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MACROLIDE-RESISTANT MYCOPLASMA PNEUMONIAE IN HOSPITALIZED SCHOOL-AGED CHILDREN: PREVALENCE, CLINICAL IMPACT, AND RISK FACTORS

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ABSTRACT

Objective: This retrospective study aimed to assess macrolide- resistant *Mycoplasma pneumoniae* (MRMP) prevalence in 6-12 year old hospitalized *Mycoplasma pneumoniae* pneumonia (MPP) patients, compare clinical characteristics and outcomes between MRMP and macrolide- susceptible *M. pneumoniae* (MSMP) cases, and identify MRMP associated factors. Method: Hospitalized children with MPP from July 2022 to July 2024 were recruited, with MRMP identified through specific mutations in the 23S rRNA gene. Multivariate logistic regression was employed to isolate independent risk factors for MRMP. Result: Out of 549 MPP children, 358 (65%) were positive for *M. pneumoniae* DNA. Among them, 272 (76%) were MRMP and 86 (24%) were MSMP. MRMP patients experienced longer fever duration and hospitalization, alongside higher rates of myocardial injury and intensive care unit (ICU) admissions. MRMP was characterized by elevated D-dimer levels, lactate dehydrogenase (LDH), serum ferritin (SF), interleukin-6 (IL-6) and interferon-gamma (IFN-γ). Radiographically, MRMP demonstrated aggressive lung involvement, including multilobar involvement. Factors independently associated with MRMP included symptom duration ≥7 days (OR= 3.74, 95% CI 2.04-6.88), multilobar involvment (OR= 4.57, 95% CI 2.25-9.28), delayed treatment escalation to tetracyclines/fluoroquinolones (OR= 13.45, 95% CI 5.47-33.07), IFN-γ (OR= 3.49, 95% CI

1.75-6.97) and viral co-infection (OR=9.78, 95% CI 4.13-23.16) Conclusion: The study establishes MRMP as a high-risk pneumonia subtype driven by IFN-γ-mediated hyperinflammation and viral co-infection synergy. These findings align with the growing global efforts to combat antimicrobial resistance in M. pneumoniae infections and build on existing guidelines by emphasizing the importance of early resistance testing and personalized treatment strategies for pediatric patients.

KEYWORDS: *Mycoplasma pneumoniae*; Macrolide resistance; Children; Prevalence; Pneumonia.

1.0 INTRODUCTION

Mycoplasma pneumoniae (*M. pneumoniae*) is a leading cause of community-acquired pneumonia (CAP) worldwide, accounting for 10–40% of cases, predominantly affecting school-aged children and young adolescents.[1,2] Standard empirical antibiotics for community-acquired pneumonia, such as beta-lactams, are ineffective against *M. pneumoniae* due to the bacterium's lack of a cell wall.[2] making it undetectable on Gram stain and challenging to culture.[3] In contrast, antibiotics like macrolides, fluoroquinolones, and tetracyclines (doxycycline or minocycline) are effective treatments.[4] with macrolides often prescribed as first-line therapy for children due to their effectiveness against M. pneumoniae and relatively low toxicity levels .[5]

Historically considered a self-limiting pathogen, *M. pneumoniae* has undergone a troubling epidemiological shift over the past two decades, driven by the global emergence of macrolide-resistant *M. pneumoniae* (MRMP) strains. Reports suggest that, resistance rates varying significantly globally of which 80%–90% are in Asian countries like China and Japan.[6,7] while North American and European countries generally have lower rates of 3% and 10% respectively, except for Italy where rate of 26% has been reported.[8] reflecting regional variations in antibiotic prescribing practices, clinical protocols, and healthcare system capabilities.[9] The factors that can reliably predict the progression of *M. pneumoniae* infection are still uncertain and lack definitive conclusions in current researches.[10] Several studies has shown that this resistance crisis has transformed MRMP into a treatment-refractory infection associated with prolonged hospitalization, extrapulmonary complications, and systemic hyperinflammation which is a stark departure from the benign course of macrolide-sensitive *M. pneumoniae* pneumonia (MSMP).[11–14] Although other studies

suggest comparable outcomes to MSMP, underscoring the need for population-specific data.[15]

The clinical ramifications of this shift are profound. MRMP patients frequently exhibit delayed defervescence despite macrolide therapy, necessitating antibiotic escalation to tetracyclines or fluoroquinolones.[13] Compounding this challenge are reports of severe pulmonary sequelae such as multilobar consolidation, necrotizing pneumonia and immune-mediated complications such as myocarditis and hemophagocytic lymphohistiocytosis (HLH), which are rare in MSMP.[16,17] Emerging evidence suggests that MRMP's virulence is amplified by a dysregulated cytokine response which correlate with radiographic severity and treatment resistance.[11,18] in this study, we hypothesized that MRMP is associated with prolonged inflammation and worse clinical outcomes compared to MSMP. However, the mechanisms linking macrolide resistance to immune hyperactivation remain poorly understood, hindering the development of targeted therapies.

Monitoring the prevalence of MRMP is crucial due to concerns regarding the limited availability of alternative treatments and potential adverse reactions.[15] The rationale for investigating *M. pneumoniae* among children aged 6-12 years in our study is based on this age group's high incidence of *M. pneumoniae* infections, which significantly affects school attendance and health outcomes. In mainland China, significant research on *M. pneumoniae* has primarily focused on studies conducted in Beijing and Shanghai.[19,20] with limited attention given to other provinces including Jiangxi province. This study aimed to determine the prevalence of MRMP in hospitalized children aged 6-12 years, to compare clinical outcome, laboratory, radiological and therapeutic distictions between MRMP and macrolide-susceptible *M. pneumoniae* (MSMP) cases and to investigate the associated factors of MRMP. We hope that this work advances our understanding of MRMP's pathobiology, contributes to the global efforts to combat antimicrobial resistance in *M. pneumoniae* infections, provides actionable tools for clinicians by providing clinical and treatment related insights.

