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Original Research Article

Clinico-epidemiological evaLuation of mAcrolide use In Respiratory tract infections (CLAIR): a retrospective study

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ABSTRACT

Background: Respiratory tract infections (RTIs) are frequently seen in clinical practice, and macrolides are widely used for their management in India. However, real-world evidence (RWE) on prescribing patterns and clinical outcomes with macrolide use in RTIs is still limited. This study evaluated utilization patterns and effectiveness of macrolides for RTIs using an electronic medical records (EMR) database.
Methods: This retrospective, observational, EMR-based study analysed anonymized HealthPlix EMR data from January 2017 to June 2025. Adult patients (≥18 years) prescribed erythromycin, roxithromycin, azithromycin, or clarithromycin with a documented follow-up within 20 days were included. Propensity score matching (PSM) was applied for comparative effectiveness analysis between azithromycin and clarithromycin.
Results: A total of 78,499 eligible RTI patients were analyzed. Azithromycin (N=64,638) and clarithromycin (N=12,448) were the most frequently prescribed macrolides. Most patients were aged <60 years. Across macrolides, fever, cold, and cough predominated in upper RTIs (URTIs) whereas cough and dyspnea in lower RTIs (LRTIs), with bronchitis being the most common LRTI diagnosis. Hypertension and diabetes mellitus were the most common comorbidities. A 5–7-day regimen predominated across macrolides. Following PSM (12,448 patients per cohort of azithromycin and clarithromycin), overall symptom resolution was significantly higher with clarithromycin than azithromycin (72.36% vs 64.33%; p<0.001), with similar findings in URTI (74.98% vs 61.15%) and LRTI (69.86% vs 67.36%) subgroups. Symptom resolution remained high after switching to clarithromycin from other antibiotics.
Conclusions: This study provides RWE on macrolide prescribing patterns in RTIs and demonstrates higher symptom resolution with clarithromycin than azithromycin in routine clinical practice.

Keywords: Macrolide, Upper and lower respiratory tract infections, Electronic medical records, Clinico-epidemiological characteristics, Symptom resolution

INTRODUCTION

RTIs are among the most common conditions encountered in routine clinical practice.[1] Their etiology, severity, clinical features, and outcome vary according to age, sex, season, population characteristics, and associated risk factors.[2] According to the National Health Portal of India (2019), acute respiratory infections constituted approximately 69% of reported communicable disease cases highlighting their significant public health burden in India.[3] Effective antimicrobial management is crucial for reducing the clinical and economic burden of RTIs. Macrolide antibiotics have been used for more than four decades in the management of RTIs.[4] Azithromycin, clarithromycin, roxithromycin, and erythromycin are commonly prescribed macrolides for respiratory conditions such as pneumonia, sinusitis, pharyngitis, and tonsillitis.[5,6] Macrolide antibiotics act as bacteriostatic agents by binding to the 50S ribosomal subunit of bacteria, thereby inhibiting bacterial protein synthesis. Their

immunomodulatory effects are mediated through interactions with phospholipids and transcription factors such as activator protein-1 (AP-1), nuclear factor-kappa B (NF-κB).[5] In addition to their primary antimicrobial effects, macrolides also exhibit anti-inflammatory and immunomodulatory effects, which may contribute to clinical benefit.[7] Despite the widespread use of macrolides in the management of RTIs, there is limited RWE characterizing prescribing patterns, patient profiles, and clinical outcomes, particularly across macrolide agents and RTI presentations. Most of the available evidence is based on controlled clinical trials or non-Indian populations and may therefore not fully reflect real-world clinical practice in India.[8]

Understanding the patient profile, dose strength, prescription duration, and clinical response is essential for optimizing therapeutic outcomes. While RCTs remain the gold standard for establishing efficacy and safety, their generalizability is often constrained by stringent eligibility criteria and controlled settings.[9,10] EMR represent an important source of RWD and enable systematic evaluation of patient characteristics, prescribing practices, and clinical outcomes across large and diverse populations.[9]

The present retrospective EMR-based study was conducted to characterize the clinico-epidemiological profile of patients prescribed clarithromycin, azithromycin, roxithromycin, or erythromycin for the management of RTIs and to evaluate real-world prescribing patterns and clinical effectiveness of macrolides.

METHODS

Study design

This retrospective, EMR-based observational RWE study evaluated aggregated and anonymized data of eligible patients obtained from the HealthPlix EMR database, which is widely used by physicians across India, spanning the period from January 2017 to June 2025.

