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The effect of macrolides on long-term mortality in patients followed in intensive care unit for community-acquired pneumonia

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Abstract

Macrolides are known for their antibacterial activity as well as immunomodulatory properties, which may be beneficial in critically ill patients. This study aimed to evaluate the impact of macrolide use on early and six-month mortality in patients treated in the intensive care unit (ICU) for community-acquired pneumonia (CAP). This retrospective study included adults hospitalized in the pulmonary ICU between 2016 and 2024 with a diagnosis of CAP. Demographic, clinical, and laboratory data were collected, along with information on nursing home residence, bed dependency, immunosuppression, and hospital stay duration. Patients were grouped by macrolide use and compared in terms of ICU and 6-month mortality. Among 334 patients included, 35.3% received macrolides. No significant differences were found between the macrolide and non-macrolide groups in terms of age, sex, comorbidities, inflammatory markers, CURB-65 scores, ventilation needs, or ICU mortality. However, six-month mortality was significantly lower in the macrolide group (18.6% vs. 28.6%, p=0.027). Patients in this group also had a shorter duration of empirical antibiotic use (6 days vs. 7 days, p=0.04) and were less likely to be bedridden (18.6% vs. 31.9%, p=0.009). Macrolide use appears to have no impact on short-term ICU mortality but may improve long-term survival by reducing 6-month mortality, likely through anti-inflammatory and immunomodulatory effects. While previous studies support their role in suppressing proinflammatory cytokines, further research is needed to determine whether this benefit stems from patient selection or the drug's direct effects.

Keywords: Community-acquired pneumonia, macrolides, intensive care unit, mortality

Introduction

Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality worldwide, particularly in older adults and those with comorbid conditions. Approximately half of all CAP patients require hospitalization and 10-20% of these patients have severe disease requiring intensive care unit (ICU) treatment. Despite improvements in the healthcare system, mortality ranges from 1% in outpatients to 4% to 18% in inpatients. In ICU where severe pneumonia is treated, this rate increases to 28% [1,2].

Severe cases of CAP rank among the leading infectious causes of mortality and frequently progress to septic shock or multi-organ failure. This high disease burden is largely due to complications such as hemodynamic instability, respiratory failure, and the frequent need for ICU interventions, including mechanical ventilation (MV) [3]. In fact, although CAP is defined as an acute illness, an increased risk of death up to 10 years after the acute attack has been reported in patients who survive after CAP. Although the reason for long-term mortality in these patients is not clearly explained, cardiac causes have been suggested [4].

The management approach for CAP is guided by the clinical severity of the illness. For patients treated in outpatient settings, current clinical guidelines suggest macrolides as the initial therapy. In individuals with comorbid conditions or those hospitalized with non-severe CAP, either respiratory fluoroquinolones alone or a combination of a β-lactam and a macrolide is commonly recommended. For patients with severe CAP hospitalized in ICU, treatment with a macrolide or fluroquinolone combined with a β-lactam antibiotic is recommended [5,6]. It is thought that the macrolide antibiotics added to the treatment in severe

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patients will lead to beneficial effects in CAP due to the immunomodulatory and anti-inflammatory effects of macrolides besides their anti-microbial activity [3]. However, macrolides effects on ICU mortality and long-term survival are still controversial. This study was conducted to assess the potential impact of macrolide therapy on mortality outcomes among patients receiving intensive care for CAP.

Material and Methods

The study received ethical approval from the Scientific Research Ethics Committee of the Ministry of Health Istanbul Health Sciences University Sureyyapasa Training and Research Hospital for Chest Diseases and Thoracic Surgery, under the decision dated 31 October 2024 and numbered 2024-25. In accordance with the ethical standards of the Declaration of Helsinki, this research included patients aged 18 years or older who were treated for CAP in the Pulmonary ICU at Istanbul Sultan Abdulhamid Han Training and Research Hospital from 2016 to 2024. Age, gender and comorbid diseases such as lung diseases, lung cancer, diabetes mellitus (DM), congestive heart failure (CHF), chronic renal failure (CRF) were noted. In addition, blood gas data (pH, lactate) and inflammatory markers [Procalcitonin (PCT), C-Reactive Protein (CRP)] were retrospectively recorded using data obtained from a computerized database. Laboratory findings obtained at the time of admission. Data on nursing home hospitalization, bed riddenness, immunosuppression, previous history of pneumonia, hospitalization day and the month of the year in which the patients were infected were also noted. The Confusion-blood urea nitrogen- respiratory rate-blood pressure- age>65 (CURB-65) score was assessed during hospitalization to determine the severity of pneumonia. The duration of antibiotic administration, the need for non-invasive mechanical ventilation (NIMV) and invasive mechanical ventilation (IMV) were recorded during ICU hospitalization. The most common causative agents of intensive care infections and carbapenem resistance were also investigated. According to antibiotic treatment, patients were divided into two groups as those who received macrolide antibiotics and those who did not, and all these data were compared in terms of ICU mortality (early mortality) and 6-month mortality. Patients with viral pneumonia, including COVID-19-related pneumonia, as well as those infected with Pseudomonas aeruginosa or methicillin-resistant Staphylococcus aureus (MRSA) at hospital admission, were excluded from the study.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. For continuous variables, either the Mann-Whitney U test or the Student's t-test was applied based on distribution normality. Categorical variables were compared using the Chi-square test. A p-value below 0.05 was accepted as the threshold for statistical significance. In addition, univariate and multivariate logistic regression analyses were performed to identify independent predictors of 6-month mortality.