2.0 MATERIALS AND METHODS

2. 1 Study setting

This study was conducted retrospectively from July 1, 2022, to July 31, 2024 at First Affiliated Hospital of Gannan Medical University, Ganzhou City, Jiangxi Province, China. The hospital is a provincial Grade A facility (the highest designation in China's hospital classification system) and serves as a general medical center in Jiangxi Province. It has

developed into a regional hub for medical treatment, scientific research, and training for Gannan Medical University. It as well serves surrounding provinces of Jiangxi, Hunan, Guangdong, and Fujian. Ethical approval for the study was obtained from the Ethics Review committee of First Affiliated Hospital of Gannan Medical University (22SC-2023 No 290). Patient consent was waived due to the exemption authorized by Ethics Committees because it was a retrospective study and the data collected was anonymized.

2.2 Study population

The study enrolled children aged 6 to 12 years who were hospitalized with community-acquired pneumonia (CAP) diagnosed as Mycoplasma pneumonia from their respiratory specimens. The diagnosis of MPP was based on Chinese guideline for diagnosis and treatment of MP (2023 edition).[21] and the inclusion criteria for cases included: i). Positive of *M. pneumoniae* infection by real-time polymarase chani reaction, (RT-PCR); ii). Analysis of mutations in domain V of the 23S rRNA gene; iii). Radiologically confirmed pneumonia. The radiological criteria for inclusion included the presence of pleural effusion, consolidations, or new infiltrates on chest radiographs.[22] Exclusion criteria were i) patient with incomplete clinical data ii) patient with chronic lung diseases, bronchial foreign bodies, Immunocompromised defined as patients with weakened immune systems due to conditions such as human immunodeficiency viruses (HIV) infection, chemotherapy, or immunosuppressive therapy >2 weeks, and congenital heart disease to avoid confounding severity from chronic conditions.

2.3 Case definition and data collection

Data retrieval involved a specific age group of children (6-12 years) who had confirmed *M. pneumoniae* pneumonia (MPP) samples. A confirmed case of *M. pneumoniae* pneumonia was defined as a symptomatic individual testing positive for *M. pneumoniae* via molecular testing (RT-PCR) at the medical facility. To avoid duplication, each patient was included only once in the analysis, with any redundant samples removed from the dataset.

Following the examination of Clinical specimens for *M. pneumoniae* DNA detection and analysis of mutations in domain V of the 23S rRNA gene, children diagnosed with MPP were categorized into two groups: MRMP and MSMP. The classification was based on the presence or absence of specific mutations at positions 2063 or 2064 within the domain V of the 23S rRNA gene. Medical records were reviewed to collect demographic data, including age, gender, duration of hospital stay, history of previous respiratory admission, Laboratory

findings, chest radiograph findings, and the presence of co-infections which was defined as detection of *M. pneumoniae* with other bacterial or viral pathogen(s). Extra-pulmonary complications such as skin rash, myocarditis, liver function abnormalities, gastrointestinal dysfunction, Kidney injury, encephalitis, hemolytic anemia and arthritis.[12] were also evaluated. Treatment details were incorporated by systematically documenting antibiotic regimens (pre-admission and inpatient), adjunctive therapies (such as corticosteroids and intravenous immunoglobulin, IVIG), and escalation protocols (macrolide to tetracycline or Fluoroquinolone transition). These variables were collected alongside clinical and laboratory data to assess their association with MRMP classification and outcomes. Treatment definitions aligned with the 2023 Chinese Guidelines.[21] ensuring consistency, macrolides as first-line therapy, escalation after 72 hours of persistent fever per 2023 guideline or clinical deterioration, and adjunctive therapies for severe inflammation. Fever was defined as a body temperature above 38°C.[23]

2.4 Specimen collection and laboratory testing

Nasopharyngeal swabs were collected within 24 hours of admission for RT–PCR tests using a commercial kit (DAAN GENE, Guangzhou, China). Samples were stored at −80 °C until used for PCR assays following the manufacturer's instructions. RT-PCR amplification was conducted using primers and probes sourced from DaAn Gene Co. Ltd., with analysis carried out on the Applied Biosystems 7600 Real-Time PCR system (Foster City, CA, USA). Evaluations of macrolide resistance were performed on children with a positive PCR result for *M. pneumoniae*, detecting resistance-associated mutations via RT-PCR targeting the A2063G and A2064G mutations of the 23S rRNA gene using a kit (MoLe Biotech Co., Ltd. Jiangsu, China). This method could detect the p1 gene of M. pneumoniae and macrolide resistance mutations with a detection limit of 500 copies/mL, based on based on the TaqMan PCR technology.[24] A positive diagnosis of *M. pneumoniae* infection and macrolide resistance was confirmed when the p1 gene's Ct values fell below 35 and mutations linked to resistance were detected. However, the assay could not differentiate between mutations at positions 2063 and 2064 in the V region of the 23S rRNA gene. Peripheral blood samples were obtained on admission for the determination of the complete blood count, C-reactive protein (CRP), aspartate aminotransferase (AST), alanane transaminase (ALT), procalcitonin (PCT), Erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), serum ferritin (SF), creatine kinase myocardial band isoenzyme (CK-MB) and D-dimer tests. Serum concentrations of chemokines and cytokines were measured to detect interleukin (IL)-10, IL-