The visit at which clarithromycin, azithromycin, roxithromycin or erythromycin was prescribed for RTI was considered as the baseline. The follow-up visit was defined as the most recent recorded visit within 20 days of baseline prescription. A visit occurring within the look-back period of 20 days prior to the baseline prescription of clarithromycin was considered the pre-baseline visit.

This study was conducted in accordance with the study protocol and applicable ethical regulatory standards. Ethical approval was obtained from the Central Independent Ethics Committee (CIEC) on 17 September 2025 (Approval No.: CIEC/2025/0304). A waiver of informed consent was granted in line with the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, as the study was retrospective in nature and analysed completely deidentified and anonymized data.

Eligibility criteria

Adult patients (≥18 years of age) prescribed Erythromycin (minimum duration: 5 to 10 days), Roxithromycin (≥5 days), Azithromycin (≥3 days) or Clarithromycin (≥5 days) with a follow-up documented within 20 days of prescription, were included in the study. Patients were excluded if they did not receive the minimum recommended duration of therapy or had clinical conditions that could potentially affect the effectiveness or gastrointestinal (GI) absorption of oral macrolides, including immunocompromised states, malignancy or malabsorption syndromes. Pregnant, lactating, and paediatric patients were also excluded.

Study outcomes

The primary objective was to evaluate clinico-epidemiological characteristics of patients prescribed macrolides for RTIs, including age, presenting symptoms, underlying etiologies, comorbidities, dose, duration of therapy and concomitant medications. The secondary objective was to assess the effectiveness of macrolides in upper RTIs (URTI) and lower RTIs (LRTI). Patients were considered clinically improved or resolved if any of the following criteria were met at the follow-up visit: Discontinuation of macrolide therapy with no initiation of another antibiotic at the same visit. Documentation of terms indicating improvement (e.g. “better”, “improved”, “resolved”, etc). Absence of previously documented RTI-related diagnoses or presenting symptoms at follow-up. Prescription of antibiotics for conditions unrelated to RTI

Effectiveness was assessed for overall URTI and LRTI categories, as well as for specific conditions such as pharyngitis, sinusitis, tonsillitis, otitis media, non-specific LRTI, acute exacerbation of chronic obstructive pulmonary disease (COPD) and asthma, pneumonia, and bronchiectasis. Exploratory endpoints included the evaluation of patients who were initially prescribed azithromycin or other antibiotics in the pre-baseline visit and were subsequently shifted to clarithromycin, along with assessment of their post-switch effectiveness.

Statistical analysis

Statistical analysis was performed using Stata version 15.1 SE. Continuous variables were summarized using the mean and standard deviation (SD). Categorical variables were presented as number (N) and percentage (%) of patients.

Assessment of effectiveness was performed at follow-up and was presented as N and Percentage of patients classified as resolved and unresolved. The statistical significance of differences in the proportion of resolution between clarithromycin and azithromycin cohorts was

evaluated using the Chi-square test at a 5% level of significance.

Given the retrospective nature of the study, potential baseline differences between treatment groups could confound comparisons of outcomes. To address this, propensity score matching (PSM) was performed to match patients in the azithromycin cohort to those in the clarithromycin cohort. Matching variables included age, diagnosis, and duration between baseline and follow-up. This approach was used to reduce selection bias and improve comparability between groups. The matched groups were subsequently compared for percentage resolution using Chi-square test. Roxithromycin and erythromycin cohorts had substantially smaller sample sizes compared to azithromycin and clarithromycin and were therefore not considered for PSM analysis. All analyses were conducted using available data, and no imputation was performed for missing values.

RESULTS

Patient disposition

Between January 2017 and June 2025, a total of 8,61,274 patients were prescribed macrolide antibiotics for RTIs on the HealthPlix EMR platform. Of these, 78,499 patients (9.11%) had a documented follow-up visit within 20 days of the macrolide prescription (clarithromycin, azithromycin, roxithromycin or erythromycin) and were included in the analysis.

In the azithromycin group (N=64,638), 44,660 patients (69.09%) presented with URTI and 19,978 (30.91%) with LRTI. Clarithromycin was prescribed to 12,448 patients, of whom 6,384 (51.29%) had LRTI and 6,064 (48.71%) had URTI.

