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Limited effect of antibiotic use on the management of pulmonary ground-glass nodules

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Although pulmonary ground-glass nodules (GGNs) are encountered as common incidental findings, limited evidence exists regarding antibiotic prescriptions in managing GGNs. This study aimed to examine the clinical impact of antibiotics in treating patients presenting with GGNs. This retrospective study was conducted at West China Hospital of Sichuan University, involving 2,609 participants with incidentally detected GGNs between August 10, 2018 and July 22, 2022. Treatments were classified into antibiotic prescription versus no antibiotic prescription. Baseline characteristics and incidences of clinical outcomes (surgical resection, lung cancer diagnosis, beneficial response, and GGN growth) were evaluated. Of the 867 participants finally analyzed (184 antibiotic users; 683 antibiotic non-users), 85.2% were never smokers, and 34.7% presented with respiratory symptoms. The decision to prescribe antibiotics was correlated with the presence of symptoms and larger nodules. After propensity score matching, a higher incidence of surgical resection was observed in antibiotic users versus matched controls (40.8% vs. 29.9%, $p = 0.049$), whereas there was a trend toward an increased rate of lung cancer diagnosis, which was not statistically significant (32.6% vs. 22.8%, $p = 0.054$). Significant differences in radiographic response were not found, even among patients with suspected infection. In conclusion, limited beneficial effects of antibiotic use in the management of GGNs were observed, even among patients with suspected infection. These findings do not support empiric antibiotic administration in GGNs and call for efforts to develop outpatient antibiotic stewardship programs.

Keywords Antibiotics, Pulmonary ground-glass nodule, Surgical resection, Lung cancer diagnosis, Imaging feature

Abbreviations

BMI	body mass index
CT	computed tomography
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CEA	carcinoembryonic antigen
CA-125	cancer antigen 125
CA19-9	carbohydrate antigen 19-9
CYFRA21-1	cytokeratin 19 fragment
GGN	ground-glass nodule
HR	hazard ratio
IQR	interquartile range
LDCT	low-dose computed tomography
Lung-RADS	Lung CT Screening Reporting and Data System
LUL	left upper lobe
LLL	left lower lobe
NSE	neuron specific enolase

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RUL	right upper lobe
RML	right middle lobe
RLL	right lower lobe
SMD	standardized mean difference

The extensive application of low-dose computed tomography (LDCT) has led to a drastic increase in the detection rate of pulmonary ground-glass nodules (GGNs), including pure GGNs and part-solid nodules[1–3]. GGNs are identified in a notable proportion of patients subjected to chest CT, with a higher prevalence in females and non-smokers in Asia[4,5]. Although the majority of GGNs are transient and likely inflammatory[2,3], persistent cases overwhelmingly indicate invasive adenocarcinoma or its precursors, such as atypical adenomatous hyperplasia and adenocarcinoma in situ[6–8]. As GGNs have an indolent behavior[9–11]but a high risk of malignancy[7,8,12], clinicians often encounter a clinical dilemma in accurately distinguishing the malignancies while avoiding overdiagnosis and overtreatment.

With the hope of avoiding unnecessary interventions, some experts advocate for the empirical use of antibiotic therapy in order to accumulate additional evidence for subsequent clinical decision-making. Clinical practice guidelines in Asia recommend considering empirical use of antibiotics if bacterial infection is suspected at the time of detecting pulmonary nodules[12]. However, the associations between antimicrobial therapy and the improvement in the appearance of lung nodules have only been analyzed in one observational study with a small sample size, and no firm association was proven[13]. Clinical evidence regarding antibiotic use in the management of GGNs remains limited, and concerns regarding the potential for antibiotic resistance have arisen[14].

In this study, our purpose was to evaluate the impact of antibiotics on surgical resection, lung cancer diagnosis, and radiographic features of GGNs after their first detection. In addition, we assessed the potential factors influencing the decision-making process for prescribing antibiotics.

Methods

Study design and patients

We conducted a retrospective analysis of a prospectively collected pulmonary nodules database at West China Hospital of Sichuan University, the largest hospital in Western China. This ongoing cohort comprises patients with pulmonary nodules incidentally detected by chest CT scan between August 10, 2018 and July 22, 2022. Participants underwent thoracic CT scans for various reasons, including routine physical examination and lung cancer screening. The study cohort included adults (age ≥ 18 years) with pure GGNs or part-solid nodules. We excluded patients who: (1) underwent only one CT scan; (2) had GGNs with a size < 0.6 cm or > 3 cm in the initial CT evaluation; (3) received antibiotic treatment within 1 month before the initial CT evaluation; (4) underwent invasive biopsy or surgical resection within 1 month after the first detection; (5) had GGNs that remained stable for 3 years or more. Ethics approval was provided by the ethics committee of West China Hospital, Sichuan University (No. 2022-1965). The study was performed in accordance with the Declaration of Helsinki. Individual informed consent was waived for the retrospective study design using anonymized data.

