



OPEN Impact of pulmonary infection and antibiotic use on recurrent myocardial infarction in patients with myocardial infarction

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This study aims to evaluate the impact of pulmonary infections and antibiotic use on the recurrence of myocardial infarction (MI) in patients. A total of 3807 MI patients were included in this study. The effects of pulmonary infections and different antibiotics on recurrent MI were investigated using multivariable logistic regression and propensity score matching (PSM) analysis. Kaplan-Meier survival curves were used to compare the risk of recurrent MI between patients with and without pulmonary infections. In the multivariable logistic regression analysis, pulmonary infections significantly increased the risk of recurrent MI in patients with non-ST-segment elevation myocardial infarction (NSTEMI) (odds ratio [OR] = 1.47, 95% confidence interval [CI]: 1.22–1.79, $P < 0.0001$) and ST-segment elevation myocardial infarction (STEMI) (OR = 1.43, 95% CI: 1.15–1.80, $P = 0.0016$). PSM analysis showed that, without adjusting for antibiotic use, pulmonary infections significantly increased the risk of recurrent MI (NSTEMI: OR = 1.41, 95% CI: 1.12–1.79, $P = 0.004$; STEMI: OR = 1.48, 95% CI: 1.13–1.95, $P = 0.0051$). However, after adjusting for antibiotic use, the impact of pulmonary infections on recurrent MI was no longer significant (NSTEMI: OR = 0.91, 95% CI: 0.57–1.45, $P = 0.691$; STEMI: OR = 1.06, 95% CI: 0.80–1.41, $P = 0.6925$). Different antibiotics had significant effects on the risk of recurrent MI: quinolone antibiotics were associated with an increased risk, while cephalosporin antibiotics and metronidazole were associated with a decreased risk. Pulmonary infections significantly increase the risk of recurrent MI in patients, and antibiotic use can modify this effect. Clinically, the use of antibiotics and management of pulmonary infections should be carefully considered to optimize treatment strategies for MI patients.

Keywords Myocardial infarction, Pulmonary infection, Recurrent myocardial infarction, Antibiotics, Propensity score matching

Myocardial infarction (MI) is one of the leading causes of death and disability worldwide¹. Despite significant advancements in acute phase treatment, MI patients still face a high risk of recurrent myocardial infarction (RMI)^{1,2}. RMI not only increases patient mortality and complication rates but also significantly elevates healthcare resource consumption and economic burden^{3,4}. Therefore, exploring the factors influencing RMI is of great clinical importance.

Pulmonary infection is a common complication among MI patients during hospitalization, which may result from an immune response triggered by infection or hospital-acquired infections due to the hospital environment and treatments⁵. Studies have shown that pulmonary infection may increase the risk of cardiovascular events by exacerbating systemic inflammatory responses and cardiac load^{6,7}. However, research on the impact of pulmonary infection on RMI in MI patients is limited, and results are controversial⁸.

Antibiotics are the primary treatment for pulmonary infections, but different types of antibiotics may have varying effects on the cardiovascular system. For instance, some antibiotics may improve outcomes through

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anti-inflammatory and immunomodulatory effects, while others may increase cardiovascular risk due to drug interactions and side effects^{9,10}. Therefore, understanding the impact of different antibiotics on RMI in MI patients can help optimize antibiotic treatment strategies and improve clinical outcomes.

This study aims to systematically evaluate the impact of pulmonary infections and antibiotic use on RMI in MI patients through multivariable logistic regression and propensity-score matching (PSM) analysis. We included 3807 MI patients and analyzed the relationship between pulmonary infections, different antibiotic uses, and RMI risk, aiming to provide evidence-based guidance for clinical practice and optimize management strategies for MI patients.

Methods

Study design and population

This retrospective cohort study included 12,857 patients admitted to a tertiary hospital for chest pain and diagnosed with acute coronary syndrome (ACS) from January 2015 to March 2023. Among these, 4,120 patients were diagnosed with myocardial infarction (MI), including both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). Exclusion criteria included: 8,737 patients with unstable angina (UA), 148 in-hospital deaths, 68 patients with mechanical complications, 38 patients with other non-cardiac diseases with a life expectancy of less than six months, and 59 patients lacking critical data. Ultimately, 3,807 MI patients were included in the analysis, comprising 2,224 NSTEMI and 1,583 STEMI patients (see Fig. 1).

Data collection

Patient demographics, medical history, clinical features, laboratory test results, and treatment information were collected through the electronic medical record system. The primary exposure factors were the presence or absence of pulmonary infection and the use of antibiotics. The diagnosis of pulmonary infection was based on clinical symptoms, imaging studies, and microbiological test results. Antibiotic use was documented in terms of specific drug types and duration of treatment. The outcome event was the occurrence of recurrent myocardial infarction, confirmed through follow-up of outpatient and inpatient records.

Handling of missing data

Missing data were addressed using multiple imputation techniques. For continuous variables, missing values were imputed using the mean imputation method, and for categorical variables, the mode imputation method was used. If core variables had missing values, those cases were excluded from the analysis. A sensitivity analysis was performed to assess the impact of imputation on the results, ensuring the robustness of our findings.

Statistical analysis

Baseline characteristics

Descriptive statistics were used to compare baseline characteristics between patients with and without pulmonary infection. Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were compared using the t-test or Mann-Whitney U test.

Multivariable logistic regression analysis

Multivariable logistic regression models were constructed to assess the impact of pulmonary infection and antibiotic use on the risk of recurrent myocardial infarction. Multivariable logistic regression models were constructed using stepwise regression to assess the impact of pulmonary infection and antibiotic use on the risk of recurrent myocardial infarction. Model A adjusted only for basic demographic variables. Model B further adjusted for sex and age. Model C additionally adjusted for other potential confounding factors, including BMI, LVEF, NT-proBNP, troponin T, LDL, PCI, Killip classification, atrial fibrillation, valvular heart disease, previous MI, hypertension, diabetes, COPD, renal insufficiency, stroke, antiplatelet drugs, number of antiplatelet drugs, statins, beta-blockers, novel oral anticoagulants, and warfarin. Model D further adjusted for antibiotic use.

To assess the validity of the logistic regression model and check for any assumptions violations, we conducted residual analysis. Residuals vs. Fitted Values plot was used to evaluate the homoscedasticity of the residuals, while Q-Q plot was employed to test the normality of the residuals. To assess the validity of the logistic regression model, we performed several diagnostic tests. The normality of residuals was evaluated using the Shapiro-Wilk test. Homoscedasticity was tested using the Breusch-Pagan test. Multicollinearity among the predictors was assessed using the Variance Inflation Factor (VIF), with a threshold of 10 indicating significant multicollinearity.