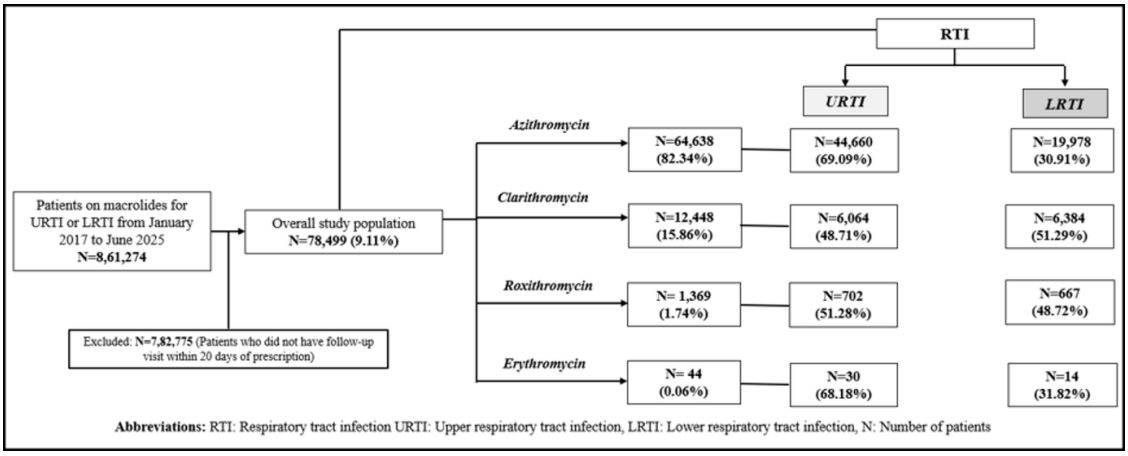

Figure 1: Patient disposition.

Table 1: Demographic characteristics of patients.

Macrolide	Age category (in years)	Overall	URTI	LRTI
		N (%)	N (%)	N (%)
Azithromycin	Overall	64,638 (100)	44,660 (100)	19,978 (100)
	<60	51755 (80.07)	38,065 (85.23)	13,690 (68.53)
	≥60	12,883 (19.93)	6,595 (14.77)	6,288 (31.47)
Clarithromycin	Overall	12,448 (100)	6,064 (100)	6,384 (100)
	<60	9,274 (74.5)	5,123 (84.48)	4,151 (65.03)
	≥60	3,174 (25.50)	941 (15.52)	2,233 (34.98)
Roxithromycin	Overall	1,369 (100)	702 (100)	667 (100)
	<60	1,064 (77.72)	606 (86.32)	458 (68.67)
	≥60	305 (22.28)	96 (13.68)	209 (31.33)
Erythromycin	Overall	44 (100)	30 (100)	14 (100)
	<60	36 (81.82)	27 (90.00)	9 (64.29)
	≥60	8 (18.18)	3 (10.00)	5 (35.71)

N: Number of patients. Data for overall, URTI: upper respiratory tract infection, LRTI: lower respiratory tract infection. URTI, and LRTI are presented horizontally. Vertically, the data is presented for all macrolides.

Figure 1 depicts overall patient inclusion and classification into URTI and LRTI cohorts. URTI and LRTI were not directly documented for all patients and were categorized based on recorded diagnoses; for example, patients with pharyngitis were categorized as URTI whereas those with bronchitis were classified as LRTI. All diagnoses were

classified into one of these two categories (Table 1 of supplementary information is not linked.).

Age distribution of patients

The mean±SD age of patients in the clarithromycin and azithromycin cohorts was 46.59±16.56 years and 43.85±16.06 years, respectively. For patients prescribed roxithromycin and erythromycin, the mean±SD was 44.86±16.25 and 43.59±14.77 years, respectively.

Across all macrolide cohorts, the largest proportion of patients belonged to the age group of less than 60 years (clarithromycin: 9274 (74.5%); azithromycin: 51755 (80.07%); roxithromycin: 1064 (77.72%); erythromycin: 36 (81.82%)). Table 1 presents the age distribution of overall population, as well as stratified by URTI and LRTI cohorts.

The majority of patients across all macrolide cohorts belonged to the age group of <60 years, both overall and among patients with URTI. In contrast, the proportion of patients aged ≥60 years was relatively higher in the LRTI subgroup compared to URTI. This suggests that LRTIs are more frequently documented among older patients.

Complaints/symptoms reported by patients

In the azithromycin group, fever was the most frequently documented complaint in URTI patients (N=14,671; 32.85%), while cough was the leading complaint in LRTI patients (N=5,464; 27.35%). Similarly, among patients in the clarithromycin cohort, fever (N=1,116; 18.40%), cough (N=1,025; 16.90%), and cold (N=746; 12.30%) were the most common symptoms, whereas cough (N=1,787; 27.99%); fever (N=1,447; 22.67%) and dyspnea (N=1,170; 18.33%) predominated in the LRTI cohort. In the roxithromycin cohort, cough was the most frequently reported symptom among URTI patients (N=210; 29.91%) and LRTI patients (N=220; 32.98%). Cough was the most common complaint among URTI patients (N=9; 30.00%) prescribed erythromycin. Fever and cough were the most frequently documented complaints in LRTI patients. Findings from the erythromycin cohort should be interpreted with caution because of the small sample size.