Data sources and definitions

Electronic health records of patients with incidentally detected GGNs were retrieved from West China Hospital of Sichuan University. Follow-up information was prospectively collected from the pulmonary nodules/lung cancer comprehensive management platform established by West China Hospital of Sichuan University. The Integrated Care Management Centre team conducted comprehensive follow-up management for patients with pulmonary nodules at different risk levels and collected detailed regular follow-up data through the pulmonary nodules/lung cancer comprehensive management platform.

The following data were collected from electronic medical records: (1) demographic information, such as age, sex, and body mass index; (2) smoking status, categorized as never smoker or current/former smoker; (3) respiratory symptoms (cough, expectoration, hemoptysis, wheezing, chest pain, dyspnea, fever, night sweats, and weight loss); (4) medical history, including personal history of cancer (except for lung cancer) and family history of cancer; (5) comorbidities; (6) the dates of CT scans and imaging features; (7) laboratory test results; (8) follow-up information including surgical resection incidences, pathological diagnoses and radiographic changes (beneficial response and growth). The timeframe between the initial CT detection of GGNs and the first follow-up CT evaluation or occurrence of other clinical outcomes was also recorded.

All image data were reconstructed with a thickness ranging from 1 to 5 mm. Recorded imaging features of GGNs included the number of concurrent GGNs, nodule size, location, nodule type, solid component size, and the Lung CT Screening Reporting and Data System (Lung-RADS) category at the first CT detection. The size of a GGN was assessed by its maximum diameter using a lung window, while for part-solid nodules, measurements encompassed both the maximum diameter of the entire nodule and that of the solid component. In cases of synchronous multiple nodules, features were defined based on the largest lesions. The classification of pure GGNs and part-solid nodules relied on the CTR, defined as the ratio of the largest solid component size to the overall tumor size. Pure GGNs were identified by a CTR of 0 while part-solid nodules were characterized by a CTR of greater than 0 but less than 1[15,16]. All detected nodules were classified according to the Lung-RADS criteria (edition 1.1)[17]. Nodules with a Lung-RADS category below 3 were classified as negative, whereas those with a Lung-RADS category of 3 or 4 were considered positive[18]. All radiographic images were initially interpreted independently by two specialists comprising a pulmonary physician and a radiologist, and any conflict between them was resolved by consensus discussion.

Treatment strategies and follow-up

The interventions consisted of either antimicrobial therapy or no antimicrobial therapy. Treatment initiation occurred after the initial detection and before the first follow-up CT scan. Controls were selected from the cohort of participants diagnosed with GGNs who did not receive antibiotic therapy during the observation period, using propensity score matching at a 1:1 ratio. We prospectively collected clinical outcomes from the date of the initial CT evaluation until the occurrence of outcome events, the date of death, or the end of the observation period (February 5, 2024), whichever occurred first. Follow-up duration referred to the time between the first and the latest chest CT evaluation during which the same GGN was observed.

Outcomes

The primary outcomes comprised surgical resection and lung cancer diagnosis. We also assessed the beneficial response and GGN growth on the first follow-up CT scan as secondary outcomes. Decisions regarding surgical resection and pathological evaluations were made by pulmonary specialists, and all outcomes were obtained in routine clinical practice. The diagnosis of lung cancer was confirmed through histology from surgical resection or biopsy, according to the 2021 World Health Organization (WHO) classification[19]. The growth of a GGN was identified when one of the following conditions was recognized: 1) ≥ 2 mm increase in the diameter of a GGN; 2) ≥ 2 mm increase in the diameter of the solid component in cases of a part-solid GGN; 3) emergence of a new solid component within a pure GGN[20,21]. The decrease of a GGN was defined as a reduction in either the overall size or solid component of ≥ 2 mm since the first detection[6]. The beneficial response was defined as either the resolution or decrease[13]. Any other condition was classified as stable. No response was defined as either stable or growth on the first follow-up evaluation.

Baseline covariates

Baseline confounders of the patients included age, sex, smoking status (never and current/former), respiratory symptoms (yes and no), personal history of cancer (except for lung cancer), family history of cancer, nodule size, GGN pattern (pure GGNs and part-solid nodules), and Lung-RADS positive status (yes and no). Additionally, we identified laboratory test results and comorbidities at baseline that might influence the treatment and clinical outcomes. Further details of the baseline covariates along with their definitions were summarized in Table S1.