6, IL-2, IL-4, IL-8, interferon-gamma (IFN-γ), and tumor necrosis factor (TNF)α as they were quantified using the Human Cytokine/Chemokine Magnetic Bead Panel (Merck Millipore) on a Luminex xMAP platform, with detection limits of 0.1–10 pg/mL and intra-/interassay coefficients of variation (CV) <10% and <15%, respectively. Additionally, nasopharyngeal aspirates were tested for respiratory viruses, including respiratory syncytial virus (RSV), adenovirus, enterovirus, influenza viruses A and B, and parainfluenza viruses, using the Resp®13 Respiratory Pathogen Multiplex PCR Kit (Ningbo Health Gene Technologies Co., Ltd., Zhejiang, China), following the manufacturer's instructions. Epstein-Barr virus (EBV) DNA was detected using the Epstein-Barr Virus Nucleic Acid Quantitative Detection Kit (Daan Gene Co., Ltd., Guangzhou, China). Sputum samples were analyzed for Chlamydia pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Legionella pneumophila, Bordetella pertussis, *M. pneumoniae*, and Streptococcus pneumoniae using the Respiratory Pathogens Nucleic Acid Detection Kit (CapitalBio Technology Co., Ltd., Beijing, China), according to the manufacturer's protocols. Quantitative bacterial cultures were considered positive at a threshold of $\geq 10^5$ colony-forming units per milliliter (CFU/mL).

Statistical Analysis

Data were first processed and arranged properly in Microsoft Excel 2016 software followed by statistical analysis. Upon arrangement and processing in Microsoft Excel, statistical analyses were performed using OriginPro 2019 software. Chi-squared tests or Fisher's exact test were used to compare categorical data, while Mann–Whitney U-test were employed to compare continuous variables. For post-hoc analysis, Bonferroni correction method was used for further comparisons between the two groups. Data are presented as percentages and mean ± standard error for quantitative and continuous data, respectively. Variables with $p < 0.1$ in univariate analyses were initially included in the multivariate logistic regression model to assess independent factors associated with MRMP. Variables demonstrating collinearity (Variance Inflation Factor [VIF] > 3) based on standard statistical practice or redundancy with stronger predictors were excluded to ensure model parsimony. Statistical significance was considered at $p < 0.05$.

3.0 RESULTS

3.1 Occurrence *Mycoplasma pneumoniae* infections and prevalence of MRMP

Between July 1 2022 and July 31 2024, 549 children aged 6 to 12 years with MPP. Among them, children 358 (65%) tested positive for MPP DNA. Of the MPP DNA cases, 272

children (76%) exhibited the A2063G or A2064G mutation in the V region of the 23S rRNA gene, indicative of MRMP. The remaining 86 children (24%) did not carry these mutations and were classified as MSMP.

Among the 272 children (76%) in the MRMP group, 141 children (51. 8%) were male and 131 (48.2%) were female. Out of the total of 86 children (24%) in the MSMP group, 58 (67. 4%) were male and 28 (32.6%) were female. In the MSMP group, there were more male children compared with the MRMP group, more children in the MRMPP group presented with cough, wheezing and and longer disease onset duration. However, some of the clinical characteristics were similar across both groups (Table 1).

3.2 Laboratory findings in comparison between MSMP and MRMP groups

Upon admission, Laboratory findings of patients with MSMP and MRMP were compared. While indicators such as WBC, lymphocyte, neutrophils, platelet count, CRP, PCT, AST, ALT, ESR, CKMB, IL-2, IL-4, TNF-α, IL-8, and IL-10 showed no significant differences between the two groups, LDH levels, IL-6, IFN –γ, Serum ferritin (SF) and D-dimer levels were notably higher in the MRMP group compared to the MSMP group as shown in Table 1. The MRMP group exhibited significantly overall higher rates of respiratory viral co-infections compared to MSMP (69.3% vs. 12.5%, p=0.004). Parainfluenza virus (12.5% vs. 0%; $p<0.001$), adenovirus (16.9% vs. 2.3%; $p<0.001$), and RSV (14.0% vs. 1.2%, $p<0.001$) were predominant in MRMP. Influenza A/B and enterovirus co-infections were also more frequent in MRMP ($p=0.03$). Epstein-Barr virus co-infection rates did not differ significantly (8.1% vs. 3.5%, p= 0.13). However, there was no significant differences observed between MRMP and MSMP groups (9.5% vs. 7.5%, p=0.707) for bacterial co-infection. *Streptococcus pneumoniae* (5.5% vs. 3.5%, p=0.41), *Haemophilus influenzae* (2.9% vs. 2.3%, p=0.76), and *Staphylococcus aureus* (1.1% vs. 1.2%, p=0.95) were detected at comparable rates as shown in Figure 1 and 2.

Table 1: Clinical characteristics and laboratory findings in comparison between the MSMP and MRMP groups.

Parameters	MSMP (86)[a]	NUMBER OF ACTUAL RESPONSE	MRMP (272)[a]	NUMBER OF ACTUAL RESPONSE	P VALUE
Male/female	58: 28	86	141: 131	272	0.011*
BMI (kg/m²)	16.8 ± 0.3	86	16.5 ± 0.2	272	0.423
Cough	37(93%)	86	125(98.5%)	272	0.007*
Wheezing	32(37.2%)	86	144(52.9%)	272	0.011*
Allergy	54(62.7%)	86	160(58.8%)	272	0.513
Disease duration from onset (days)	6±0.36	86	7±0.35	272	0.001*
Referred cases due to no improvement	84 (97.7%)	86	268 (98.5%)	272	0.160
Laboratory findings					
White blood cell count($\times 10^9$/L)	7.53±0.55	86	7.98±0.26	272	0.856
Neutrophils (%)	66.17±1.82	86	64.31±1.26	272	0.812
Lymphocyte (%)	23.23±1.47	86	24.40±1.02	272	0.192
Platelet ($\times 10^9$/L)	293.5±9.9	86	315.9±12.9	272	0.153
C-reactive protein (mg/L)	14.01±2.28	86	15.18±1.36	272	0.374
Procalcitonin (ng/Dl)	0.13±0.01	85	0.17±0.02	269	0.136
ESR (mm/h)	25.92±3.21	86	28.11±5.13	267	0.315
ALT (IU/L)	12.05±0.72	86	14.0±0.77	272	0.177
AST (IU/L)	26.73±0.82	86	28.59±0.67	272	0.327
LDH (IU/L)	306.13±12.8	85	322.33±7.57	271	0. 042*
D-dimer (μg/ml)	0.45±0.34	85	0.59±0.05	270	0.038*
CKMB (μg/ml)	16.01±4.32	86	16.21±4.62	272	0.751
IL-2 (pg/ml)	5.42±0.12	84	6.23±0.55	270	0.526
IL-4 (pg/ml)	2.55±1.11	84	2.82±1.32	270	0.178
IL-6 (pg/ml)	8.21±0.05	87	19.05±1.03	270	0.021*
TNF-α (pg/ml)	10.52±0.56	86	14.01±3.1	272	0.096
IFN –γ (pg/ml)	10.21±2.11	86	19.27±3.55	272	0.003*
IL-8(pg/ml)	14.31±3.14	84	15.61±1.91	271	0.065
IL-10(pg/ml)	4.53±0.06	84	5.52±1.11	271	0.614
SF(ng/ml)	1171.5±177	76	1611.9±292.2	265	0.001*