Result

In this study, 334 patients were evaluated. Their mean age was 75.17 years (SD ±13.98). The gender distribution included 41% women and 59% men. Of the patients, 44.3% had lung disease, 21.3% had DM, 12.3% had CRF, 32.6% had CHF, 11.4% had lung cancer and 13.2% were immunosuppressed. It was noted that 3.6% of the patients were hospitalized in nursing facilities and 26.9% were bedridden.

The most common CURB-65 score was 3 (n=142, 42.5%) and 63.8% had a CURB-65 score ≥3. According to the time of admission, most patients applied in February (32.6%), followed by March (24%) and January (20.7%). The proportion of patients with previous pneumonia was 31.4%.

The number of patients treated with macrolide therapy was 118 (35.3%) and the mean duration of treatment was 6.18±3.35 days. The mean time for empirical antibiotic use in the whole group was 7.38±4.88 days. Carbapenem resistance was detected in 12.3% of the patients. The main isolated pathogens were Pseudomonas aeruginosa (3.6%), Acinetobacter Baumanni (4.2%) and Klebsiella Pneumoniae (4.2%). IMV was required in 58.7% and NIMV in 23.1% of patients followed up in ICU.

The median duration of hospitalization was 9 days (0-183 days). ICU mortality (early mortality) was 52.1% and mortality within 6 months was 24.85%. Mean CRP level was 128.11±90.16 mg/L, PCT median was 0.51 ng/mL (0.01-10), pH mean was 7.34±0.11 and lactate level was 2.42±1.73 mmol/L (Table 1).

There were no significant differences in age (p=0.796), length of hospitalization (p=0.37), CRP (p=0.882), PCT (p=0.598), pH (p=0.077) and lactate level (p=0.422) between patients with and without macrolide treatment. However, the duration of empirical antibiotic use was shorter in the macrolide group (p=0.04).

The rate of bedridden patients was lower in the macrolide group (18.6% vs 31.9%, p=0.009). And also six-month mortality was significantly lower in the macrolide group (18.6% vs 28.6%, p=0.027). Other clinical parameters such as sex, coexisting diseases, need for IMV/NIMV, CURB-65 classification, and ICU mortality did not differ significantly between the groups (p>0.05). (Table 2).

Univariate logistic regression analysis identified several variables significantly associated with 6-month mortality among ICU patients with community-acquired pneumonia. Higher lactate levels (OR:1.216;95% CI:1.056–1.401; p=0.007), lower arterial pH values (OR:0.000;95% CI:0.000–0.001; p<0.001), CURB-65≥3(OR:0.261;95% CI:0.152–0.450; p<0.001), CHF (OR:0.507;95% CI:0.276–0.933; p=0.029), lung cancer (OR:0.176;95% CI:0.041–0.750; p=0.019), need for IMV (OR:0.167;95% CI:0.093–0.299; p<0.001), and carbapenem resistance (OR:0.188;95% CI:0.0540.651; p=0.008) were significantly associated with increased mortality risks.

Treatment with macrolides also showed a significant association with reduced mortality in the univariate analysis (OR:1.806;95%CI:1.065–3.063;p=0.028).

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In the multivariate logistic regression analysis, only arterial pH (OR:0.000;95%CI:0.000–0.000;p<0.001) and IMV requirement (OR:0.060;95%CI:0.013–0.285;p<0.001) remained independently associated with 6-month mortality. Although lactate level (OR:1.322;95%CI:0.997–1.753;p=0.053) and carbapenem resistance (OR:0.155;95%CI:0.022–1.099;p=0.062) approached statistical significance, they did not retain independent predictive value. The initially observed protective effect of macrolide treatment was not statistically significant after adjustment for other covariates (OR:1.447;95%CI:0.471–4.439;p=0.519) (Table 3).