Propensity score matching (PSM)

A 1:1 propensity score matching method was used to reduce the impact of potential confounders. Matching variables included sex, age, BMI, LVEF, NT-proBNP, troponin T, LDL, PCI, Killip classification, atrial fibrillation, valvular heart disease, previous MI, hypertension, diabetes, COPD, renal insufficiency, stroke, antiplatelet drugs, number of antiplatelet drugs, statins, beta-blockers, novel oral anticoagulants, and warfarin. After matching, the incidence of recurrent myocardial infarction was compared between patients with and without pulmonary infection using the chi-square test or Fisher's exact test.

Kaplan-Meier survival analysis

The Kaplan-Meier method was used to plot survival curves and compare the cumulative incidence of recurrent myocardial infarction between patients with and without pulmonary infection. Differences between groups were compared using the log-rank test.

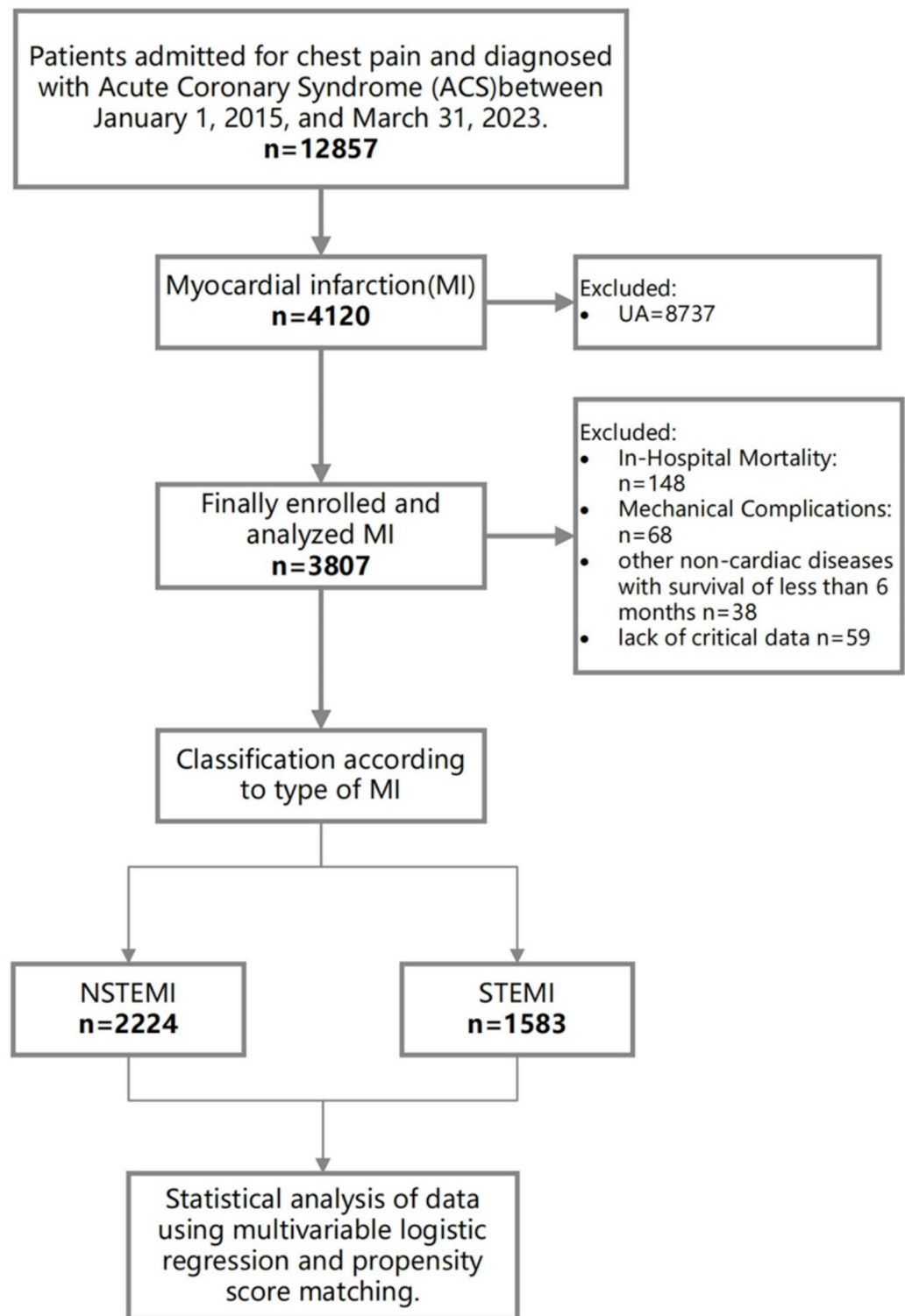


Fig. 1. Flow diagram for participant screening, eligibility and analysis.

Analysis of the impact of antibiotic use on recurrent myocardial infarction

The impact of different antibiotics (e.g., quinolones, cephalosporins, new beta-lactams, penicillins, aminoglycosides, nitroimidazoles) on the risk of recurrent myocardial infarction was assessed using multivariable logistic regression models, adjusting for potential confounders.

All statistical analyses were performed using R software version 4.2.0 (<http://www.R-project.org>). A two-sided P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

This study included a total of 3,807 myocardial infarction (MI) patients, of whom 2,224 did not experience recurrent myocardial infarction (RMI) and 1,583 did. The baseline demographic and clinical characteristics of the patients are presented in Table 1.

In terms of gender distribution, the proportion of males was 72.65% in the RMI group and 70.41% in the non-RMI group, with no statistically significant difference ($P = 0.133$). The mean age of patients in the RMI group was 65.56 years, while in the non-RMI group, it was 66.42 years, a statistically significant difference (P