Statistical analysis

Baseline characteristics were summarized as medians and interquartile ranges (IQRs) for quantitative variables, and percentages for qualitative variables. Intergroup comparisons were performed by the Student t-test, the Mann-Whitney U test or the Pearson' s chi-squared test. Propensity score matching was conducted in a 1:1 ratio to mitigate selection bias and minimize the impact of confounding variables, with a caliper width of 0.2. The matching process included age, sex, smoking status, symptoms, personal history of cancer, family history of cancer, nodule size, and Lung-RADS positive status. Balance between groups was assessed utilizing standardized mean differences (SMDs), with an SMD below 0.1 indicating covariate balance[22]. Cox regression models were performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) and to compare the cumulative incidence of clinical outcomes during the follow-up period. Survival functions were developed using the Kaplan-Meier method, with group comparisons conducted utilizing the log-rank test. Subgroup analyses were further conducted to stratify the impact of antibiotics on populations with varying characteristics, including age (<65 years and ≥ 65 years), sex (male and female), the presence of symptoms (yes and no), GGN pattern (pure GGNs and part-solid nodules), and Lung-RADS positive status (yes and no). Given the potential for multiple comparisons, the findings from subgroup analyses should be considered exploratory. All statistical analyses were conducted using R version 4.2.1 and SPSS version 23.0. Statistical significance was defined as a p-value less than 0.05 (two-tailed).

Results

Baseline characteristics

A total of 2,609 patients with incidentally detected pulmonary ground-glass nodules were identified during a median follow-up period of 42.0 months (IQR, 37.0 to 47.0 months). After exclusions, 867 participants were finally enrolled in the study cohort, with 184 receiving antibiotic treatment and 683 not receiving antibiotics (Fig. 1). Table 1 presented the baseline characteristics before and after 1:1 propensity score matching for each group. The median age was 52.0 years (IQR, 44.0 to 61.0 years), with 68.1% being female and 85.2% being never smokers. Respiratory symptoms were observed in 34.7% of the patients and cough (26.9%) was the most common symptom, followed by expectoration (15.6%) and dyspnea (8.8%) (Table S2). Hypertension affected 14.3% of the participants, followed by asthma (4.7%) and chronic obstructive pulmonary disease (4.5%). 63.6% of the pulmonary ground-glass nodules were pure GGNs, and approximately 34.9% were identified as Lung-RADS positive. At baseline, 23.6% of the participants had a family history of cancer, and 5.0% had a personal history of cancer. Antibiotic users tended to present respiratory symptoms (58.7% vs. 28.3%, $p<0.001$), have larger nodules at the first detection (0.8 cm vs. 0.8 cm, $p=0.024$) and undergo a first follow-up CT scan sooner (3.0 months vs. 4.0 months, $p<0.001$) compared to non-users. For tumor markers, there were significant differences in NSE and CA19-9 levels between the two groups. After propensity score matching, our analysis eventually enrolled 184 antibiotic users and 184 matched controls, with baseline covariates well balanced between these two groups (Figure S1).