Across all macrolide cohorts, URTI was mainly characterized by fever, cold, and cough, whereas LRTI was predominantly associated with cough, fever, and dyspnea. Notably, cough was the most consistently reported symptom among patients with LRTI across all macrolide cohorts. Overall, symptom patterns were broadly similar across macrolides.

Underlying conditions/etiologies

The most commonly documented underlying conditions among patients prescribed macrolide antibiotics are summarized in Table 2. In the azithromycin cohort, URTI (general/non-specific diagnosis) (N=25,738; 57.63%), rhinitis (N=7,439; 16.66%) and pharyngitis (N=4,177; 9.35%) were the most frequently reported conditions among URTI patients. Among patients with LRTI, bronchitis was the most common diagnosis (N=10,297; 51.54%), followed by LRTI (general/non-specific diagnosis) (N=6,937; 34.72%). Similarly in the clarithromycin cohort, URTI (general/non-specific diagnosis) (N=2,346; 38.69%) and rhinitis (N=1,246; 20.55%) were the predominant diagnoses among URTI patients. Among LRTI patients, bronchitis was the most common condition (N=3,047; 47.73%), followed by a general/non-specific mention of LRTI (N=2,460; 38.53%). A similar pattern of documented diagnoses was observed in the roxithromycin and erythromycin cohorts, although findings from the erythromycin cohort should be interpreted with caution because of limited sample size.

The above findings indicate that a general/non-specific diagnosis of URTI was the most frequently documented condition among patients categorized under the URTI cohort, whereas bronchitis was the most commonly documented diagnosis among patients with LRTI across all macrolide cohorts.

Comorbidities

Across all macrolide cohorts, hypertension and diabetes mellitus were the most frequently documented comorbidities. In the azithromycin cohort, hypertension and diabetes mellitus were documented in 4,388 patients (9.83%) and 2,248 patients (5.03%), respectively among patients with URTI. However, among patients with LRTI, these two conditions were documented in 3,299 (16.51%) and 1,588 (7.95%) patients respectively. Similarly in the clarithromycin cohort, hypertension and diabetes mellitus were reported for 525 patients (8.66%), and 276 patients (4.55%), respectively in the URTI group; whereas in the LRTI subgroup, the same conditions were reported for 1,038 (16.26%) and 570 patients (8.93%), respectively. The pattern was similar in the case of roxithromycin and erythromycin cohorts. Given the limited availability of data, findings should be interpreted with caution in the erythromycin cohort.

Dose and duration of therapy

In the azithromycin cohort, 41,840 patients (64.73%) received azithromycin for 5-7 days, and azithromycin 500 mg was the most frequently prescribed dose strength, accounting for 50,732 patients (78.49%). This prescription trend was consistent across azithromycin 250 mg dose strength, as well. Similarly, the majority of patients were prescribed clarithromycin for 5-7 days (N=11,965; 96.12%). The pattern was the same for both clarithromycin 250 mg and clarithromycin 500 mg dose strengths. Among patients prescribed roxithromycin, it was also predominantly prescribed for a 5-7-day regimen (N=1,302; 95.11%). The pattern was similar in the case of erythromycin. The findings suggest that a 5–7-day prescription duration was the most commonly prescribed regimen across all macrolide cohorts. In the clarithromycin

cohort, over 96% of patients received a prescription for this duration. Prescriptions exceeding 7 days were relatively uncommon.

Concomitant medications

In the azithromycin cohort, paracetamol (N=12,749; 28.55%) and levocetirizine+montelukast (N=10,083; 22.58%) were the most frequently co-prescribed medications, followed by gastroprotective combinations and other antihistamines for URTI patients. Among patients with LRTI, bronchodilators and inhaled corticosteroid therapy, particularly budesonide + formoterol (N=3,122; 15.63%) along with corticosteroids such as methylprednisolone (N=2,946; 14.75%) and mucolytic/bronchodilator combinations were commonly prescribed. Similarly, in the clarithromycin cohort, levocetirizine +montelukast (N=1,128; 18.60%), domperidone +rabeprazole (N=1,030; 16.99%), and paracetamol (N=907; 14.96%) were the most frequently co-prescribed medications for URTI patients.