Variables	Whether myocardial infarction recurred		
	NO N = 2224	YES N = 1583	P-value
Demographics			
Male, N (%)	1566 (70.41%)	1150 (72.65%)	0.133
Age, years	66.42 ± 12.19	65.56 ± 12.07	0.032
BMI, kg/m ²	19.71 ± 3.04	19.74 ± 3.11	0.786
Medical history, N (%)			
Auricular fibrillation	192 (8.63%)	146 (9.22%)	0.528
V alvular heart disease	419 (18.84%)	302 (19.08%)	0.854
Previous myocardial infarction	166 (7.46%)	54 (3.41%)	< 0.001
Hypertension	1504 (67.63%)	1029 (65.00%)	0.091
Diabetes mellitus	771 (34.67%)	504 (31.84%)	0.068
COPD	456 (20.50%)	337 (21.29%)	0.557
Renal insufficiency	471 (21.18%)	364 (22.99%)	0.182
Stroke	375 (16.86%)	260 (16.42%)	0.721
Clinical conditions at admission			
LVEF, %	53.70 ± 12.56	51.47 ± 10.76	< 0.001
NTproBNP, pg/ml	3210.11 ± 6690.12	4110.36 ± 8008.28	< 0.001
Troponin T, ng/mL	2.89 ± 2.86	3.17 ± 2.91	0.004
Low-density Lipoprotein, mmol/L	2.70 ± 0.96	2.81 ± 0.93	< 0.001
Myocardial infarction classification, N (%)			< 0.001
NSTEMI	1510 (67.90%)	752 (47.50%)	
STEMI	714 (32.10%)	831 (52.50%)	
Pulmonary infection, N (%)	548 (24.64%)	509 (32.15%)	< 0.001
Killip classification, N (%)			0.531
1	651 (29.27%)	470 (29.69%)	
2	816 (36.69%)	546 (34.49%)	
3	437 (19.65%)	331 (20.91%)	
4	320 (14.39%)	236 (14.91%)	
Treatment, N (%)			
PCI	1700 (76.44%)	1340 (84.65%)	< 0.001
Antiplatelet drugs	2195 (98.70%)	1571 (99.24%)	0.108
Number of antiplatelet agents			< 0.001
0	29 (1.30%)	12 (0.76%)	
1	82 (3.69%)	20 (1.26%)	
2	1628 (73.20%)	1155 (72.96%)	
3	444 (19.96%)	361 (22.80%)	
4	38 (1.71%)	34 (2.15%)	
5	3 (0.13%)	1 (0.06%)	
Statins	2193 (98.61%)	1568 (99.05%)	0.214
β-blockers	1950 (87.68%)	1418 (89.58%)	0.071
Novel oral anticoagulants	68 (3.06%)	49 (3.10%)	0.947
Warfarin	18 (0.81%)	9 (0.57%)	0.383
Antibiotics	569 (25.58%)	528 (33.35%)	< 0.001

Table 1. Baseline characteristics of recurrent myocardial infarction in patients with myocardial infarction. Categorical variables were presented as n (%). Values for continuous variables are given as means ± SD. BMI: Body mass index; COPD: Chronic Obstructive Pulmonary Disease; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro b-type natriuretic peptide; NSTEMI: Non-st-segment elevation myocardial infarction; STEMI: St-segment elevation myocardial infarction; PCI: percutaneous coronary intervention.

= 0.032). The mean body mass index (BMI) showed no significant difference between the RMI and non-RMI groups (19.74 ± 3.11 vs. 19.71 ± 3.04 , $P = 0.786$).

Regarding medical history, there were no statistically significant differences between the RMI and non-RMI groups for atrial fibrillation (9.22% vs. 8.63%, $P = 0.528$), valvular heart disease (19.08% vs. 18.84%, $P = 0.854$), hypertension (65.00% vs. 67.63%, $P = 0.091$), diabetes (31.84% vs. 34.67%, $P = 0.068$), chronic obstructive pulmonary disease (COPD) (21.29% vs. 20.50%, $P = 0.557$), renal insufficiency (22.99% vs. 21.18%, $P = 0.182$), and stroke (16.42% vs. 16.86%, $P = 0.721$). However, the incidence of previous MI was significantly lower in the RMI group compared to the non-RMI group (3.41% vs. 7.46%, $P < 0.001$).

Regarding clinical condition at admission, the left ventricular ejection fraction (LVEF) was significantly lower in the RMI group compared to the non-RMI group (51.47% vs. 53.70%, $P < 0.001$). Levels of N-terminal pro-B-type natriuretic peptide (NTproBNP) were significantly higher in the RMI group than in the non-RMI group (4110.36 ± 8008.28 pg/mL vs. 3210.11 ± 6690.12 pg/mL, $P < 0.001$). Troponin T levels were also higher in the RMI group (3.17 ± 2.91 ng/mL vs. 2.89 ± 2.86 ng/mL, $P = 0.004$). Low-density lipoprotein (LDL) levels were significantly higher in the RMI group compared to the non-RMI group (2.81 ± 0.93 mmol/L vs. 2.70 ± 0.96 mmol/L, $P < 0.001$).

Regarding MI type, the proportion of non-ST-segment elevation myocardial infarction (NSTEMI) was significantly lower in the RMI group compared to the non-RMI group (47.50% vs. 67.90%), while the proportion of ST-segment elevation myocardial infarction (STEMI) was significantly higher in the RMI group (52.50% vs. 32.10%, $P < 0.001$). The incidence of pulmonary infection was also significantly higher in the RMI group compared to the non-RMI group (32.15% vs. 24.64%, $P < 0.001$).

In terms of treatment, the proportion of patients undergoing percutaneous coronary intervention (PCI) was significantly higher in the RMI group compared to the non-RMI group (84.65% vs. 76.44%, $P < 0.001$). The use of antibiotics was also significantly higher in the RMI group (33.35% vs. 25.58%, $P < 0.001$). There were no significant differences between the two groups regarding the use of antiplatelet drugs, statins, and beta-blockers.

In summary, patients with recurrent myocardial infarction exhibited significant differences in age, history of previous myocardial infarction, LVEF at admission, NTproBNP levels, troponin T levels, LDL levels, type of myocardial infarction, and incidence of pulmonary infection compared to those without recurrence. These differences suggest that patients with recurrent myocardial infarction may have higher risk characteristics.

Hypothesis testing and assumption checks

Supplementary Table 1 presents the results of hypothesis testing. The Shapiro-Wilk test for normality indicated that the residuals do not follow a normal distribution (P -value < 0.05). The Breusch-Pagan test for homoscedasticity showed the presence of heteroscedasticity (P -value < 0.05), meaning that the variance of the residuals changes with the fitted values. These results suggest that while the residuals are not normally distributed and there is heteroscedasticity in the model, these issues are typically addressed through model adjustments, and the analysis was conducted accordingly.

Multicollinearity assessment and VIF results

Supplementary Table 2 presents the VIF values for all variables. Most variables have low VIF values (below 10), indicating no significant multicollinearity. However, Beta-lactam antibiotics (VIF = 11.68) and Use of antibiotics (VIF = 10.78) have VIF values greater than 10. These variables, however, were not included in the multivariable regression analysis. Instead, Use of antibiotics was analyzed separately, so their impact on the model is minimal.