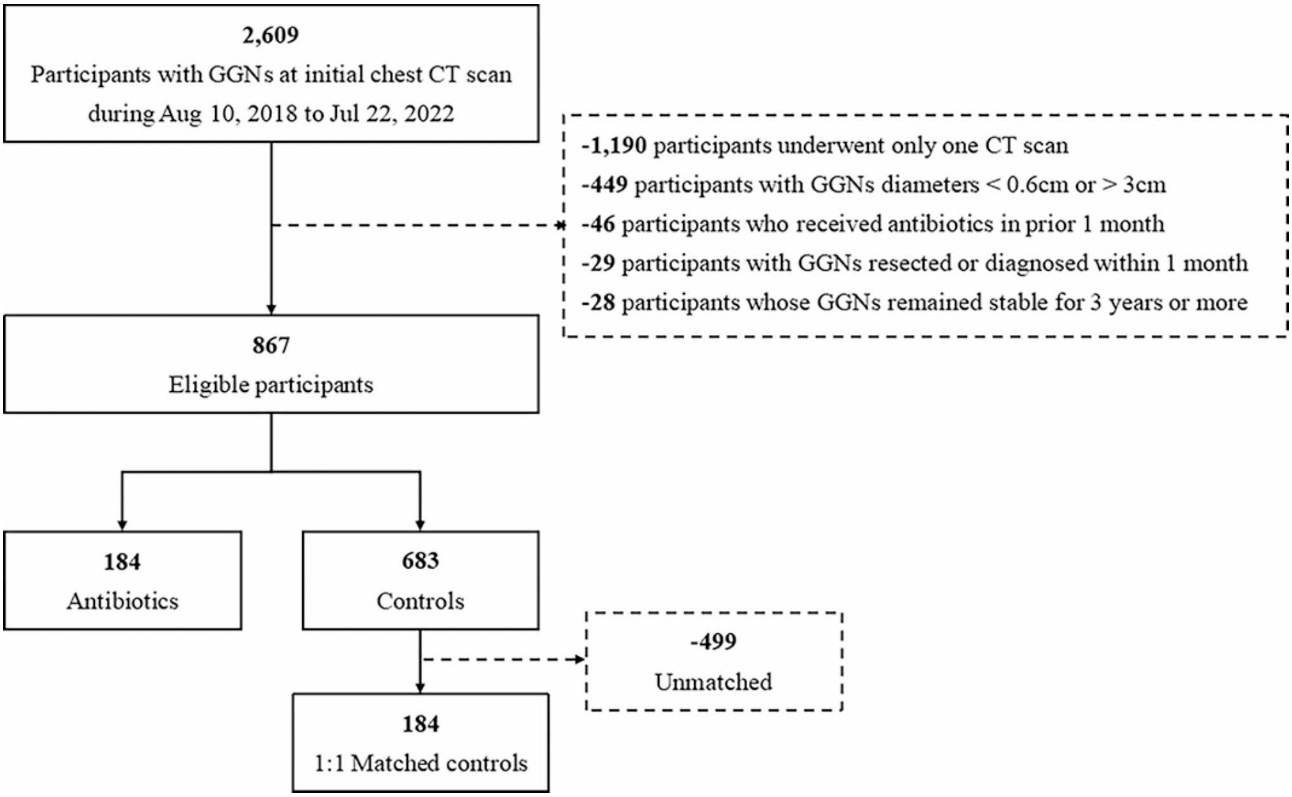

Fig. 1. Flowchart of construction of the cohort.

Clinical outcomes

The crude incidence rates of clinical outcomes were summarized in Table 2. Antibiotic prescription was associated with a significantly higher incidence of surgical resection compared to matched controls (40.8% vs. 29.9%, $p=0.049$), while there was a trend toward an increased rate of lung cancer diagnosis with no significant difference (32.6% vs. 22.8%, $p=0.054$). When evaluating nodules on the first follow-up CT scan, the rates of beneficial response (7.6% vs. 7.1%, $p=0.532$), GGN growth (9.2% vs. 7.6%, $p=0.205$), and stability (83.2% vs. 85.9%, $p=0.138$) did not significantly differ between these two groups. The cumulative incidences of clinical outcomes were presented in Fig. 2 and Figure S2. Compared to the control group, the HR of the antibiotics group for lung cancer diagnosis was 1.45 (0.98 to 2.16), while that for beneficial response was 1.27 (CI, 0.60 to 2.71). The characteristics of GGNs diagnosed with lung cancer were provided in Table S3. Among the 215 patients diagnosed with lung cancer, 95.8% experienced no response to antibiotic treatment on the first follow-up CT scan, and 47.4% were classified as having minimally invasive adenocarcinoma, followed by invasive adenocarcinoma (45.6%). Significant differences in the histological classification and imaging characteristics were not found between antibiotic users and non-users.

Subgroup analyses

According to the subgroup analyses of primary outcomes (Fig. 3), antibiotic recipients without respiratory symptoms were more likely to undergo subsequent surgical resection (HR, 1.96; CI, 1.12 to 3.42). Antibiotic recipients presenting with GGNs identified as Lung-RADS positive exhibited a higher probability of lung cancer diagnosis (HR, 1.92; CI, 1.06 to 3.47). The incidences of surgical resection and lung cancer diagnosis remained consistent across populations of varying age or sex. Furthermore, the probability of beneficial response and GGN growth did not vary by age, sex, presence of symptoms, GGN pattern, or Lung-RADS positive status (Figure S3). Among patients presenting with respiratory symptoms that suggested infection, no significant differences were observed between the two groups in all outcomes. Additionally, among patients showing a beneficial response on the first follow-up CT scan, the incidences of surgical resection and lung cancer diagnosis did not significantly differ between the groups (Table S4).

Discussion

In this study, we assessed the appearance of GGNs at baseline in participants who did and did not receive antibiotic treatment after initial detection, and followed up their CT screening and the incidences of clinical outcomes. We found that the rate of surgical resection was significantly higher among antibiotic recipients compared to matched controls, whereas there was a trend toward an increased incidence of lung cancer diagnosis, which was not significant. Radiographic responses, including beneficial response and GGN growth, did not significantly differ between the two groups, even among patients exhibiting respiratory symptoms that suggested infection.