In LRTI patients, the mucolytic combination of acebrophylline with acetylcysteine was prescribed to 1,758 patients (27.54%). Steroids such as methylprednisolone (N=1,360; 21.30%) and deflazacort (N=759; 11.89%) were also commonly used. In the roxithromycin cohort, antihistamines and paracetamol were commonly prescribed for URTI patients, while in LRTI patients, corticosteroids, bronchodilators, and gastroprotective agents were frequently used. Although the cohort size was limited for erythromycin, URTI patients frequently received paracetamol and antihistamine combinations. In LRTI patients, bronchodilators and methylxanthine derivatives (e.g., etofylline +theophylline) were prescribed in a small proportion of cases.

Concomitant therapies across macrolide cohorts were primarily symptom- and severity-driven, with URTI management focused on antihistamines, antipyretics, and gastroprotective agents, whereas LRTI treatment involved greater use of corticosteroids, bronchodilators, and mucolytics. This pattern was consistent across azithromycin and clarithromycin cohorts.

Secondary endpoint–effectiveness of macrolides in URTI and LRTI

Resolution of symptoms

Propensity score-matching was applied to match patients from the azithromycin cohort to those in the clarithromycin cohort, resulting in 12,448 patients in each arm. The roxithromycin and erythromycin cohorts had comparatively smaller sample sizes and were therefore not included in the PSM analysis. Overall, a higher proportion of patients achieved resolution in the clarithromycin cohort (N=9,007; 72.36%) compared with the azithromycin cohort (N=8,008; 64.33%) ($p<0.001$). Similar trends were observed following stratification by infection type in the PSM-matched cohorts (Table 3). Among patients with URTI, symptoms resolution was achieved in 4,547 patients (74.98%) in the clarithromycin cohort compared to 3,708 patients (61.15%) in the azithromycin cohort ($p<0.001$). Likewise, among patients with LRTI, 4,460 patients (69.86%) achieved symptom resolution in the clarithromycin cohort whereas in the azithromycin cohort, the proportion of resolved patients was lower (N=4,300; 67.36%) ($p<0.001$). Among patients prescribed roxithromycin, symptoms were resolved in 458 patients (65.24%) with URTI and 423 patients (63.42%) with LRTI. In the erythromycin cohort, 22 patients (73.33%) with URTI achieved symptom resolution; however, these findings should be interpreted with caution because of the limited sample size. The p-value (Chi-Sq. test, $p<0.001$) indicates a highly statistically significant association between the type of macrolide prescribed and symptom resolution in the overall population. The observation was similar upon stratification by the type of infection (URTI and LRTI).

Resolution of symptoms with clarithromycin and azithromycin- stratification by indications in URTI group

In the matched URTI population (N=6,064 per cohort), symptom resolution was observed in a higher proportion of patients treated with clarithromycin (N=4,547; 74.98%) compared with azithromycin (N=3,708; 61.15%). Across individual indications (pharyngitis, sinusitis, tonsillitis, and otitis media), clarithromycin demonstrated higher resolution percentage compared with azithromycin in propensity score-matched cohorts. This difference was statistically significant ($p < 0.001$) for overall URTI population, pharyngitis, tonsillitis, and otitis media and is presented in Table 4.

Resolution of symptoms with clarithromycin and azithromycin- stratification by indications in LRTI group

In the matched LRTI cohort (N=6,384 per group), symptom resolution was observed in 4,460 patients (69.86%) prescribed clarithromycin compared with 4,300 (67.36%) prescribed azithromycin. The difference between two cohorts was statistically significant ($p=0.003$). Resolution outcomes stratified by LRTI indications are summarized in Table 5.

Exploratory endpoint–effectiveness following switch to clarithromycin from azithromycin or other antibiotics

Within 20 days before initiation of clarithromycin, 147 patients (2.13%) were prescribed azithromycin, and 1,128 patients (16.36%) had a documented prescription of antibiotics other than azithromycin for the management of RTIs (Table 6).

Effectiveness following switch to clarithromycin

Among the patients who switched from azithromycin to clarithromycin (n=147), clinical resolution was achieved

in 112 patients (76.19%). Resolution was observed in 44 of 50 patients (88.00%) with URTI and in 68 of 97 patients (70.10%) with LRTI. Among patients who transitioned from antibiotics other than azithromycin (n=1,128), clinical resolution was achieved in 774 patients (68.62%). Resolution was observed in 361 of 506 patients (71.34%) with URTI and in 413 of 622 patients (66.40%) with LRTI.

Among patients with documented prior antibiotic exposure, symptom resolution was observed in 76.19% of patients previously prescribed azithromycin and in 68.62% of the patients previously prescribed other antibiotics. Similar findings were observed across URTI and LRTI cohorts, with the highest resolution proportion among URTI patients who switched from azithromycin (88.00%). Effectiveness following switch to clarithromycin is summarized in Table 7.

Table 2: Underlying conditions for patients.