For items with missing responses, the number of actual responses was entered in the column on the right.

[a] Values are presented as mean± standard error or number (%)

* $P < 0.05$ statistically significant difference.

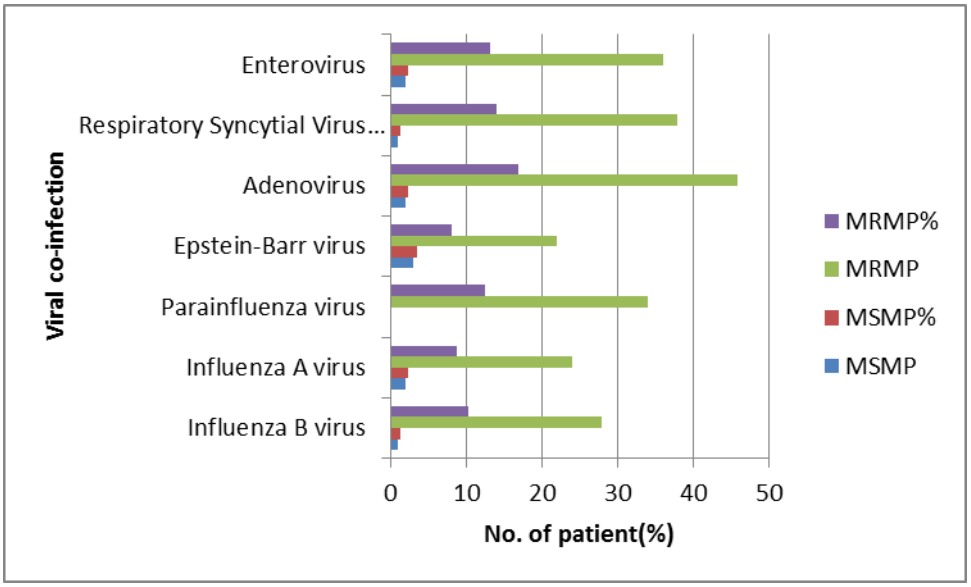

Figure 1: Respiratory virus co-infection in comparison between the MSMP and MRMP groups.

Values are presented as number (%). P value = 0.004

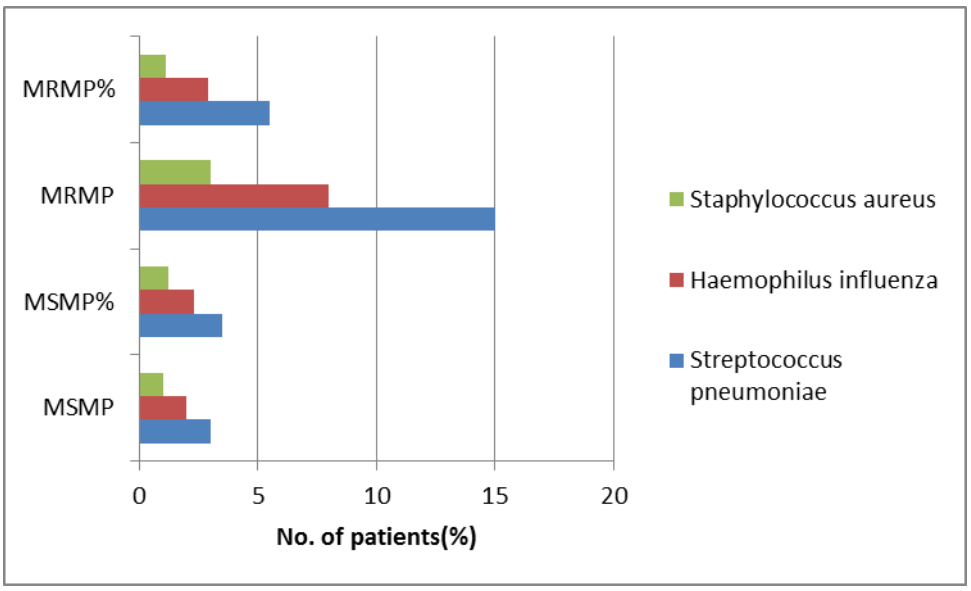

Figure 2: Bacteria co-infection in comparison between the MSMP and MRMP groups.

Values are presented as number (%), P value = 0.707

3.3 Chest radiological findings in comparison between MSMP and MRMP groups

Differences in radiological findings between the MSMP and MRMP groups were statistically significant (p=0.022) as represented in Table 2. The multilobar lung involvement was significantly higher in the MRMP group compared to the MSMP group (p = 0.000), with lobar or segmental consolidation being the most common finding 111 (40.8%) cases, followed by patchy consolidation in 77 (28.3%) cases, parahilar peribronchial infiltration in

51 (18.8%) cases, diffuse opacity in 17 (6.3%) cases, and diffuse infiltration in 15 (5.5%) cases. In contrast, In contrast, the MSMP group showed lower rates of these radiological findings. There was no significant difference between the two groups in the incidence of pleural effusion (p = 0.643).