Characteristics	Before matching				After 1:1 propensity score matching		
	Overall (*n* = 867)	Antibiotics (*n* = 184)	Controls (*n* = 683)	*P* value	Antibiotics (*n* = 184)	Controls (*n* = 184)	*P* value
Follow-up duration, months	42.0 (37.0, 47.0)	40.0 (36.0, 45.0)	42.0 (38.0, 47.0)	0.001	40.0 (36.0, 45.0)	42.0 (37.3, 46.0)	0.039
Age, years	52.0 (44.0, 61.0)	51.8 (42.6, 61.4)	52.0 (44.1, 60.6)	0.665	51.8 (42.6, 61.4)	52.0 (41.9, 60.0)	0.901
Male, n (%)	277 (31.9)	57 (31.0)	220 (32.2)	0.750	57 (31.0)	58 (31.5)	0.910
BMI, kg/m^2	22.6 (21.0, 24.1)	22.3 (21.0, 24.0)	22.7 (21.0, 24.1)	0.531	22.3 (21.0, 24.0)	22.7 (21.0, 24.2)	0.668
Smoking status, n (%)							
Never	739 (85.2)	154 (83.7)	585 (85.7)	0.507	154 (83.7)	153 (83.2)	0.889
Current or former	128 (14.8)	30 (16.3)	98 (14.3)		30 (16.3)	31 (16.8)	
Symptoms present, n (%)	301 (34.7)	108 (58.7)	193 (28.3)	< 0.001	108 (58.7)	106 (57.6)	0.833
Comorbidities							
Hypertension, n (%)	124 (14.3)	29 (15.8)	95 (14.3)	0.524	29 (15.8)	22 (12.0)	0.291
Asthma, n (%)	41 (4.7)	11 (6.0)	30 (4.4)	0.368	11 (6.0)	17 (9.2)	0.238
COPD, n (%)	39 (4.5)	13 (7.1)	26 (3.8)	0.058	13 (7.1)	8 (4.3)	0.261
Bronchiectasis, n (%)	27 (3.1)	6 (3.3)	21 (3.1)	0.897	6 (3.3)	11 (6.0)	0.214
Diabetes, n (%)	32 (3.7)	9 (4.9)	23 (3.4)	0.331	9 (4.9)	6 (3.3)	0.429
Personal history of cancer, n (%)	43 (5.0)	7 (3.8)	36 (5.3)	0.416	7 (3.8)	5 (2.7)	0.557
Family history of cancer, n (%)	205 (23.6)	50 (27.2)	105 (22.7)	0.204	50 (27.2)	48 (26.1)	0.814
Nodule number	2 (1, 3)	2 (1, 3)	2 (1, 3)	0.201	2 (1, 3)	2 (1, 3)	0.185
Nodule size, cm†	0.8 (0.7, 1.0)	0.8 (0.7, 1.1)	0.8 (0.7, 1.0)	0.024	0.8 (0.7, 1.1)	0.8 (0.7, 1.1)	0.811
GGN pattern, n (%)							
Pure	551 (63.6)	110 (59.8)	441 (64.6)	0.231	110 (59.8)	116 (63.0)	0.521
Part-solid	316 (36.4)	74 (40.2)	242 (35.4)		74 (40.2)	68 (37.0)	
Location, n (%)‡							
LUL	205 (23.6)	32 (17.4)	173 (25.3)	0.264	32 (17.4)	41 (22.3)	0.297
LLL	122 (14.1)	28 (15.2)	94 (13.8)		28 (15.2)	26 (14.1)	
RUL	313 (36.1)	71 (38.6)	242 (35.4)		71 (38.6)	79 (42.9)	
RML	64 (7.4)	16 (8.7)	48 (7.0)		16 (8.7)	15 (8.2)	
RLL	163 (18.8)	37 (20.1)	126 (18.5)		37 (20.1)	23 (12.5)	
Lung-RADS positive, n (%)††	303 (34.9)	71 (38.6)	232 (34.0)	0.243	71 (38.6)	65 (35.3)	0.517
First follow up CT scan interval, months	4.0 (2.0, 6.0)	3.0 (2.0, 5.0)	4.0 (3.0, 6.0)	< 0.001	3.0 (2.0, 5.0)	3.0 (3.0, 6.0)	0.010
Laboratory parameters							
CEA, ng/mL	1.69 (1.25, 2.20)	1.70 (1.19, 2.30)	1.69 (1.26, 2.17)	0.702	1.70 (1.19, 2.30)	1.67 (1.21, 2.22)	0.952
NSE, ng/mL	12.57 (11.53, 13.59)	12.00 (10.90, 13.17)	12.66 (11.80, 13.68)	< 0.001	12.00 (10.90, 13.17)	12.57 (11.65, 13.83)	0.003
CA-125, U/mL	13.33 (10.98, 16.62)	13.42 (10.88, 17.26)	13.32 (10.99, 16.45)	0.571	13.42 (10.88, 17.26)	13.56 (11.12, 16.89)	0.818
CA19-9, U/mL	10.79 (8.70, 13.20)	10.09 (8.52, 12.03)	10.93 (8.80, 13.62)	0.004	10.09 (8.52, 12.03)	10.90 (8.95, 13.32)	0.008
CYFRA21-1, ng/mL	1.87 (1.60, 2.22)	1.83 (1.55, 2.21)	1.88 (1.60, 2.22)	0.294	1.83 (1.55, 2.21)	1.89 (1.58, 2.18)	0.465