Conditions*	Azithromycin		Clarithromycin		Roxithromycin		Erythromycin	
	URTI	LRTI	URTI	LRTI	URTI	LRTI	URTI	LRTI
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	44,660 (100)	19,978 (100)	6,064 (100)	6,384 (100)	702 (100)	667 (100)	30 (100)	14 (100)
URTI	5,7238 (57.63)	--	2,346 (38.69)	--	369 (52.56)	--	16 (53.33)	--
Bronchitis[1]	--	10,297(51.54)	--	3,047 (47.73)	--	306 (45.88)	--	6 (42.86)
Rhinitis[2]	7,439 (16.66)	--	1,246 (20.55)	--	125 (17.81)	--	1 (3.33)	--
LRTI	--	6,937 (34.72)	--	2,460 (38.53)	--	263 (39.43)	--	6 (42.86)
Pharyngitis[3]	4,177 (9.35)	--	832 (13.72)	--	69 (9.83)	--	8 (26.67)	--
Bronchial asthma[4]	--	1,426 (7.14)	--	896 (14.04)	--	--	--	1 (7.14)
Sinusitis[5]	2,548 (5.71)	--	1,074 (17.71)	--	75 (10.68)	--	1 (3.33)	--
Otitis Media[6]	1,944 (4.35)	--	450 (7.42)	--	29 (4.13)	--	1 (3.33)	--
Viral fever	1,431 (3.20)	442 (2.21)	138 (2.28)	135 (2.11)	--	--	--	--
Acute exacerbation[7]	--	1,376 (6.89)	--	404 (6.33)	--	27 (4.05)	--	2 (14.29)
Pneumonia[8]	--	1,452 (7.27)	--	691 (10.82)	--	100 (14.99)	--	1 (7.14)
Otitis externa[9]	709 (1.59)	--	80 (1.32)	--	--	--	--	--
Tonsillitis[10]	587 (1.31)	--	184 (3.03)	--	22 (3.13)	--	1 (3.33)	--
Bronchiectasis	--	539 (2.70)	--	253 (3.96)	--	15 (2.25)	--	2 (14.29)
Laryngitis[11]	534 (1.20)	--	149 (2.46)	--	16 (2.28)	--	1 (3.33)	--

*Conditions documented by treating doctor in the prescription. URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection. This represents the top conditions recorded for patients prescribed macrolide antibiotics for URTI and LRTI. One patient can have more than one documented diagnosis.

Table 3: Effectiveness of macrolide antibiotics.

Infections	Resolution status	Azithromycin N (%)	Clarithromycin N (%)	Roxithromycin N (%)	Erythromycin N (%)	P value#
URTI+LRTI	Resolved	8,008 (64.33)	9,007 (72.36)	881 (64.35)	34 (77.27)	<0.001***
	Unresolved	4,440 (35.67)	3,441 (27.64)	488 (35.65)	10 (22.73)	
	Total	12,448	12,448	1,369	44	
URTI	Resolved	3,708 (61.15)	4,547 (74.98)	458 (65.24)	22 (73.33)	<0.001***
	Unresolved	2,356 (38.85)	1,517 (25.02)	244 (34.76)	8 (26.67)	
	Total	6,064	6,064	702	30	
LRTI	Resolved	4,300 (67.36)	4,460 (69.86)	423 (63.42)	12 (85.71)	<0.001***
	Unresolved	2,084 (32.64)	1,924 (30.14)	244 (36.58)	2 (14.29)	
	Total	6,384	6,384	667	14	

URTI: Upper respiratory tract infection, LRTI: Lower respiratory tract infection. #P value was calculated using Chi-Sq. test at 5% level of significance. ***P value is significant at 0.001 level of significance.

Table 4: Key indications were considered for evaluation of indication-wise resolution.

Indications	Resolution status	Azithromycin N (%)	Clarithromycin N (%)	P value#
Overall	Resolved	3,708 (61.15)	4,547 (74.98)	<0.001***
	Unresolved	2,356 (38.85)	1,517 (25.02)	
	Total	6,064	6,064	
Pharyngitis	Resolved	537 (64.54)	629 (75.60)	<0.001***
	Unresolved	295 (35.46)	203 (24.40)	

Continued.