Table 2: Radiological findings in comparison between the MSMP and MRMP groups.

	MSMP (86)[a]	MRMP (272)[a]	P value
Pulmonary involvement[b]			
Unilobar	22 (25.6%)	103 (37.8%)	0.038*
Multilobar	15 (17.4%)	135 (49.6%)	0.000*
Chest radiography findings			
Lobar consolidation	13(15.1%)	111(40.8%)	0.000*
Patchy Consolidation	11(12.8%)	77 (28.3%)	0.003*
Peribronchial infiltration	6(7%)	51(18.8%)	0.007*
Diffuse nodular opacity	0	17 (6.3%)	0.006*
Diffuse infiltration	6 (7%)	15 (5.5%)	0.621
Pleural effusion	4 (5%)	19 (7%)	0.643

[a] Values are presented as cases and percentages (%)

[b] Location of abnormality on chest radiography

[*] P < 0.05 statistically significant difference

3.4 Clinical outcome in comparison between MSMP AND MRMP groups

The MRMP patients had significantly longer hospitalization durations compared to the MSMP patients, with mean hospital stay of 6.89 ± 0.28 days for MRMP and 5.82 ± 0.31 days for MSMP (p = 0.021). Similarly, the MRMP group had longer duration of fever during illness with mean days of 7.2 ± 0.18 compared to 5.12 ± 0.2 days in the MSMP group (p = 0.013). Myocardial/pericardial damage (2.6% vs. 0%, p=0.04) and electrolyte imbalance (2.9% vs. 0%, p=0.03) were significantly more common in MRMP compared to MSMP. No other complications differed significantly between groups. There were no significant differences between the two groups in terms of previous respiratory admissions or ICU admissions (Table 3).

3.5 Antibiotic utilization, treatment response, and adjunctive therapies

Pre-admission antibiotic use (≤5 days) did not differ overall (25.6% vs. 25.0%, p=0.92), but subgroup analysis revealed higher macrolide pretreatment in MSMP (20.9% vs. 11.8%, p=0.04) and exclusive cephalosporin use in MRMP (5.9% vs. 0%, p=0.02). Inpatient management diverged sharply with macrolide monotherapy dominated MSMP (80.2% vs. 4.0% in MRMP, p=0.000), while tetracycline monotherapy was exclusive to MRMP (25.7%

vs. 0%, p=0.000). Combination therapy with cephalosporins was more frequent in MRMP (18.0% vs. 8.1%, p=0.03), whereas penicillin combinations were higher in MSMP (11.6% vs. 5.1%, p=0.04). Antibiotic escalation (macrolide to tetracycline/fluoroquinolone) occurred in 72.8% of MRMP patients (72.8% vs. 0% in MSMP, p=0.000), paralleling prolonged defervescence in MRMP (5.3 ± 0.07 vs. 2.1 ± 0.08 days, p=0.000). Adjunctive corticosteroids (41.9% vs. 16.3, p=0.000) and IVIG (8.1% vs. 0%, p=0.003) were more common in MRMP, emphasizing its greater severity.

Table 3: Clinical outcomes in comparison between MSMP and MRMP groups.

	MSMP(86)[a]	MRMP(272)[a]	P value
Duration of fever during illness	5.12±0.2	7.2±0.18	0.013*
Duration of hospitalization	5.82±0.31	6.89±0.28	0.021*
Previous Respiratory admissions			
-Any previous visit	13(15%)	43(15.8%)	0.89
-No previous visit	73(84.9%)	228(83.8%)	0.90
Extra-pulmonary manifestation			
Gastrointestinal symptoms	4(4.7%)	8(2.9%)	0.49
Myocardial/pericardial damage	0	7(2.6%)	0.04*
Liver dysfunction	2(2.3%)	7(2.6%)	0.85
Skin rash	5(5.8%)	11(4%)	0.54
Electrolyte Imbalance	0	8(2.9%)	0.03*
Acute Kidney injury	2(2.3%)	2(0.7%)	0.25
Blood system disease	4(4.7%)	5(1.8%)	0.12
ICU admission	0	11(4.0%)	0.03*
Oxygen supplementation	24 (28%)	120 (44%)	0.003*
Mechanical Ventilation	0	6 (2.2%)	0.04*
Flexible bronchoscopy	5 (5.8%)	43 (15.8%)	0.02*
Mortality	0	0	NA
Receipt of antibiotics prior to admission (≤5d)	22 (25.6%)	68 (25.0%)	0.92
Macrolides	18 (20.9%)	32 (11.8%)	0.04*
Penicillin	4 (4.7%)	20 (7.4%)	0.37
Cephalosporins	0	16 (5.9%)	0.02*
Inpatient Antibiotic Monotherapy[+]	69 (80.2%)	11 (4.0%)	0.000*
Macrolide-only	0	70 (25.7%)	0.000*
Tetracycline-only	0	4 (1.5%)	0.57
Fluoroquinolone-only			
Inpatient Combination Therapy[+]	7 (8.1%)	49 (18.0%)	0.03*
With Cephalosporins	10 (11.6%)	14 (5.1%)	0.04*
With Penicillin			
Antibiotic Escalation	0	198 (72.8%)	0.000*
Macrolide→ Tetracycline/Fluoroquinolone	2.1 ± 0.08	5.3 ± 0.07	0.000*
Time to Defervescence Post-			

Macrolide (days)	14 (16.3%)	114 (41.9%)	0.000*
Adjunctive Therapies	0	22 (8.1%)	0.003*
Corticosteroids			
IVIG			

[a] Values are presented as mean± standard error or number (%)

[*] P < 0.05 statistically significant difference

→ Antibiotic switch from Macrolide to tetracycline/Fluoroquinolone

[+]Inpatient monotherapy and combination therapy groups are mutually exclusive.

