., Legionella pneumophila), and false-negative results are possible with routine serological testing. Therefore, we cannot rule out the possibility that the observed clinical benefit of erythromycin was partly due to its antimicrobial activity against undetected atypical pathogens, rather than exclusively its immunomodulatory effects.

Finally, another limitation of our current study is that our machine learning models are not conformal. Conformal prediction is a user-friendly framework that allows a model to quantify the uncertainty of its predictions, for example, by producing a prediction set containing the true label with a user-specified probability (e.g., 90%). This is highly desirable in a high-stakes clinical context, as it can alert clinicians when the model is uncertain about a particular patient, especially if the patient's characteristics are dissimilar to those in the training data. Our current ensemble model provides a point prediction of 'Success' or 'Failure' but does not offer this formal measure of confidence. The development and validation of a conformal version of our prediction tool is a critical next step for this research, which would enhance the model's safety and trustworthiness, making it more suitable for prospective evaluation and real-world clinical integration.

Conclusion

This study provides evidence suggesting that the combination of Ery and TZP may be beneficial in the treatment of AECOPD complicated by bacterial LRTIs. Furthermore, we present a novel ML-based tool

designed to support clinical decision-making by considering both therapeutic benefits and the need to minimize antimicrobial exposure and the risk of adverse drug reactions. Although these findings require confirmation in external cohorts, they represent a contribution toward more personalized and evidence-based management strategies for AECOPD with bacterial LRTIs.

Availability of data and material

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

TY, FFM, and JMW designed the study. YMY, TZ, and XZ served as the principal authors, responsible for conceiving, executing, and refining the majority of the analyses. Additionally, they played a pivotal role in drafting and polishing the manuscript. TY, YL, DQ, ZJZ, XJL, and FFM performed the statistical analysis of the data, contributed to editing the manuscript, and provided feedback. TY, FFM, and JMW supervised the project. All authors participated

sufficiently in the study and take responsibility for the integrity of the work.

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Declarations

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics approval and consent to participate

This investigation was designed as a retrospective analysis based on previously collected clinical data and was conducted under a waiver of informed consent. The waiver was formally reviewed and approved by the Ethics Committee of Shanghai Pudong Hospital, Fudan University Pudong Medical Center, prior to the initiation of

the study. Furthermore, the study protocol, developed in strict compliance with the ethical principles outlined in the Declaration of Helsinki and its subsequent revisions, received approval from the same committee (Approval No: 2024-KY-001-E01).

Consent for publication

Not applicable.

Abbreviations

AECOPD	Acute exacerbations of chronic obstructive pulmonary disease
COPD	Chronic obstructive pulmonary disease
LRTIs	Lower respiratory tract infections
TZP	Piperacillin-tazobactam
ML	Machine learning
SEL	Stacking ensemble learning
IPTW	Inverse probability of treatment weighting
EGFR	Estimated glomerular filtration rate