Table 1. Characteristics of the participants at baseline. Data are n (%) or median (IQR). Significant at $p < 0.05$. Abbreviations: IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GGN, ground-glass nodule; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; Lung-RADS, Lung CT Screening Reporting and Data System; CEA, carcinoembryonic antigen; NSE, neuron specific enolase; CA-125, cancer antigen 125; CA19-9, carbohydrate antigen 19- 9; CYFRA21-1, cytokeratin 19 fragment. †Nodule size refers to the longest diameter among the axial, coronal, and sagittal planes. ‡For multiple GGNs, the lobe of the largest GGN is indicated. ††Participants with Lung-RADS of 3, 4A, 4B, or 4X were classified as positive.

Notably, 95.8% of the participants diagnosed with lung cancer showed no response to antibiotic treatment on the first follow-up CT scan. To the best of our knowledge, this is the first observational study analyzing the effectiveness of antibiotics for pulmonary ground-glass nodules in China. Our findings indicated the limited impact of antibiotic administration on the management of GGNs, even in patients with suspected infection.

Current guidelines recommend a close follow-up approach with CT screening for managing GGNs due to their indolent clinical course[1,23,24], which may exacerbate patient concerns, such as radiation exposure, anxiety, and additional cost[25]. Consequently, patients often prefer alternative treatments such as antibiotic prescriptions, which they perceive to be safer and more cost-effective. Therefore, some experts have suggested the empirical use of antimicrobial therapy in cases of suspected bacterial infection, hoping to avoid unnecessary interventions[26]. Nevertheless, little is known about the factors contributing to clinicians' decision-making when prescribing antibiotics for patients presenting with GGNs. We assessed potential factors and found that the presence of respiratory symptoms and larger nodules may influence the decision to prescribe antibiotics, whereas a prior

Clinical outcomes	Controls ($n = 184$)	Antibiotics ($n = 184$)		
	n (%)	*n* (%)	HR (95% CI)	*P* value*
GGN that underwent surgical resection, n (%)	55 (29.9)	75 (40.8)	1.39 (0.98 to 1.97)	0.049
Diagnosed as lung cancer, n (%)	42 (22.8)	60 (32.6)	1.45 (0.98 to 2.16)	0.054
Nodule identified on first follow-up CT scan, n (%)				
Beneficial response†	13 (7.1)	14 (7.6)	1.27 (0.60 to 2.71)	0.532
Growth‡	14 (7.6)	17 (9.2)	1.45 (0.69 to 3.06)	0.205
Stable††	158 (85.9)	153 (83.2)	1.22 (0.97 to 1.52)	0.138

Table 2. Outcomes of ground-glass nodules after follow-up in antibiotics group vs. matched controls. Abbreviations: GGN, ground-glass nodule; CI, confidence interval; HR, hazard ratio. †Beneficial response was defined as either resolution or a decrease in the total size or solid component of ≥ 2 mm from the initial evaluation. ‡Growth was defined as an increase of 2 mm or more in total size or in the solid component, or an emerging a new solid component. ††Other conditions were defined as stable. *P value for log-rank test. Abbreviations: GGN, ground-glass nodule; CT, computed tomography. Abbreviations: HR, hazard ratio; CI, confidence interval; GGN, ground-glass nodule; Lung-RADS, Lung CT Screening Reporting and Data System.

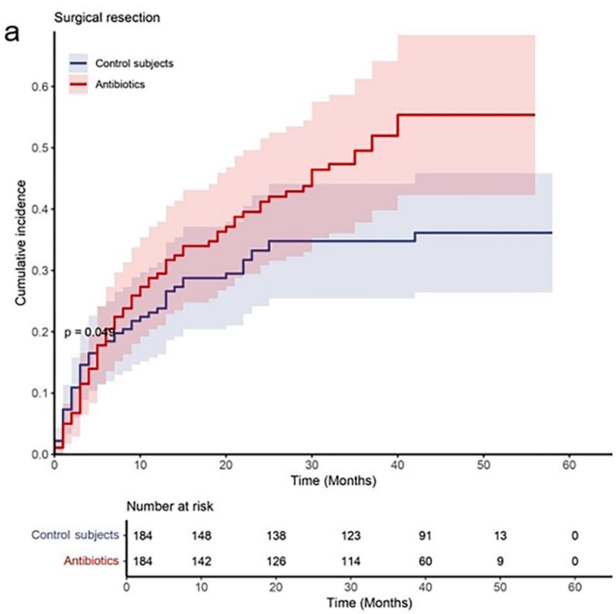

Fig. 2. Cumulative incidence of primary outcomes in study population. (**a**) Surgical resection; (**b**) Diagnosed as lung cancer.

study only observed an association with larger nodule size[13]. Notably, subjective physician judgment also played a significant role in this decision-making process, which potentially contributed to the conflicts. Additionally, baseline NSE and CA19-9 levels significantly differed between antibiotic users and non-users, which might be attributed to comorbidities and selection bias.