Multiple logistic regression analysis

In a multiple logistic regression model, multilobar pulmonary involvement (aOR = 4.57, 95% CI: 2.25–9.28, p < 0.001), antibiotic escalation (adjusted odds ratio [aOR] = 13.45, 95% CI: 5.47–33.07, p < 0.001), and respiratory viral co-infections (aOR = 9.78, 95% CI: 4.13–23.16, p < 0.001), emerged as the factors associated with MRMP. Interferon-gamma (IFN-γ) levels (aOR = 3.49, 95% CI: 1.75–6.97, p < 0.001) and prolonged disease duration (≥7 days from symptom onset) (aOR = 3.74, 95% CI: 2.04–6.88, p < 0.001) further increased the likelihood of MRMP. Variables such as IL-6 and duration of fever, while significant in univariate analyses, were excluded due to collinearity with retained predictors (IFN-γ and disease duration, respectively) as shown in Table 4.

Table 4: Multiple logistic regression analysis for associated factors of MRMP.

Variable	B(R.C)	S.E	P.value[a]	OR	95%CI Lower	Upper
Prolonged disease duration (≥7 days from symptom onset)	1.32	0.31	<0.001	3.74	2.04	6.88
Viral Co-infection	2.28	0.44	<0.001	9.78	4.13	23.16
Elevated IFN-γ (>15 pg/mL)	1.25	0.35	<0.001	3.49	1.75	6.97
Multiple lobe Involvement	1.52	0.36	<0.001	4.57	2.25	9.28
Antibiotic Escalation	2.60	0.46	<0.001	13.45	5.47	33.07

[a] P < 0.05 statistically significant difference

4.0 DISCUSSION

This study we analyzed differences in Laboratory, radiological characteristics and treatment and clinical outcomes between MSMP and MRMP cases, as well as factors linked to MRMP. Our findings may provide important insights into the trend of MRMP infections in children, especially considering the increasing incidence. Previous studies have indicated that school-aged children are particularly affected by MRMP infections.[1,25]

In our study, 76% of children diagnosed with MPP were found to have MRMP, signifying that macrolide resistance is a prevalent crisis in children aged 6–12 years. This is similar to the previous studies that have shown high MRMP prevalence among school-aged children.[1,26] This finding underscores the heightened vulnerability of school-aged children to the rapid transmission of pathogens due to their frequent interactions in densely populated settings such as schools and childcare centers, can facilitate the transmission of resistant MPP bacterial strains.[9]

The clinical impact of MRMP infections remains a topic of discussion. While MRMP infections are often considered more severe, the evidence is inconclusive with conflicting findings on disease severity across different studies.[10,13] Some research suggests similar hospital stays and fever duration between MRMP and MSMP patients.[15] Contrary to our study which observed longer hospital stays and fever duration in the MRMP group similar to Chen et al.,. who reported prolonged hospital stays and fever.[27] This could be attributed to a heightened immune response in MRMP cases. The cellular immune response plays a key role in *M. pneumoniae* infection progression, with disruptions leading to increased inflammation in the lungs and systemically.[10] Our study found elevated inflammatory markers, including Serum IL-6, IFN-γ, SF, LDH, and D-dimer in children with MRMP, indicating an exaggerated immune response as seen in previous studies.[9,16] IFN-γ, a Th1-polarizing cytokine, emerged as an independent factor of MRMP, corroborating its role in perpetuating macrophage activation and alveolar injury which correlate with radiographic severity. The heightened IFN-γ levels observed in MRMP patients likely stem from prolonged bacterial persistence due to macrolide resistance, which sustains antigenic stimulation and dysregulates host immunity. Macrolide resistance delays pathogen clearance, allowing *M. pneumoniae* to continuously activate Toll-like receptors (TLRs) on dendritic cells and macrophages, driving a Th1-polarized immune response. This results in excessive IFN-γ secretion by CD4+ T cells and NK cells, perpetuating alveolar inflammation and tissue injury.[18,28] However, there were no significant differences in other laboratory indicators like CRP or procalcitonin levels.

LDH levels have been shown to be more elevated than CRP in MPP.[29] suggesting LDH as a potential prognostic indicator of disease severity and treatment efficacy, as it is overexpressed in this disease, and it is conveniently, making it easily accessible for clinical purposes.[4] Morever, *M. pneumoniae* infections can lead to systemic inflammation, which in turn can cause hypercoagulability due to an imbalance in the clotting and fibrinolysis

systems.[30] D-dimer, a fibrin degradation product known for its involvement in the coagulation pathway, can be disrupted in severe infections like MRMP.[16,26] Elevated D-dimer levels have been linked to severe clinical manifestations in MPP cases and may help monitor disease severity and treatment effectiveness.[30] Monitoring D-dimer levels could provide valuable insights for treatment decisions and potentially improve outcomes in MRMP cases by identifying high-risk patients. Further research is needed to establish D-dimer's role in managing MRMP alongside other established markers of disease severity in MPP. Children with MRMP pneumonia may require extended hospital stays to manage symptoms and prevent complications effectively.