Table 1. Descriptive and Clinical Characteristics of Patients Followed in Intensive Care Unit for Community-Acquired Pneumonia

Variables	Mean±sd, Median (min-max) or n (%)
Age	75.17±13.98
Gender	
Female	137 (41)
Male	197 (59)
CRP	128.11±90.16
Procalcitonin	0.51 (0.01-10)
ph	7.34 ± 0.11
Lactate	2.42 ± 1.73
CURB 65	
0	13 (3.9)
1	31 (9.3)
2	76 (22.8)
3	142 (42.5)
4	63 (18.9)
5	8 (2.4)
Comorbidities	
Lung Diseases	148 (44.3)
DM	71 (21.3)
CRF	41 (12.3)
CHF	109 (32.6)
Lung Cancer	38 (11.4)
Aspiration Pneumonitis	59 (17.7)
Immunosuppression	44 (13.2)
Nursing-Home Patients	12 (3.6)
Bed Dependency	90 (26.9)
Previous Pneumonia	105 (31.4)
With Macrolides	118 (35.3)
Without Macrolides	213 (63.8)
Number of Days Macrolides Administration	6.18±3.35
Empirical Antibiotic Days	7.38±4.88
Carbepenem Resistance	41 (12.3)
Secondary Infectious Agents	
Pseudomonas Aeruginosa	12 (3.6)
Acinetobacter Baumanni	14 (4.2)
Klebsiella Pneumonia	14 (4.2)
IMV Need	196 (58.7)
NIMV Need	77 (23.1)
Days of Hospitalization	9 (0-183)
ICU Mortality	174 (52.1)
6-Month Mortality	83 (24.85)

CRP: C-reactive protein, CURB-65: Confusion- blood urea nitrogen- respiratory rate- blood pressure- age>65, DM:diabetes mellitus, CRF: chronic renal disease, CHF: Congestive heart failure, IMV: Invasive mechanical ventilation, NIMV: Non-inveasive mechanical ventilation, ICU: Intensive care unit

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Table 2. Comparison of clinical and laboratory characteristics of patients according to macrolide use

Variables	With Macrolides Treatment n (%), mean±sd or median (min-max)	Mesh removed patient n (%), mean±sd or median (min-max)	P value
Age	78.5 (24-98)	76 (19-104)	0.796
Gender			0.054
Female	56 (47.5)	78 (36.6)	
Male	62 (52.5)	135 (63.4)	
CRP	120.7 (3-374)	120 (2-406)	0.882
Procalcitonin	0.75 (0.01-9.8)	0.44 (0.01-10)	0.598
pH	7.325 ± 0.12	7.36 ± 0.11	0.077
Lactate	1.88 (0.5-10)	2.1 (0.4-13.35)	0.422
CURB 65 ≥3	71 (60.2)	139 (65.6)	0.329
Lung Diseases	58 (49.2)	87 (40.8)	0.145
DM	30 (25.69)	40 (18.8)	0.188
CHF	41 (34.7)	66 (31)	0.484
CRF	13 (11)	27 (12.7)	0.789
Lung Cancer	13 (11)	25 (11.7)	0.987
Immunosuppression	15 (12.7)	29 (13.6)	0.95
Aspiration Pneumonitis	15 (12.7)	44 (20.7)	0.097
Nursing-Home Patients	2 (1.7)	10 (4.7)	0.225
Bed Dependency	22 (18.6)	68 (31.9)	**0.009**
Previous Pneumonia	34 (29.3)	70 (33.5)	0.439
Empirical Antibiotic Days	6 (1-27)	7 (1-29)	**0.04**
Carbepenem Resistance	9 (19.6)	32 (29.4)	0.288
IMV Need	67 (56.8)	126 (59.2)	0.675
NIMV Need	32 (27.1)	45 (21.1)	0.217
Day of hospitalization	9 (1-56)	11 (0-117)	0.37
ICU Mortality	58 (49.2)	113 (53.1)	0.497
6-Month Mortality	22 (18.6)	61 (28.6)	**0.027**

CRP: C-reactive protein, CURB-65: Confusion- blood urea nitrogen- respiratory rate- blood pressure- age>65, DM:Diabetes mellitus, CRF: Chronic renal failure, CHF: Congestive heart failure, IMV: Invasive mechanical ventilation, NIMV: Non-inveasive mechanical ventilation, ICU: Intensive care unit

Table 3. Logistic regression analysis of predictors of 6-month mortality in icu patients with community-acquired pneumonia