Despite the empirical administration of antibiotics in general practice, it remains unclear whether prescribing antibiotics for GGNs is clinically meaningful. In our study, we found that the rate of radiographic beneficial response was similar between antibiotic users and control subjects, consistent with prior reports[13]. Furthermore, we did not observe any beneficial effect associated with antibiotic prescription for GGNs, even among symptomatic patients deemed most likely to benefit from antibiotics. By contrast, antibiotic recipients were more likely to undergo subsequent surgical resection, and there was a trend toward an increased incidence of lung cancer diagnosis, especially in the Lung-RADS positive subgroup. One possible interpretation might be that antibiotic prescription could contribute to accumulating further evidence for clinical decision-making, such as surgical resection and lung cancer diagnosis, particularly in high-risk patients who exhibited no response to antimicrobial therapy. These results provided additional evidence for the findings of the previous nationwide study, which considered antibiotic exposure as a risk-enhancing factor for lung cancer[27]. Our findings indicated a limited clinical benefit of antibiotic prescription in patients presenting with pulmonary ground-glass nodules, which did not achieve the expected effect. Therefore, the empirical administration of antibiotics in patients with GGNs should be considered cautiously.

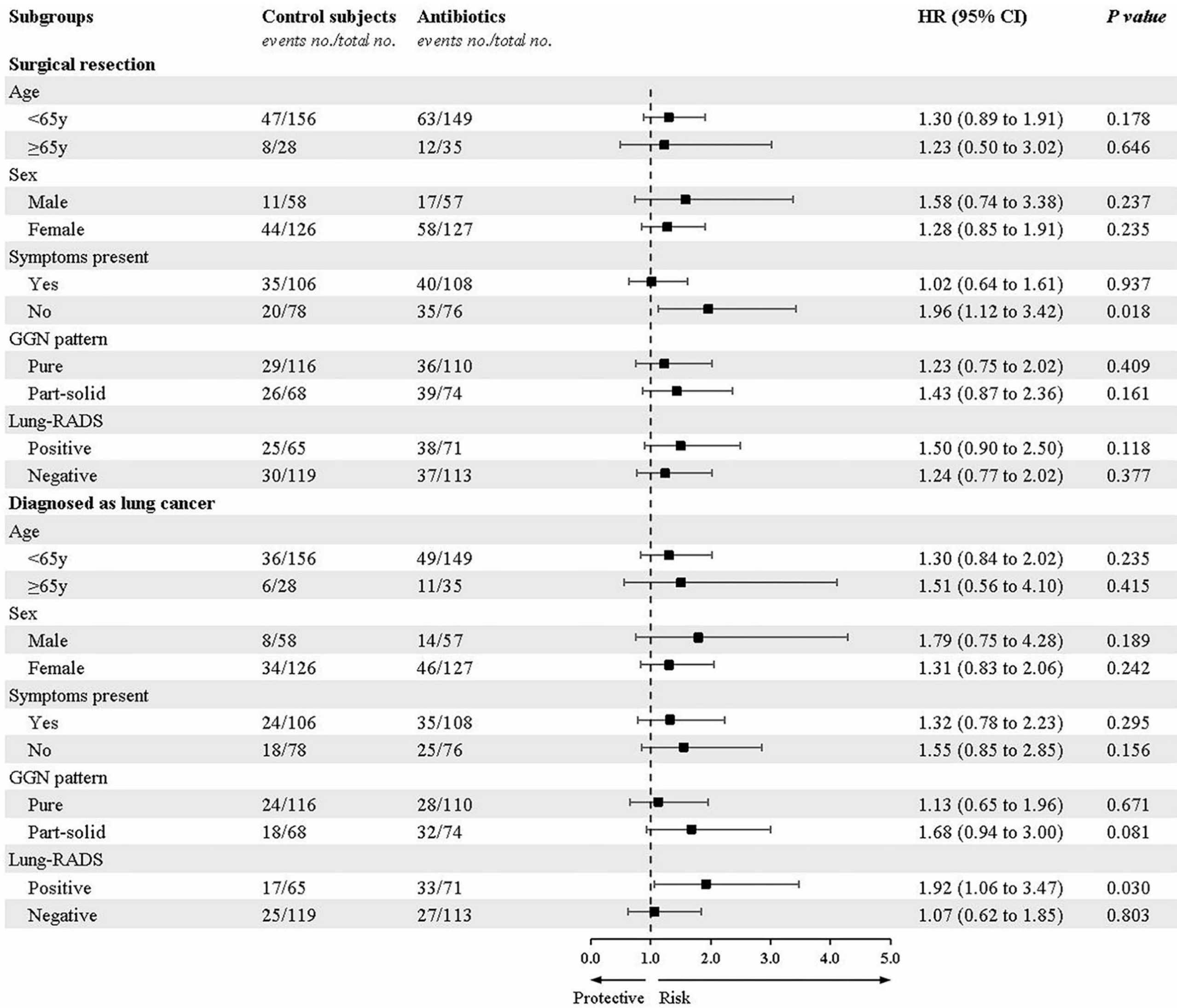

Fig. 3. Estimated relative risks of primary outcomes in subgroup analyses.

In our study, only 34.7% of the patients exhibited respiratory symptoms, indicating a notable proportion of patients received antimicrobial therapy when it was not recommended. Worldwide, China is one of the largest antibiotic consumers with inappropriate prescriptions higher than in western countries, and antibiotic use in China far exceeds the recommended level[28–31]. Our findings also reflected the clinical problem of antibiotic overuse in the real-world setting and emphasized the necessity for strict control over the administration of antibiotics in clinical practice. Although previous studies made efforts to select candidates for antibiotic prescription with potential benefits after the detection of lung nodules[32], there remains a lack of robust evidence supporting its clinical benefit. Consequently, there is a need for judicious antibiotic prescription and clinicians should prescribe antibiotics cautiously with thorough consideration of their potential detrimental effects. At the same time, patients should only take antibiotics under the guidance of clinicians, rather than taking antibiotics indiscriminately by themselves. Moreover, as retail pharmacies are among the main sources of acquiring antibiotics in China[33], there is an urgent need for the government to enhance the enforcement of regulations pertaining to antibiotic dispensation. We thus call for further studies involving antibiotic prescription in patients presenting with GGNs to develop antibiotic stewardship programs for them.