Previous studies have reported viral co-infections in children with MRMP ranging from 20% to 50%.[31] In our study, we found a higher prevalence of respiratory virus co-infections (69.3%) in the MRMP group compared to the MSMP group, consistent with other research.[32] This suggests that children with MRMP pneumonia may be more susceptible to viral co-infections, potentially leading to more severe illness. Following the 2023 COVID-19 period, there has been an increase in viral co-infections attributed to decreased population immunity after the relaxation of non-pharmaceutical interventions.[33] This trend, particularly in school-aged children, can be exacerbated by the contagious nature of MRMP with close contact in school settings and presence of asymptomatic carriers, contribute to the occurrence of multiple viral co-infection.[31] Our study revealed that viral co-infections were linked to more severe clinical presentations in the MRMP group, resulting in longer recovery times. Viruses such as RSV and influenza may suppress innate immunity via IFN-α inhibition, creating a permissive niche for *M. pneumoniae* proliferation and cytokine-driven damage as viral co-infections may synergistically enhance IFN-γ production via shared TLR pathways such as TLR3/7 activation by viral RNA.[34] This synergy likely explains MRMP’s higher oxygen supplementation, mechanical ventilation rates and use of flexible bronchoscopy which lead to higher ICU admissions in our study which is also observed in previous studies.[13,16] The higher rate of viral co-infections in MRMP may further necessitate bronchoscopic evaluation to identify secondary pathogens or assess airway inflammation, particularly when non-invasive tests are inconclusive.[35] However, bronchoscopy itself may delay definitive treatment in resource-limited settings, as clinicians await microbiological results before adjusting therapy. Future research should explore age-specific analyses to better understand the prevalence and impact of specific respiratory viruses in children with MRMP, aiding in more effective clinical management strategies for this pediatric population. Furthermore,

thorough diagnostic testing for viral and bacterial co-infections in children, particularly with MPP, is crucial for personalized treatment and to lessen the strain on healthcare resources.

Radiological findings also differed significantly between the MRMP and MSMP groups. Children in the MRMP group showed more severe radiological features and greater lung involvement, with more lobes affected compared to those in the MSMP group. This reflects a more aggressive parenchymal invasion in MRMP may lead to more extensive lung damage, likely exacerbated by delayed effective treatment.[5] Similar reports have indicated that radiological findings tend to be more serious in the MRMP patients.[12] which could contribute to more severe respiratory symptoms and a more complicated clinical course. These radiologic differences may reflect the more aggressive or refractory nature of MRMP infections, potentially explaining the longer hospital stays observed in this group. Additionally, clinicians should note that macrolide resistant strains may present more widespread lung involvement, necessitating closer monitoring and more aggressive but sufficient treatment. Currently, Studies investigating the extent of pneumonic lesions in *M. pneumoniae* pneumonia with respect to macrolide resistance are currently limited. Therefore, there is a need for large-scale studies to verify the aforementioned results.

In our study MRMP patients exhibited extrapulmonary complication, prolonged defervescence, a delay attributed to ineffective empiric macrolide therapy and the subsequent need for antibiotic escalation to tetracyclines/fluoroquinolones. This is similar to previous studies where MRMP cases were likely to switch to alternative antibiotics and delayed defervescence after macrolide treatmentas well as extrapulmonary complications.[12,13,36] The delayed defervescence post macrolide initiation in MRMP highlights the ineffectiveness of empiric use of macrolide in resistant strains, a critical concern given rising global resistance rates.[37,38] Hence, Our data strongly support recent studies on the recommendation for early transition to tetracyclines or fluoroquinolones in suspected MRMP.[37,39] and emphasizing the need for early resistance-guided therapy, particularly given the increased odds of severe outcomes with delayed antibiotic escalation. Adjunctive corticosteroids and IVIG were disproportionately used in MRMP, likely targeting IL-6/IFN-γ-mediated hyperinflammation. However, their heterogeneous efficacy in prior trials warrants caution, emphasizing the need for biomarker-guided immunomodulation.[9] Hence clinicians must weigh treatment risks and benefits to personalize medication choices to each patient's clinical context.

5.0 Challenges and recommendations

Since this was a retrospective study, there may be selection bias as the data were collected from patients who were hospitalized at our institution. Patients with milder cases of *M. pneumoniae* infection may not have been hospitalized, and thus, not included in the study. This could lead to an overestimation or underestimation of the severity of MRMP. Future studies should conduct prospective cohort studies to confirm the causal relationships between the identified risk factors and MRMP. Additionally, randomized controlled trials are needed to evaluate the effectiveness of different immunomodulatory therapies in treating MRMP associated hyperinflammation in children.

Fig. 3 provides a framework for addressing the challenges posed by MRMP infections, particularly in First Affiliated Hospital of Gannan Medical University and other areas with similar context of high prevalence and increased severity, characterized by prolonged fever, hospital stays, multilobar involvement, and viral co-infections. Practitioners should consider diagnostic strategy that emphasizes early genetic screening for A2063G/A2054G mutations, monitoring biomarkers such as IFN-γ, D-dimer, LDH, and IL-6 levels, and use of chest radiography to assess multilobar involvement. Predictive risk factors including co-infection, prolonged disease duration (≥7 days), high IFN-γ levels, multilobar pneumonia, and a history of antibiotic escalation emphasizes the need for targeted interventions. Moreover, treatment pathway should consider advising against macrolide monotherapy in suspected MRMP cases, and recommend alternative therapies such as uing tetracyclines or fluoroquinolones instead. Additionally, practitioners should consider corticosteroids and IVIG in severe cases to manage inflammation and immune response. Finally, preventive strategy that underscores the importance of strengthening MRMP surveillance, educating clinicians on early signs and laboratory markers must be developed that consider region-specific antibiotic stewardship programs, and promote infection control, particularly in schools and childcare settings to mitigate transmission. Through this integrated approach, a robust foundation for managing MRMP infections can be established, which can enhance clinical practices and public health strategies.