Model diagnostics: residuals and normality check

In Supplementary Fig. 1, the Residuals vs. Fitted Values plot is presented to assess the fit of the logistic regression model. The plot shows that the residuals (differences between observed and predicted values) are randomly distributed around zero, indicating that the model does not exhibit patterns of heteroscedasticity or misspecification. The absence of any discernible trend or curvature supports the validity of the model's assumptions regarding homoscedasticity.

Supplementary Fig. 2 shows the Q-Q plot of the residuals from the logistic regression model. This plot is used to test the normality of the residuals. The points closely align with the diagonal line, suggesting that the residuals are approximately normally distributed, which is a key assumption for logistic regression. Minor deviations from the line are expected, but no significant departure from normality is observed.

Multivariable logistic regression analysis

Table 2 presents the impact of pulmonary infection on outcomes based on multivariable logistic regression analysis. In the multivariable logistic regression analysis, the adverse outcome being analyzed was defined as the occurrence of RMI in patients with MI.

In Model A, which considers only the impact of pulmonary infection, results show that pulmonary infection significantly increases the risk of adverse outcomes in both NSTEMI (non-ST-segment elevation myocardial infarction) and STEMI (ST-segment elevation myocardial infarction) patients. Specifically, pulmonary infection was associated with a 1.47-fold increase in the risk of adverse outcomes in NSTEMI patients (OR = 1.47, 95% CI: 1.22–1.79, $P < 0.0001$), a 1.43-fold increase in STEMI patients (OR = 1.43, 95% CI: 1.15–1.80, $P = 0.0016$), and a 1.46-fold increase in the overall population (OR = 1.46, 95% CI: 1.26–1.69, $P < 0.0001$).

After adjusting for sex and age in Model B, pulmonary infection still significantly increased the risk of adverse outcomes in both NSTEMI and STEMI patients. Pulmonary infection was associated with a 1.48-fold increase in the risk of adverse outcomes in NSTEMI patients (OR = 1.48, 95% CI: 1.22–1.80, $P < 0.0001$), a 1.47-fold increase in STEMI patients (OR = 1.47, 95% CI: 1.17–1.85, $P = 0.0009$), and a 1.48-fold increase in the overall population (OR = 1.48, 95% CI: 1.28–1.72, $P < 0.0001$).

Exposure	NSTEMI		STEMI		Total	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Model A						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	1.47 (1.22, 1.79)	< 0.0001	1.43 (1.15, 1.80)	0.0016	1.46 (1.26, 1.69)	< 0.0001
Model B						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	1.48 (1.22, 1.80)	< 0.0001	1.47 (1.17, 1.85)	0.0009	1.48 (1.28, 1.72)	< 0.0001
Model C						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	1.35 (1.09, 1.66)	0.0052	1.50 (1.18, 1.92)	0.0011	1.42 (1.21, 1.66)	< 0.0001
Model D						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	1.23 (0.95, 1.58)	0.1164	1.21 (0.91, 1.61)	0.2004	1.22 (1.01, 1.47)	0.0429

Table 2. Impact of pulmonary infection on outcome events in the multivariate logistic regression analysis. Bold represent significant values ($p < 0.05$). Abbreviations: OR: odds Ratio; CI: confidence interval; Ref: reference. Model A adjust for: None. Model B adjust for: Sex; Age. Model C adjust for: Sex; Age; BMI; LVEF; NTproBNP; Troponin T; Low-Density Lipoprotein; PCI; Killip classification; Auricular fibrillation; Valvular heart disease; Previous myocardial infarction; Hypertension; Diabetes mellitus; COPD; Renal insufficiency; Stroke; Antiplatelet drugs; Number of antiplatelet agents; Statins; β -blockers; Novel oral anticoagulants; Warfarin. Model D adjust for: Antibiotics.

In Model C, further adjustments were made for sex, age, BMI, LVEF, NTproBNP, troponin T, LDL, PCI, Killip classification, atrial fibrillation, valvular heart disease, previous MI, hypertension, diabetes, COPD, renal insufficiency, stroke, antiplatelet drugs, number of antiplatelet drugs, statins, beta-blockers, novel oral anticoagulants, and warfarin. The results still showed that pulmonary infection significantly increased the risk of adverse outcomes in NSTEMI and STEMI patients. Pulmonary infection was associated with a 1.35-fold increase in the risk of adverse outcomes in NSTEMI patients (OR = 1.35, 95% CI: 1.09–1.66, $P = 0.0052$), a 1.50-fold increase in STEMI patients (OR = 1.50, 95% CI: 1.18–1.92, $P = 0.0011$), and a 1.42-fold increase in the overall population (OR = 1.42, 95% CI: 1.21–1.66, $P < 0.0001$).

In Model D, which further adjusted for antibiotic use, the impact of pulmonary infection on the risk of adverse outcomes in NSTEMI and STEMI patients was reduced. Pulmonary infection was not significantly associated with an increased risk of adverse outcomes in NSTEMI patients (OR = 1.23, 95% CI: 0.95–1.58, $P = 0.1164$) or STEMI patients (OR = 1.21, 95% CI: 0.91–1.61, $P = 0.2004$). However, in the overall population, pulmonary infection still significantly increased the risk of adverse outcomes (OR = 1.22, 95% CI: 1.01–1.47, $P = 0.0429$).

In summary, the multivariable logistic regression analysis showed that pulmonary infection significantly increases the risk of adverse outcomes in MI patients, especially when antibiotic use is not adjusted for.

Propensity score matching analysis

Table 3 shows the baseline characteristics of patients with and without pulmonary infection before and after propensity score matching (PSM). In the PSM analysis, adverse outcomes refer to the RMI in patients.

Before PSM, there were significant differences in several baseline characteristics between the pulmonary infection group ($N = 1057$) and the non-pulmonary infection group ($N = 2750$). The proportion of males was significantly lower in the pulmonary infection group (68.21% vs. 72.55%, $P = 0.008$), and the mean age was higher (69.24 ± 11.49 years vs. 64.84 ± 12.17 years, $P < 0.001$). The pulmonary infection group had a lower BMI (19.41 ± 3.07 kg/m² vs. 19.84 ± 3.06 kg/m², $P < 0.001$) and higher rates of atrial fibrillation (13.43% vs. 7.13%, $P < 0.001$), valvular heart disease (22.33% vs. 17.64%, $P < 0.001$), diabetes (40.11% vs. 30.95%, $P < 0.001$), renal insufficiency (33.68% vs. 17.42%, $P < 0.001$), and stroke (22.80% vs. 14.33%, $P < 0.001$).