The main strength of this study is the collection of comprehensive, detailed, regular follow-up data from a large sample size of individuals presenting with GGNs. This is the first observational study evaluating the clinical impact of antimicrobial therapy on managing pulmonary ground-glass nodules in China. Our findings not only provide valuable insights for clinical decision-making, but also can optimize the antibiotic prescribing and the lung nodule management strategies.

This study has several limitations. First, it was a single-center retrospective study, which may be subject to potential selection bias. The CT screening intervals were not strictly controlled, and a significant proportion of patients underwent only one CT scan without subsequent follow-up. Moreover, the 3-year follow-up period may not be long enough for individuals presenting with GGNs. Therefore, further prospective studies with a larger sample size and extended follow-up periods are required to validate our results. Second, given the lack of standardized criteria and detailed prescription records for antibiotic use in outpatients, this study may not accurately represent the actual antibiotic intake and was unable to stratify the types of antibiotics used. Third, as this was a retrospective study, certain data, such as white blood cell count and C-reactive protein levels, were not consistently available in the outpatient setting. The lack of these data may limit our ability to fully differentiate whether the patient had an infection or not. In addition, not all GGNs suspected of malignancy were diagnosed due to their indolent clinical course and the prolonged follow-up period required. Thus, the incidences of surgical resection and diagnosed lung cancer might have been underestimated. Finally, the findings may not be generalized to other ethnicities and countries, as all participants included in our study were Chinese.

Conclusion
This retrospective study suggested that antibiotics were associated with a higher incidence of surgical resection in individuals presenting with pulmonary ground-glass nodules, and there was a trend toward an increased incidence of lung cancer diagnosis, which did not reach statistical significance. Little beneficial effect of antibiotic use in the management of GGNs was observed, even among patients with suspected infection. Therefore, this study cannot support the empirical use of antimicrobial therapy in patients with GGNs and calls for efforts to develop outpatient antibiotic stewardship programs.

Data availability
The data of this study are available on request by contacting the corresponding author.

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Author contributions

YL and DL had full access to all the data in this study and take responsibility for the integrity of the data and statistical analysis. YL and DL conceived and designed the study. YL, JZ, LY, HZ, YX, RX, and SL acquired the data. YL, JZ, JG, WL, and DL contributed substantially to manuscript writing, data interpretation and analysis.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

Ethics approval was provided by the ethics committee of West China Hospital, Sichuan University (No. 2022-1965). The patient informed consent was waived by the ethics committee of West China Hospital for the retrospective cohort study design utilizing anonymized data from electronic medical records.

Additional information

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