Variables	Univariate		Multivariate*	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.994 (0.977-1.012)	0.49		
Gender	1.071 (0.631-1.819)	0.8		
Lung Diseases	1.490 (0.885-2.509)	0.13		
CRP	0.999 (0.996-1.002)	0.439		
Procalcitonin	1.094 (0.961-1.244)	0.175		
pH	0.000 (0.000-0.001)	**<0.001**	**0.000 (0.000-0.000)**	**<0.001**
Lactate	1.216 (1.056-1.401)	**0.007**	**1.322 (0.997-1.753)**	**0.053**
CURB 65 ≥ 3	0.261 (0.152-0.450)	**<0.001**		
DM	1.185 (0.637-2.205)	0.592		
CHF	0.507 (0.276-0.933)	**0.029**		
CRF	1.178 (0.548-2.532)	0.675		
Lung Cancer	0.176 (0.041-0.750)	**0.019**		
Immunosuppression	0.769 (0.341-1.737)	0.528		
Aspiration Pneumonitis	0.687 (0.329-1.434)	0.317		
Bed Dependency	0.578 (0.304-1.096)	0.093		
Previous Pneumonia	0.709 (0.395-1.272)	0.248		
Macrolide Treatment	1.806 (1.065-3.063)	**0.028**	1.447 (0.471-4.439)	0.519
Duration of Macrolide Treatment	0.989 (0.877-1.115)	0.853		
Empirical Antibiotic Days	0.967 (0.914-1.023)	0.248		
Carbepenem Resistance	0.188 (0.54-0.651)	**0.008**	0.155 (0.022-1.099)	0.062
IMV Need	0.167 (0.093-0.299)	**<0.001**	**0.060 (0.13-0.285)**	**<0.001**
NIMV Need	10.4833 (5.787-18.990)	**<0.001**		
Day of Hospitalization	0.955 (0.928-0.984)	0.002		

*Backward wald method, CRP: C-reactive protein, CURB-65: Confusion- blood urea nitrogen- respiratory rate- blood pressure- Age>65, DM:Diabetes mellitus, CRF: Chronic renal failure, CHF: Congestive heart failure, IMV: Invasive mechanical ventilation, NIMV: Non-inveasive mechanical ventilation

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Discussion

Despite adequate antibiotherapy, respiratory support therapies and improvements in intensive care facilities, the increase in mortality in CAPs is concerning. Despite the limited understanding of the complex inflammatory cascade in CAP, current evidence suggests that survival is compromised by unregulated inflammation, which is further aggravated by comorbid illnesses. Macrolides have been reported to be of significant benefit when inflammatory responses are high, such as in CAP [1]. The benefit of macrolides is thought to be due to their anti-inflammatory and immunomodulatory effects. They are also known to be effective in the treatment of bronchiolitis obliterans syndrome, diffuse pan-bronchiolitis (DPB) and even chronic obstructive pulmonary diseases. There are also observational studies showing that macrolides reduce mortality and morbidity in CAP [7-9]. In our study, there was no difference between macrolide users and non-users in the days of hospitalization, need for IMV and NIMV, early ICU mortality and carbepenem resistance. However, 6-month mortality was lower in the macrolide group. The fact that macrolides had no effect on early ICU mortality but decreased 6-month mortality may be related to the anti-inflammatory and immunomodulatory effects of these agents. It was thought that these effects might decrease the inflammatory response due to CAP. In support of this view, macrolides are known to reduce pro-inflammatory cytokines (interleukin 1, tumor necrosis factor α [TNF-α], interleukin 6 [IL-6], interferon-γ (IFN-γ) and interleukin 8 [IL-8]), oxidative metabolism and neutrophil chemotaxis. Furthermore, it may suppress microbial virulence mechanisms like biofilm development and alleviate mucus hypersecretion, thereby enhancing mucociliary clearance [7,3,10]. In addition, the fact that inflammation is more severe in patients with severe CAP [2] suggests that macrolides, an anti-inflammatory treatment, may be more beneficial in the long term. Perhaps, while the anti-microbial properties of macrolides are more prominent in the acute period, their anti-inflammatory and immune modulatory effects may be more effective in the long term. The decrease in long-term mortality in our study may be related to these mechanisms of macrolides.

Long-term mortality has been shown to be higher in inpatients with CAP. Long-term mortality has also been associated with comorbidities and whether patients are mobilized or not. Although the causes of long-term mortality in CAP have not been clarified, it is thought to be related to persistent systemic inflammatory response. Especially high CRP level is an independent predictor of long-term mortality [11,12]. Although there was no difference between groups in terms of early and late mortality, as we look in general, patients who were followed up as inpatients for CAP in our study were older, had high CRP levels and comorbid diseases. Considering all these high inflammatory conditions, we concluded that the role of macrolides in reducing inflammation is indeed effective.