There were also significant differences in clinical conditions at admission. The pulmonary infection group had a lower left ventricular ejection fraction (LVEF) ($49.95 \pm 12.46\%$ vs. $53.85 \pm 11.49\%$, $P < 0.001$), higher NTproBNP levels (5801.94 ± 9238.93 pg/ml vs. 2732.12 ± 6161.71 pg/ml, $P < 0.001$), higher troponin T levels (3.16 ± 2.97 ng/mL vs. 2.95 ± 2.85 ng/mL, $P = 0.037$), and lower low-density lipoprotein (LDL) levels (2.67 ± 0.95 mmol/L vs. 2.77 ± 0.95 mmol/L, $P = 0.002$). There was no significant difference in the proportion of NSTEMI and STEMI patients between the groups (58.47% vs. 59.78%, $P = 0.460$), but the pulmonary infection group had a higher proportion of patients with higher Killip class ($P < 0.001$).

Regarding treatment, the pulmonary infection group had a lower proportion of patients undergoing PCI (73.60% vs. 82.25%, $P < 0.001$) and lower use of antiplatelet drugs (98.30% vs. 99.16%, $P = 0.020$) and statins

	Pulmonary infection status(Before PSM)			Pulmonary infection status(After PSM)		
	NO N = 2750	YES N = 1057	P value	NO N = 1026	YES N = 1026	P value
Demographics						
Male, N (%)	1995 (72.55%)	721 (68.21%)	0.008	696 (67.8)	704 (68.6)	0.740
Age, years	64.84 ± 12.17	69.24 ± 11.49	< 0.001	68.20 ± 11.87	69.03 ± 11.54	0.109
BMI, kg/m ²	19.84 ± 3.06	19.41 ± 3.07	< 0.001	19.36 ± 3.05	19.42 ± 3.06	0.648
Medical history, N (%)						
Auricular fibrillation	196 (7.13%)	142 (13.43%)	< 0.001	109 (10.6)	127 (12.4)	0.240
Valvular heart disease	485 (17.64%)	236 (22.33%)	< 0.001	223 (21.7)	230 (22.4)	0.750
Previous myocardial infarction	147 (5.35%)	73 (6.91%)	0.065	70 (6.8)	67 (6.5)	0.860
Hypertension	1817 (66.07%)	716 (67.74%)	0.329	681 (66.4)	690 (67.3)	0.708
Diabetes mellitus	851 (30.95%)	424 (40.11%)	< 0.001	367 (35.8)	410 (40)	0.056
COPD	569 (20.69%)	224 (21.19%)	0.733	224 (21.8)	218 (21.2)	0.788
Renal insufficiency	479 (17.42%)	356 (33.68%)	< 0.001	293 (28.6)	330 (32.2)	0.084
Stroke	394 (14.33%)	241 (22.80%)	< 0.001	214 (20.9)	224 (21.8)	0.628
Clinical conditions at admission						
LVEF, %	53.85 ± 11.49	49.95 ± 12.46	< 0.001	50.78 ± 12.18	50.26 ± 12.34	0.343
NTproBNP, pg/ml	2732.12 ± 6161.71	5801.94 ± 9238.93	< 0.001	4747.07 ± 8467.84	5396.87 ± 8763.20	0.088
Troponin T, ng/mL	2.95 ± 2.85	3.16 ± 2.97	0.037	3.04 ± 2.93	3.14 ± 2.95	0.446
Low-density lipoprotein, mmol/L	2.77 ± 0.95	2.67 ± 0.95	0.002	2.72 ± 0.97	2.67 ± 0.96	0.245
Myocardial infarction classification, N (%)			0.460			0.323
NSTEMI	1644 (59.78%)	618 (58.47%)		621 (60.5)	598 (58.3)	
STEMI	1106 (40.22%)	439 (41.53%)		405 (39.5)	428 (41.7)	
Killip classification, N (%)			< 0.001			0.223
1	915 (33.27%)	206 (19.49%)		233 (22.7)	206 (20.1)	
2	993 (36.11%)	369 (34.91%)		358 (34.9)	366 (35.7)	
3	529 (19.24%)	239 (22.61%)		245 (23.9)	233 (22.7)	
4	313 (11.38%)	243 (22.99%)		190 (18.5)	221 (21.5)	
Treatment, N (%)						
PCI	2262 (82.25%)	778 (73.60%)	< 0.001	770 (75)	764 (74.5)	0.799
Antiplatelet drugs	2727 (99.16%)	1039 (98.30%)	0.020	1011 (98.5)	1009 (98.3)	0.859
Number of antiplatelet agents			0.043			0.346
0	23 (0.84%)	18 (1.70%)		15 (1.5)	17 (1.7)	
1	65 (2.36%)	37 (3.50%)		25 (2.4)	34 (3.3)	
2	2034 (73.96%)	749 (70.86%)		764 (74.5)	726 (70.8)	
3	570 (20.73%)	235 (22.23%)		200 (19.5)	232 (22.6)	
4	55 (2.00%)	17 (1.61%)		20 (1.9)	16 (1.6)	
5	3 (0.11%)	1 (0.09%)		2 (0.2)	1 (0.1)	
Statins	2724 (99.05%)	1037 (98.11%)	0.017	1009 (98.3)	1009 (98.3)	1.000
β-blockers	2425 (88.18%)	943 (89.21%)	0.372	913 (89)	916 (89.3)	0.887
Novel oral anticoagulants	67 (2.44%)	50 (4.73%)	< 0.001	39 (3.8)	44 (4.3)	0.654
Warfarin	17 (0.62%)	10 (0.95%)	0.280	6 (0.6)	10 (1)	0.452
Outcome event						
Recurrent myocardial infarction	1074 (39.05%)	509 (48.16%)	< 0.001	400 (39)	493 (48.1)	< 0.001
PSM for the variable 'antibiotic use'						
Variables not subjected to PSM	299 (10.87%)	798 (75.50%)	< 0.001	147 (14.3)	770 (75)	< 0.001
Variables subjected to PSM	299 (10.87%)	798 (75.50%)	< 0.001	299 (53.6)	299 (53.6)	1.000

Table 3. Baseline characteristics before and after propensity-score matching. Bold represent significant values ($p < 0.05$). PSM: Propensity-Score Matching; other abbreviations can be found in Table 1.

(98.11% vs. 99.05%, $P = 0.017$). The use of novel oral anticoagulants was higher in the pulmonary infection group (4.73% vs. 2.44%, $P < 0.001$).