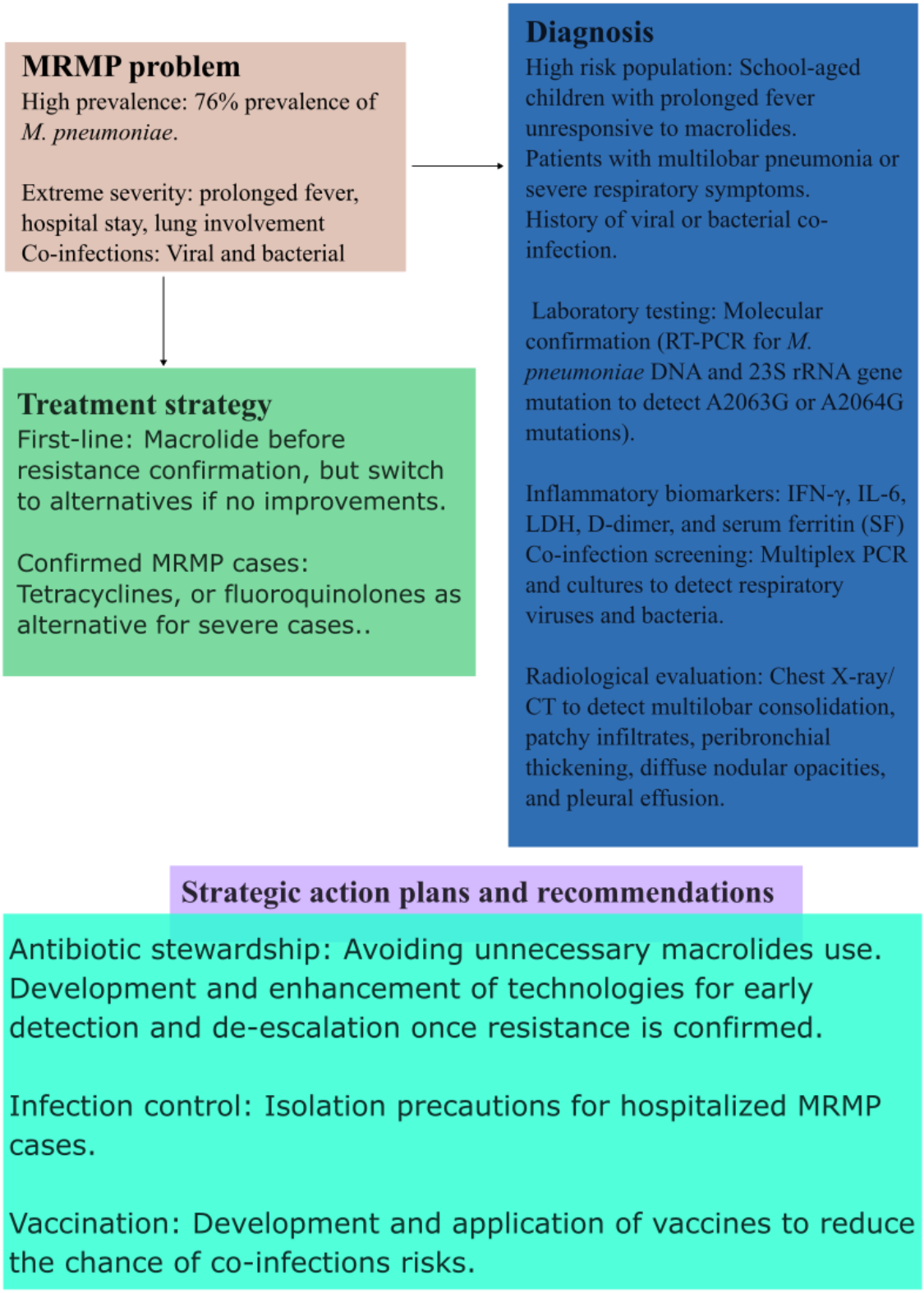

Figure 3: MRMP management: Diagnosis, treatment, and prevention strategies.

6.0 CONCLUSION

Our study establishes MRMP as a hyper inflammatory, treatment-refractory pneumonia subtype prevalent in school-aged children, marked by prolonged fever, severe radiological lung involvement, and extrapulmonary complications driven by dysregulated IFN-γ-mediated immune responses. Elevated inflammatory biomarkers (IL-6, IFN-γ, LDH, D-dimer) and frequent viral co-infections synergistically exacerbate alveolar injury and systemic inflammation, necessitating ICU admissions and advanced respiratory support. The ineffectiveness of empiric macrolides underscores the urgency of early molecular resistance testing and prompt transition to tetracyclines or fluoroquinolones to mitigate complications. Radiographic severity and delayed defervescence further validate MRMP's aggressive phenotype. While adjunctive immunomodulation reflects attempts to temper cytokine storms, biomarker-guided strategies are imperative to optimize outcomes. In an era of rising antimicrobial resistance, these findings directly inform global efforts to refine CAP guidelines, optimize stewardship, and mitigate the burden of refractory *M. pneumoniae* infections. We advocate for updated guidelines prioritizing resistance-guided therapy, stringent antibiotic stewardship, and age-specific co-infection screening to address MRMP rising burden. We hope our study will be essential in providing actionable insights for clinicians and policymakers during pediatric MRMP management.

AUTHOR CONTRIBUTIONS STATEMENT

Conceptualization, E.B. K.L and X.R.; methodology, E.B.; software, B.M.; validation, E.B., L.H and L.J.; formal analysis, E.B., and X.R; investigation, E.B., and J.Y.; resources, K.L., and L.H; data curation, E.B., X.R and L.J; writing—original draft preparation, E.B.; writing—review and editing, X.R., L.H., L.J., and J.Y.; visualization, B.M., and L.J; supervision, X.R., and K.L.; project administration, X.R;. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

ABBREVIATIONS

The following abbreviations are used in this manuscript

M. Pneumoniae, Mycoplasma pneumoniae; MSMP, macrolide susceptible *Mycoplasma pneumoniae*; MRMP, macrolide resistant *Mycoplasma pneumoniae*; No. of pt, number of patients; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; IL-6, Interleukin-6; SF, serum ferritin; IL-2, Interleukin-2 IL; IL-4, Interleukin-4; ESR, erythrocyte sedimentation rate; IL-8, Interleukin-8; IL-10, Interleukin-10; IFN- γ , Interferon gamma ; TNF- α ,Tumor necrosis factor alpha ; SF, Serum ferritin; ICU - Intensive care unit; NA, not applicable; B (R.C), regression coefficient; S.E, standard error; OR, odds ratio; CI, confidence interval.

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