The incidence of both early and late cardiovascular events is also increased in CAP, and inflammatory markers remain elevated in the late period [13,14]. Although cardiac side effects were not observed in our study; it is suggested that not only the disease itself but also the adverse events it causes exacerbate inflammation. According to the results of our study, macrolides are thought to control the inflammatory consequences of both CAP and related diseases.

Macrolides' immunomodulatory effects were first studied in DPB. DPB patients are frequently infected with macrolide-resistant Pseudomonas aeruginosa and yet these patients benefit from macrolide therapy. This has been attributed to the immunomodulatory effects of macrolides. This effect has been demonstrated in many inflammatory respiratory diseases [15]. Macrolide efficacy against non-infectious causes actually explains the reduction in 6-month mortality in this study.

Initiating combination therapy with β-lactams and macrolides within 4 to 8 hours of admission in adult patients hospitalized for CAP has been associated with a reduction in short-term mortality [16]. As this research was designed as a retrospective observational study, data on the time of antibiotic initiation were not available. Perhaps the reason why there was no significant difference in early hospital mortality between the macrolide group and the non-users may be due to the delay in antibiotic initiation.

In the ACCESS study carried out in 2024 among patients hospitalized for CAP, it was reported that clarithromycin treatment given 500 mg 2 times a day for 7 days increased the early clinical response with clarithromycin compared to placebo, and clarithromycin alleviated the inflammatory burden of CAP. This was associated with reversal of the inflammatory dysregulation caused by CAP [17]. In our study, the mean number of antibiotic days was found to be 6 in the group receiving macrolides and 7 in the group not receiving macrolides, which was statistically significantly higher ($p=0.04$). Considering that 7 days of treatment is required for early clinical response, this may be the reason why macrolides were not beneficial in early mortality in our study.

Although the difference did not reach statistical significance, both the overall hospital stay and ICU mortality were observed to be lower in the macrolide-treated group compared to those who did not receive macrolides, which is consistent with previous literature [4].

Bartel Index (BI) is a scoring method that evaluates the functional status of patients. In a study performed in patients with CAP, reported by Murcia et al., mortality rates of patients with BI ≤ 80 were found to be higher and even reported that mortality was 4 times higher in bedridden patients. [18]. In our study, it was observed that the patients in the group who did not receive macrolides were more bedridden, that is, more functionally limited, and this may be considered as the reason why macrolides were ineffective in early mortality.

On the other hand, in the multivariate regression analysis

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conducted in this study, macrolide use was not found to have a statistically significant benefit on 6-month mortality. This discrepancy may be attributed to unmeasured confounding variables, differences in patient populations such as the presence of bedridden status and pulmonary malignancies, and variability in the infecting pathogens. Additionally, the inability to reach a sample size with sufficient statistical power may have contributed to this result. Although limited data, there are studies in the literature that have reported no beneficial effect of macrolides on mortality [19]. Nevertheless, in our study, macrolide use was found to be associated with a favorable effect on mortality in the univariate regression analysis. Further prospective studies with larger cohorts are warranted to validate these findings.

Conclusion

This study shows that macrolide use in ICU patients can reduce 6-month mortality. Macrolides are thought to provide a potential survival advantage in favorable patient groups. However, whether this effect depends on patient selection or directly on the immunomodulatory effects of the drug should be evaluated in prospective larger and controlled studies.

Limitations

This study has several limitations inherent to its retrospective design. First, retrospective data collection may lead to selection bias and information bias due to missing or incomplete data. Additionally, the inability to control for all potential confounding variables limits the ability to draw causal inferences. The heterogeneity of clinical management and antibiotic prescribing practices, which may vary over time and across clinicians, also introduces potential variability in outcomes. Also information regarding antibiotic use prior to hospital admission may be incomplete or inaccurate. And radiologically, the severity of pneumonia and treatment responses could also be evaluated.

Furthermore, as this was a single-center study, the generalizability of the findings may be limited. These limitations highlight the need for well-designed, adequately powered prospective randomized controlled trials to confirm the impact of macrolide use on long-term mortality in ICU patients with community-acquired pneumonia.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study received ethical approval from the Scientific Research Ethics Committee of the Ministry of Health Istanbul Health Sciences University Sureyyapasa Training and Research Hospital for Chest Diseases and Thoracic Surgery, under the decision dated 31 October 2024 and numbered 2024-25.

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