After PSM, 1,026 patients were matched in each group. Post-matching, there were no significant differences in most baseline characteristics between the groups. The proportion of males (67.8% vs. 68.6%, $P = 0.740$) and mean age (69.03 ± 11.54 years vs. 68.20 ± 11.87 years, $P = 0.109$) were similar. There were no significant differences in BMI (19.42 ± 3.06 kg/m² vs. 19.36 ± 3.05 kg/m², $P = 0.648$), atrial fibrillation (12.4% vs. 10.6%, $P = 0.240$), valvular heart disease (22.4% vs. 21.7%, $P = 0.750$), previous MI (6.5% vs. 6.8%, $P = 0.860$), hypertension

(67.3% vs. 66.4%, $P = 0.708$), diabetes (40% vs. 35.8%, $P = 0.056$), COPD (21.2% vs. 21.8%, $P = 0.788$), renal insufficiency (32.2% vs. 28.6%, $P = 0.084$), and stroke (21.8% vs. 20.9%, $P = 0.628$).

Regarding clinical conditions at admission, there were no significant differences between the matched groups in LVEF ($50.26 \pm 12.34\%$ vs. $50.78 \pm 12.18\%$, $P = 0.343$) or NTproBNP levels (5396.87 ± 8763.20 pg/ml vs. 4747.07 ± 8467.84 pg/ml, $P = 0.088$). There were also no significant differences in the proportion of NSTEMI and STEMI patients (58.3% vs. 60.5%, $P = 0.323$) or Killip class ($P = 0.223$).

In terms of treatment, there were no significant differences between the matched groups in the proportion of patients undergoing PCI (74.5% vs. 75%, $P = 0.799$), use of antiplatelet drugs (98.3% vs. 98.5%, $P = 0.859$), or use of statins (98.3% vs. 98.3%, $P = 1.000$).

In summary, after PSM, the pulmonary infection and non-pulmonary infection groups were well-balanced in most baseline characteristics, reducing the impact of potential confounders and making the subsequent analysis more reliable.

Outcomes in propensity score matching analysis

Table 4 presents the impact of pulmonary infection on outcomes in the propensity score matching (PSM) analysis.

In the analysis without matching for antibiotic use, pulmonary infection significantly increased the risk of adverse outcomes in both NSTEMI (non-ST-segment elevation myocardial infarction) and STEMI (ST-segment elevation myocardial infarction) patients. Specifically, for NSTEMI patients, pulmonary infection increased the risk of adverse outcomes by 1.41 times (OR = 1.41, 95% CI: 1.12–1.79, $P = 0.004$); for STEMI patients, the risk increased by 1.48 times (OR = 1.48, 95% CI: 1.13–1.95, $P = 0.0051$); and in the overall population, the risk increased by 1.44 times (OR = 1.44, 95% CI: 1.21–1.72, $P < 0.0001$).

In the analysis with matching for antibiotic use, the impact of pulmonary infection on adverse outcomes was reduced and no longer significant. For NSTEMI patients, pulmonary infection was not significantly associated with the risk of adverse outcomes (OR = 0.91, 95% CI: 0.57–1.45, $P = 0.691$); for STEMI patients, there was also no significant association (OR = 1.06, 95% CI: 0.80–1.41, $P = 0.6925$); and in the overall population, there was no significant association either (OR = 1.02, 95% CI: 0.80–1.29, $P = 0.8966$).

These results indicate that pulmonary infection significantly increases the risk of adverse outcomes in myocardial infarction patients when antibiotic use is not adjusted for. However, when considering antibiotic use, the impact of pulmonary infection on adverse outcomes is no longer significant, suggesting that antibiotic use may play a role in modulating the effect of pulmonary infection on the prognosis of myocardial infarction patients.

Kaplan-Meier survival analysis

Figure 2 shows the Kaplan-Meier survival curves for patients with STEMI (A) and NSTEMI (B), stratified by the presence or absence of pulmonary infection. The curves depict the probability of being free from recurrent myocardial infarction over time for both groups.

Figure 2A demonstrates that for STEMI patients, those with pulmonary infection (red curve) had a significantly lower probability of being free from recurrent myocardial infarction compared to those without pulmonary infection (blue curve) ($P < 0.0001$). The survival probability for the pulmonary infection group remained lower than that of the non-infection group throughout the entire follow-up period.

Figure 2B shows that for NSTEMI patients, those with pulmonary infection (red curve) also had a significantly lower probability of being free from recurrent myocardial infarction compared to those without pulmonary infection (blue curve) ($P < 0.0001$). Similar to STEMI patients, the survival probability for the pulmonary infection group in NSTEMI patients remained lower than that of the non-infection group throughout the follow-up period.

These results indicate that pulmonary infection significantly increases the risk of recurrent myocardial infarction in both STEMI and NSTEMI patients, further supporting the adverse impact of pulmonary infection on the prognosis of myocardial infarction patients.

	NSTEMI		STEMI		Total	
'Antibiotic use' is not added to match						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	1.41 (1.12, 1.79)	0.004	1.48 (1.13, 1.95)	0.0051	1.44 (1.21, 1.72)	< 0.0001
Added 'Antibiotic use' to match						
Pulmonary infection						
NO	Ref.		Ref.		Ref.	
YES	0.91 (0.57, 1.45)	0.691	1.06 (0.80, 1.41)	0.6925	1.02 (0.80, 1.29)	0.8966

Table 4. Impact of pulmonary infection on outcome events in the propensity-score matching analysis. Bold represent significant values ($p < 0.05$). Abbreviations can be found in Table 1.