Indications	Resolution status	Azithromycin N (%)	Clarithromycin N (%)	P value#
	Total	832	832	
Sinusitis	Resolved	779 (72.53)	821 (76.44)	0.127NS
	Unresolved	295 (27.47)	253 (23.56)	
	Total	1,074	1,074	
Tonsillitis	Resolved	112 (60.87)	131 (71.20)	0.036*
	Unresolved	72 (39.13)	53 (28.80)	
	Total	184	184	
Otitis Media	Resolved	228 (50.67)	289 (64.22)	<0.001***
	Unresolved	222 (49.33)	161 (35.78)	
	Total	450	450	

N: Number of patients, NS: Non-significant, #P value was calculated using Chi-Sq. test at 5% level of significance., ***P value is significant at 0.001 level of significance. *P value is significant at 0.05 level of significance.

Table 5: Key indications were considered for evaluation of indication-wise resolution.

Indications	Resolution status	Azithromycin N (%)	Clarithromycin N (%)	P value#
Overall	Resolved	4,300 (67.36)	4,460 (69.86)	0.003**
	Unresolved	2,084 (32.64)	1,924 (30.14)	
	Total	6,384	6,384	
LRTI mentioned in diagnosis	Resolved	697 (66.95)	764 (73.39)	<0.001***
	Unresolved	344 (33.05)	277 (26.61)	
	Total	1,041	1,041	
Acute exacerbation	Resolved	273 (67.57)	299 (74.01)	0.044*
	Unresolved	131 (32.43)	105 (25.99)	
	Total	404	404	
Pneumonia	Resolved	521 (75.40)	544 (78.73)	0.141NS
	Unresolved	170 (24.60)	147 (21.27)	
	Total	691	691	
Bronchiectasis	Resolved	141 (55.73)	157 (62.06)	0.148NS
	Unresolved	112 (44.27)	96 (37.94)	
	Total	253	253	

N: Number of patients, NS: Non-significant, #P value was calculated using Chi-Sq. test at 5% level of significance. ***P value is significant at 0.001 level of significance. **P value is significant at 0.005 level of significance. *P value is significant at 0.05 level of significance.

Table 6: Prescription of antibiotics prior to clarithromycin.

Prior prescription	N (%)
Azithromycin	147 (2.13)
Antibiotics other than azithromycin	1,128 (16.36)

N: Number of patients. Percentage was calculated using 6,893 as denominator, patients who had a visit documented prior to the prescription of clarithromycin. Not all patients had antibiotics prescribed in the prior visit.

Table 7: Effectiveness of clarithromycin-switch from other antibiotics.

Infections	Resolution status	*Switch from azithromycin to clarithromycin*	*Switch from antibiotics other than azithromycin to clarithromycin*
Overall	Unresolved	35 (23.81)	354 (31.38)
	Resolved	112 (76.19)	774 (68.62)
	Total	147	1,128
URTI	Unresolved	6 (12.00)	145 (28.66)
	Resolved	44 (88.00)	361 (71.34)
	Total	50	506
LRTI	Unresolved	29 (29.90)	209 (33.60)
	Resolved	68 (70.10)	413 (66.40)
	Total	97	622

URTI: Upper respiratory tract infection, N: Number of patients, LRTI: Lower respiratory tract infection.

DISCUSSION

This RWE study evaluated patient characteristics, prescribing patterns, and effectiveness of macrolides in RTIs. The study population comprised 78,499 patients. Although azithromycin was prescribed more frequently overall, the highest proportion of LRTI cases within a treatment cohort was observed in the clarithromycin group.

Our study showed that the mean age ranged from 43.59±14.77 years in the erythromycin cohort to 46.59±16.56 years in the clarithromycin cohort, with the majority of patients across all macrolide groups in the age range of 18-60 years, closely aligning with 46.1±18.1 years reported in the SWORD survey conducted in 2022.[11] The predominance of patients in below 60 years age group may indicate higher exposure risk and greater social and occupational mobility in this population. Although this age group demonstrates higher infection incidence, severity and mortality are generally lower compared to the elderly population.[12,13] The clinical presentation observed in the study aligns with the known patterns of URTI and LRTI.

Among patients with URTI, fever, cold, and cough were the leading complaints, whereas cough and dyspnea were predominantly documented in the LRTI cohort across macrolide groups, aligning with established clinical understanding. A retro-prospective study of URTI patients by Moitra et al. reported cough, fever, sore throat, and rhinorrhoea as the most common symptoms, affecting 86.5% of the study population.[14] Mandell and Read reported cough as the most predominant symptom associated with LRTI.[15] Similarly, in a Danish general practice, cough, fever, dyspnea and increased purulent sputum were the most frequently reported symptoms among patients of bronchitis and pneumonia (categorized as LRTI).[16] Bronchitis was the most frequently documented underlying condition among patients in the LRTI cohort across macrolide groups. This finding is consistent with the existing epidemiological evidence indicating that community-acquired pneumonia (CAP) and acute exacerbation of chronic bronchitis (AECB) are among the most commonly encountered LRTIs in outpatient settings.[17] In the URTI cohort, non-specific URTI was the most frequently recorded diagnosis, followed by rhinitis and pharyngitis. Bade et al. have reported sinusitis, rhinitis, tonsillitis, pharyngitis, laryngitis and otitis media as common URTIs.[18] These conditions are reflected in the current study population, as evidenced by their substantial representation among recorded diagnoses.