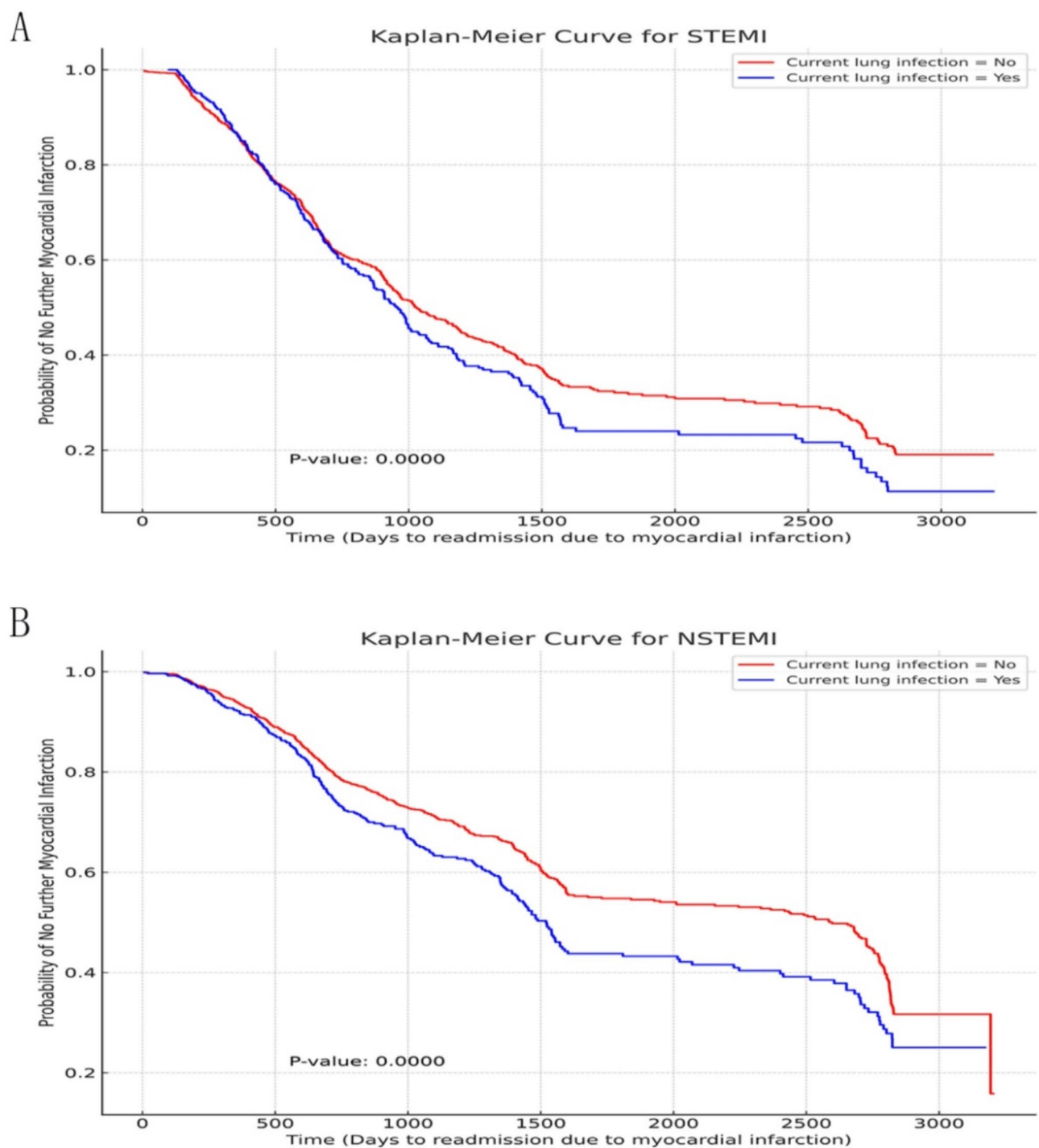


Fig. 2. Kaplan-Meier survival analysis showing the probability of being free from recurrent myocardial infarction in patients with STEMI and NSTEMI with and without pulmonary infection. **(A)** STEMI patients: red curve indicates those with pulmonary infection, blue curve indicates those without. Pulmonary infection significantly reduces the probability ($P = 0.0000$). **(B)** NSTEMI patients: red curve indicates those with pulmonary infection, blue curve indicates those without. Pulmonary infection significantly reduces the probability ($P = 0.0000$).

Impact of different antibiotics on recurrent myocardial infarction

Figure 3 shows the impact of different antibiotics on rehospitalization due to myocardial infarction, presenting the regression coefficient values for various antibiotics.

The data indicate significant differences in the impact of different antibiotics on the risk of rehospitalization in myocardial infarction patients. Notably, the use of quinolone antibiotics is associated with an increased risk of

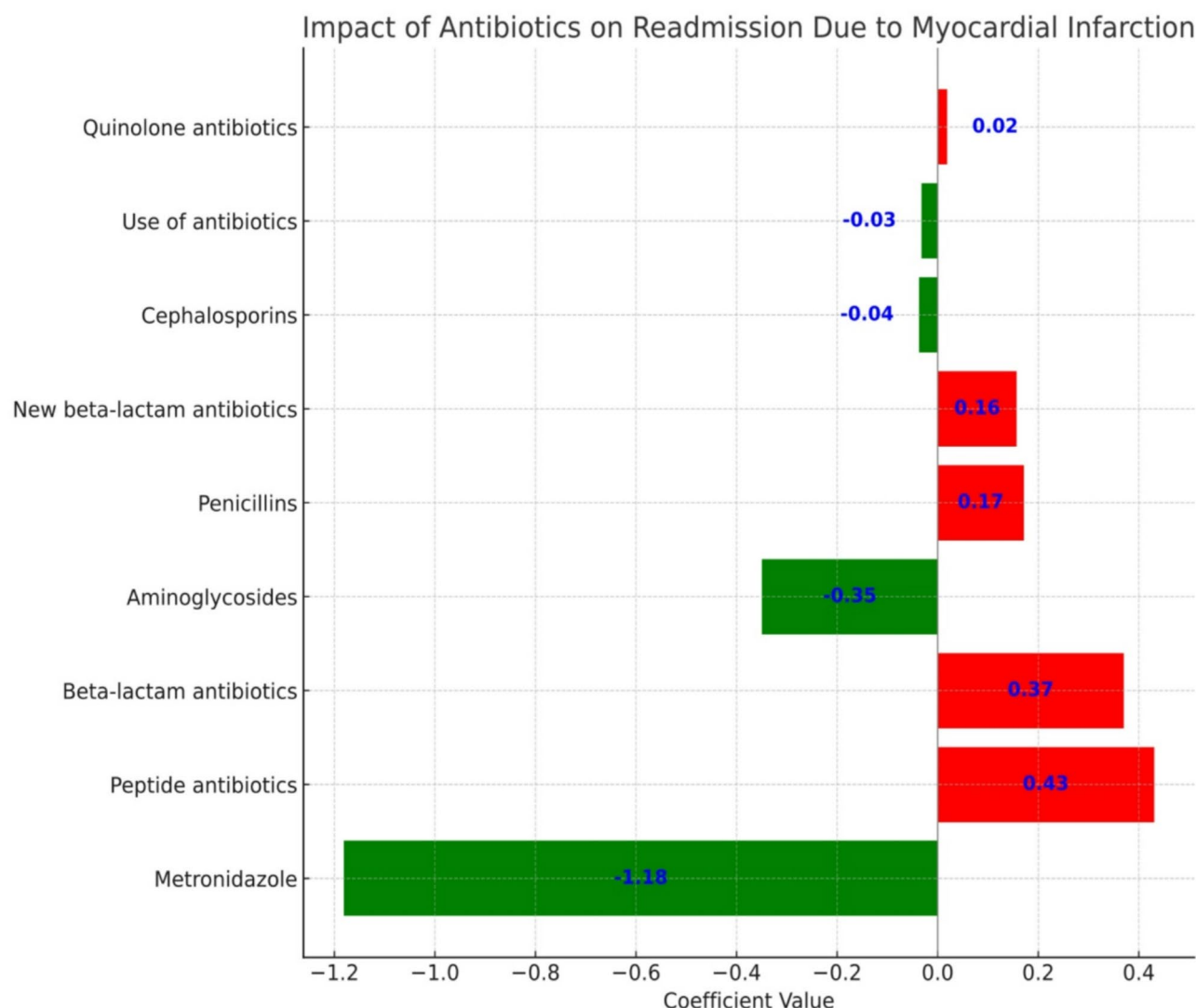


Fig. 3. The impact of different antibiotics on rehospitalization due to myocardial infarction.

rehospitalization (coefficient = 0.02), whereas the use of cephalosporin antibiotics (coefficient = -0.04) and other antibiotics (coefficient = -0.03) is associated with a reduced risk.