The prescribing pattern observed in this study demonstrates a clear preference for the guidelines (NICE, WHO, ICMR) aligned short-course therapy. These macrolides were predominantly prescribed for a 5-7-day duration across dose strengths, reflecting trend towards rational prescribing practices. Most macrolides evaluated in this study are categorized under the World Health Organization (WHO) Watch group in the Access, Watch, Reserve (AWaRE), indicating higher potential for development of antimicrobial resistance and the need for cautious and judicious use (https://aware.essentialmeds.org/list). This is also in line with the previous real-world evidence reporting a mean antibiotic treatment duration of 7.52±2.11 days.[19]

The effectiveness outcomes observed in this study support the appropriateness of the prescribing practices and recommended treatment durations. A substantial proportion of patients across macrolide groups achieved resolution in URTI and LRTI cohorts within the documented follow-up period, suggesting that the commonly prescribed regimens were adequate to achieve clinical resolution in routine clinical practice. The favourable response rates reinforce the continued utility of macrolides in the management of RTIs. Recent Indian real-world studies have also reported favourable clinical outcomes with clarithromycin and azithromycin in RTIs, further supporting the relevance of findings from the present study.[20,21]

The comparative effectiveness analysis performed using the propensity score-matched cohorts of azithromycin and clarithromycin provided further insights into differences between the two macrolides. Clarithromycin demonstrated a higher proportion of symptom resolution compared with azithromycin in both overall and stratified analyses by specific indications in the URTI and LRTI cohorts. In a study by Müller, the percentage of cure or improvement was 95% with azithromycin and 96% with clarithromycin in URTI; although the clinical efficacy was similar in both groups, it was numerically higher with clarithromycin.[22] In a study by Lima et al clarithromycin was reported to be 40 times more potent than azithromycin against pneumococci.[23] The present real-world data suggest a potential incremental benefit with clarithromycin, which might be attributed to its favourable pharmacokinetic and pharmacodynamic properties.[17]

The evaluation of effectiveness of clarithromycin among patients with prior antibiotic exposure further strengthens the clinical interpretation of these findings. Among patients who transitioned from azithromycin or other antibiotics, a substantial proportion achieved symptom resolution, indicating that clarithromycin may provide clinical benefits in patients with suboptimal response to initial therapy. A meta-analysis by Gálvez-Múgica et al has reported superior clinical effectiveness of clarithromycin compared with cephalosporins and amoxicillin-clavulanic acid in the treatment of LRTIs, which provides supportive evidence for the present real-world observations.[24]

While the present findings suggest a potential advantage of clarithromycin in certain clinical conditions, treatment selection in routine practice is influenced by multiple factors including patient characteristics, prior antibiotic exposure, local resistance patterns, tolerability, drug–drug

interactions and the load of comorbid conditions. All the macrolides evaluated in this study remain established therapeutic options for the management of respiratory tract infections, and differences observed in real-world settings should be interpreted in the context of underlying clinical heterogeneity.

The present study has several notable strengths. It is based on a large, real-world longitudinal dataset derived from routine clinical practice, thereby enhancing the generalizability of findings. The inclusion of multiple macrolide antibiotics enabled a comprehensive evaluation of patient profile (clinical manifestations and underlying conditions) for which these agents were prescribed, prescribing patterns, and clinical outcomes across diverse RTIs. Additionally, the use of PSM for comparative effectiveness analysis between azithromycin and clarithromycin helped reduce confounding and strengthen the robustness of the findings. Despite its strengths, this retrospective study has certain limitations. Data on antibiotic susceptibility and resistance were not available, limiting pathogen-specific interpretation of effectiveness. As the data were derived from outpatient-based records, the findings may not be fully generalizable to hospitalized or more severe patient populations.

CONCLUSION

In conclusion, this real-world analysis provides comprehensive insights into the prescribing patterns and effectiveness of macrolides in the management of RTIs in routine clinical practice. The findings indicate that macrolide therapy was commonly prescribed and associated with favourable clinical outcomes. The comparative analysis suggests a potential incremental effectiveness advantage with clarithromycin in symptoms resolution of RTIs. Overall, these findings support the continued and judicious use of macrolides, while emphasizing the importance of rational antibiotic prescribing in real-world settings.

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