Among specific antibiotic categories, the use of new beta-lactam antibiotics (coefficient = 0.16) and penicillin antibiotics (coefficient = 0.17) is significantly associated with an increased risk of rehospitalization. Conversely, the use of aminoglycoside antibiotics (coefficient = -0.35) and nitroimidazole antibiotics (such as metronidazole, coefficient = -1.18) significantly reduces the risk of rehospitalization.

The use of beta-lactam antibiotics (coefficient = 0.37) and peptide antibiotics (coefficient = 0.43) is also significantly associated with an increased risk of rehospitalization.

These results suggest that different types of antibiotics have varying effects on the risk of rehospitalization in myocardial infarction patients. This variation should be considered in clinical treatment to optimize patient management strategies.

Discussion

This study systematically evaluated the impact of pulmonary infection and antibiotic use on the risk of recurrent myocardial infarction (RMI) in patients with myocardial infarction (MI). We found that pulmonary infection significantly increased the risk of RMI, and antibiotic use played a crucial role in modulating this risk.

Firstly, the analysis of baseline characteristics revealed significant differences between the pulmonary infection group and the non-infection group in terms of age, BMI, medical history, and clinical conditions at admission. These differences could influence the risk of RMI, so we adjusted for these potential confounders in the multivariable analysis. The results showed that pulmonary infection significantly increased the risk of RMI in both NSTEMI and STEMI patients, consistent with previous studies^{11,12}. Pulmonary infection may increase the risk of cardiovascular events by exacerbating systemic inflammation and cardiac load^{8,13–15}. This inflammatory response contributes to endothelial dysfunction, which impairs vascular reactivity and increases

vascular resistance¹⁶. Additionally, pulmonary infection induces myocardial stress through augmented cytokine release and changes in cardiac workload, further heightening the risk of recurrent myocardial infarction¹⁷.

Secondly, the propensity score matching (PSM) analysis further confirmed the impact of pulmonary infection on the risk of recurrent myocardial infarction (RMI). After matching, the baseline characteristics of the two groups were balanced, reducing the influence of potential confounders. The matching analysis showed that, without adjusting for antibiotic use, pulmonary infection significantly increased the risk of RMI. However, when adjusting for antibiotic use, the impact of pulmonary infection on RMI was no longer significant, suggesting that antibiotic use plays a crucial role in modulating this risk. This is consistent with studies that have shown antibiotics' potential to reduce inflammation and improve cardiovascular outcomes. For instance, certain antibiotics, such as macrolides, have been found to decrease systemic inflammation, which can mitigate the negative cardiovascular effects associated with infection¹⁸. On the other hand, other studies have pointed out that some antibiotics, such as quinolones, may exacerbate cardiovascular risks^{19,20}.

Therefore, this study analyzed the impact of different antibiotics on the risk of RMI. The results showed that the use of quinolone antibiotics was associated with an increased risk of rehospitalization, while cephalosporin and nitroimidazole antibiotics were associated with a reduced risk. This finding is consistent with some studies, suggesting that different types of antibiotics may have varying effects on the cardiovascular system when treating pulmonary infections^{9,10}. For example, quinolone antibiotics have been reported to be associated with QT interval prolongation and arrhythmias^{19,20}, while cephalosporin antibiotics^{21,22}, aminoglycoside antibiotics²³, and nitroimidazole antibiotics²⁴ have been less frequently associated with cardiovascular adverse events. Additionally, this study also found that beta-lactam antibiotics and penicillin antibiotics were associated with an increased risk of RMI, which is consistent with previous reports^{25,26}. Given the varying effects of these antibiotics on MI patients, this study suggests that the type of antibiotic selected when managing MI patients with concurrent pulmonary infections should be carefully considered, as it may influence their cardiovascular outcomes.

Limitations and clinical significance

However, this study has several limitations. First, as a retrospective study, despite our efforts to adjust for potential confounding factors, we cannot completely rule out all possible confounders. Second, the data were sourced from a single center, which may introduce selection bias, and thus the generalizability of the results should be approached with caution. Finally, the information on antibiotic use was based on electronic medical records, which may be incomplete or inaccurate.

Despite these limitations, the study has important clinical implications. The results indicate that pulmonary infection significantly increases the risk of RMI in MI patients, and antibiotic use plays a crucial role in modulating this risk. This suggests that clinicians should closely monitor for pulmonary infections in MI patients and make informed antibiotic choices to minimize the risk of RMI and improve long-term patient outcomes.

Conclusion

This study systematically evaluated the impact of pulmonary infection and antibiotic use on the risk of RMI in MI patients. The findings demonstrate that pulmonary infection significantly increases the risk of RMI, and antibiotic use is crucial in modulating this risk. These insights provide clinicians with a new perspective on managing MI patients, emphasizing the need to consider antibiotic selection carefully when treating pulmonary infections to optimize treatment outcomes and improve patient prognosis.

Data availability

The datasets generated and analyzed during the current study are not publicly available due the database owner is reluctant to make them public but are available from the corresponding author upon reasonable request.

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Author contributions

Zc.L., Z.G. and L.P.: established the hypothesis, performed the statistical analysis, wrote the manuscript. X.H., L.Y., C.H., K.G., H.L., L.G., Y.L., L.P., and Jp.Z.: interpreted statistical analysis and conducted multivariate analysis. Zc.L.: data collection and participated follow-up. My.J.: initiated the study hypothesis, edited the manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Xiangtan Central Hospital (Xiangtan, China, No.2023-02-001) and conformed to the principles outlined in the Declaration of Helsinki. The need for informed consent was waived by the ethics committee Review Board of Xiangtan Central Hospital, because of the retrospective nature of the study.

Additional information

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